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Levofloxacin/amoxicillin-based schemes *vs* quadruple therapy for *Helicobacter pylori* eradication in second-line

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Abstract

Worldwide prevalence of *Helicobacter pylori* (*H. pylori*) infection is approximately 50%, with the highest being in developing countries. We compared cure rates and tolerability (SE) of second-line anti-*H. pylori* levofloxacin/amoxicillin (LA)-based triple regimens *vs* standard quadruple therapy (QT). An English language literature search was performed up to October 2010. A meta-analysis was performed including randomized clinical trials comparing 7- or 10-d LA with 7-d QT. In total, 10 articles and four abstracts were identified. Overall eradication rate in LA was 76.5% (95% CI: 64.4%-97.6%). When only 7-d regimens were included, cure rate was 70.6% (95% CI: 40.2%-99.1%), whereas for 10-d combinations, cure rate was significantly higher (88.7%; 95% CI: 56.1%-109.9%; $P < 0.05$). Main eradication rate for QT was 67.4% (95% CI: 49.7%-67.9%). The 7-d LA and QT showed comparable efficacy [odds ratio (OR): 1.09; 95% CI: 0.63-1.87], whereas the 10-d LA regimen was significantly more effective than QT (OR: 5.05; 95% CI: 2.74-9.31; $P < 0.001$; $I^2 = 75\%$). No differences were reported in QT eradication rates among Asian and European studies, whereas LA regimens were more effective in European populations (78.3% *vs* 67.7%; $P = 0.05$). Incidence of SE was lower in LA therapy than QT (OR: 0.39; 95% CI: 0.18-0.85; $P = 0.02$). A higher rate of side effects was reported in Asian patients who received QT. Our findings support the use of 10-d LA as a simple second-line treatment for *H. pylori* eradication with an excellent eradication rate and tolerability. The optimal second-line alternative scheme might differ among countries depending on quinolone resistance.

Key words: *Helicobacter pylori*; Second-line treatment; Levofloxacin; Quadruple regimen

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INTRODUCTION

Since 1982, when Warren and Marshall first discovered *Helicobacter pylori* (*H. pylori*) in the stomach, eradication of the infection has being recognized as crucial for prevention and treatment of gastroduodenal and more recently even extraintestinal diseases[1-4]. The worldwide prevalence of *H. pylori* infection is approximately 50%, with the highest being in developing countries[5]. Standard first-line therapy consists of a proton pump inhibitor (PPI) plus clarithromycin and amoxicillin or metronidazole[6] and achieves successful eradication in up to 80% of patients. During the past decade, an alarming decrease in eradication rates has been observed[7], mostly due to antibiotic resistance to clarithromycin and metronidazole[3,8]. Conversely, resistance to amoxicillin and tetracycline remains a rare occurrence worldwide[9-11]. Choice of a second or even third course of therapy is more controversial[6,9,12-14]. Recently, the concept of cumulative eradication rate has been introduced in treatment of *H. pylori* infection focusing on final cure rate after one or more courses of treatment. In this perspective, if the overall eradication rate is considered even after four consecutive empirical treatments, 99.5% of patients can be cured[15]. Currently, the recommended second-line regimen is a 7-14-d complex scheme consisting of PPI, bismuth, tetracycline and metronidazole[16,17]. However, bismuth salts, applied to decrease bacterial load, are no longer available in many countries[18]. Eradication rate of the quadruple regimen ranges from 65% to 80% and a high incidence of side effects are noted (up to 50% of patients), with consequently poor compliance[19-22]. For this reason, a triple therapy consisting of PPI, metronidazole and amoxicillin or tetracycline for a minimum of 7 d has been recommended as an alternative[6]. Meanwhile, new drugs, such as levofloxacin, rifabutin, furazolidone and azithromycin have been tested in various combinations and doses to overcome falling eradication rates[13,14,23-31].

Among those, levofloxacin-based second-line schemes represent the most promising alternative[32,33]. In particular, association with amoxicillin has been extensively studied, due to rare *H. pylori* resistance. Currently, a 10-d triple levofloxacin (250 mg BD)/amoxicillin (LA)-based therapy has been recommended as second-line therapy in Italy, and as third-line empirical treatment by European guidelines[6,16]. However, heterogeneity in terms of dosage, combination and duration of treatment do not allow a definitive conclusion.

Moreover, in consideration of differences in quinolone resistance among countries, the ideal second-line treatment for *H. pylori* infection may differ between areas, countries and races[10,20,34].

Here we compare eradication rates and tolerability exclusively of second-line anti-*H. pylori* LA-based triple schemes and standard quadruple therapy (QT) in European and Asian studies, in order to guide clinical decision making.

Studies providing information on use of anti-*H. pylori* LA-based triple therapy and standard quadruple scheme in second-line were identified through a systematic search in the MEDLINE and EMBASE databases by using various combinations of the terms "*H. pylori*", "levofloxacin", "amoxicillin", "quadruple", "bismuth", "second-line" and "rescue". Additionally, references of retrieved articles were screened for further studies (cross-referencing). We also performed a full manual search of all review articles, recently published editorials and all retrieved original studies presented at Digestive Disease Week, United European Gastroenterology Week, and European Helicobacter Study Group conferences. In addition, reference lists from relevant identified papers were manually searched. All original research articles and abstracts published until the 31 October 2010 were included. The search was limited to randomized controlled trials (RCTs) and studies comparing the two regimens (LA *vs* QT). Two investigators (Di Caro S and Fini L) independently extracted data by using a structured form. Only data from patients undergoing second-line eradication treatments were included in the analysis. There was a > 95% agreement in data extraction between the two investigators.

The following data were extracted from the articles: first author, year of publication, characteristics of study population (sample size, race, sex, age range and mean of study participants), therapy scheme (drugs, duration of treatment, dosage), intention-to-treat (ITT) and per-protocol eradication rates, incidence of side effects, discontinuation due to side effects.

Study outcomes for the meta-analysis were *H. pylori* eradication and incidence of adverse effects. Sub-analyses were performed comparing 7-d *vs* 10-d levofloxacin-based regimens in terms of efficacy and adverse events between European and Asian populations. Eradication rate analysis was based on ITT data. In the tolerability analysis, patients who discontinued treatment due to severe side effects were included.

The meta-analysis was performed using the Preferred Reporting Items for Systematic reviews and Meta-Analyses 2009 guidelines. Odds ratio (OR) was used as a measure of association, and summary ORs along with 95% CI were calculated based on a random-effects model using the DerSimonian and Laird methods. Heterogeneity was evaluated to establish if any clinical, methodological, or statistical variability existed among studies included. If significant heterogeneity existed, the random-effects model was used. Also, inconsistency statistic (I^2) was calculated to evaluate level of heterogeneity (0%-30%: homogeneity; 30%-50%: moderate heterogeneity; 50%-80%: substantial heterogeneity; > 80%: considerable heterogeneity). A pooled analysis was used to assess differences between levofloxacin regimens (7 d *vs* 10 d) and study populations. All statistical tests were two-sided and conducted at a significance level of 0.05. Independent academic biostatisticians from Baylor University Medical Center (Daoud Y) performed the statistical analysis. Data were analyzed with Review Manager (RevMan) 5.1 developed by the Cochrane collaboration.

Table 1 Demographic data of patients, extracted from the published papers (n = 9)

Ref.	Pts	Days of tp	Test confirming infection	Test confirming eradication	Age (yr)		Male (%)		Smokers (%)		Clinic (%)	
					L + A	Q	L + A	Q	L + A	Q	L + A	Q
Nista *et al*[21]	140	10	UBT and/or biopsy	UBT	47 ± 10	48 ± 10	47	49	NA	NA	UD = 37; DD = 33; RD = 30	UD = 40; DD = 34; RD = 26
Perri *et al*[29]	113	7	UBT	UBT	46 ± 16	45 ± 15	48	47	17	20	N = 63; OE = 3; G = 9; GU = 3; D = 10; DU = 9; O = 3	N = 67; OE = 5; G = 2; GU = 0; D = 19; DU = 5; O = 2
Bilardi *et al*[39]	90 (40)	10	UBT and/or biopsy	UBT	56 ± 10	54 ± 13	30	35	64	52	NA	NA
Gisbert *et al*[28]	500 (150)	7-10	UBT	UBT	48 ± 13[1]		39[1]		23[1]			FD = 76; DU = 24[1]
Lee *et al*[80]	126 (23)	7	Rapid urea test	UBT	50 ± 14[1]		63[1]		24[1]			GU = 44; DU = 32; GA = 11; A = 3; F = 1; FD = 9
Wong *et al*[19]	106 (61)	7	Rapid urea test and/or biopsy	UBT	47 ± 12[1]	45 ± 13[1]	44[1]	42[1]	20[1]	19[1]	N = 64; E = 6; GU = 6; DU = 24	N = 77; E = 8; GU = 0; DU = 15
Zhang *et al*[37]	95	7			49		NA	NA	NA	NA	GU/DU = 24; G = 62; GA = 14	
Jung *et al*[42]	76	7	Rapid urea test and/or UBT	Rapid urea test or UBT	48 ± 12	50 ± 10	58	58	NA	NA	GU = 39; DU = 32; GA = 10; G = 19	GU = 38; DU = 33; GA = 18; G = 11
Kuo *et al*[41]	166	7	Rapid urea test and/or biopsy or culture	Rapid urea test and/or biopsy or UBT	50 ± 12	49 ± 14	53	48	14	12	GU = 23; DU = 41; G = 36	GU = 25; DU = 40; G = 35

[1]Demographic data were reported together for both arms. In studies including patients after failure of more than one therapy, extrapolated data on patients pre-treated in second-line are reported in parenthesis; in those cases demographic data are referred to the entire study population. Pts: Patients (total number); L + A: Levofloxacin/amoxicillin-based therapy; Days of therapy (tp): Duration of L + A scheme; UBT: Urea breath test; Q: Quadruple standard therapy; UD: Ulcer-like dyspepsia; DD: Dysmotility-like dyspepsia; RD: Reflux-like dyspepsia; N: Normal; OE: Esophagitis; G: Gastritis; GU: Gastric ulcer; D: Duodenitis; O: Other; FD: Functional dyspepsia; DU: Duodenal ulcer; A: Adenoma; E: Erosion; GA: Gastric atrophy; F: Family history; NA: Not available.

TEN-DAY LEVOFLOXACIN SECOND-LINE SCHEMES DISPLAY SIGNIFICANTLY HIGHER ERADICATION RATE AND LOWER INCIDENCE OF SIDE EFFECTS

Out of 79 titles initially generated by literature searches, 14 studies (10 articles and four abstracts) fulfilling the inclusion criteria were eligible for our analysis. All studies were published from September 2003 to May 2009 and included 677 patients in the LA-based triple therapy group and 608 subjects in the QT group. First-line therapy was a standard triple anti-*H. pylori* scheme. Tolerability data were available in seven articles. Demographic and clinical data of patients available are reported in Table 1. Studies were divided into two categories based on ethnicity of the study population (Asian and Caucasian population). In all studies, *H. pylori* infection was determined by ^{13}C urea breath test (UBT), rapid urea test, histology or culture before treatment, and histology and/or ^{13}C-UBT after administration of eradication therapy. Heterogeneity of data available on levofloxacin dose, ranging from 300 mg/d to 1 g/d (Table 1), does not allow a definitive conclusion.

Data on comparison of second-line levofloxacin-based triple regimens to bismuth-based QT after failure of one cycle of eradication therapy are listed in Table 2.

In our analysis, we extrapolated exclusively the data matching our strict inclusion criteria. We also re-calculated all the eradication percentages from the included studies. In all cases, the results matched the reported data, except one.

In an Italian population study, 10-d levofloxacin-based triple scheme in association with either amoxicillin or tinidazole, was superior to both 7-d and 14-d QT. Specifically, triple therapy eradication rates were 94% with amoxicillin *vs* 63% and 68% at 7 d and 14 d, respectively for QT. A high incidence of adverse events

Table 2 Levofloxacin-based second-line therapies *vs* quadruple bismuth-based regimens for *Helicobacter pylori* treatment

Ref.	Ethnicity	Scheme	Success					Side effects			Discontinuing therapy because of side effects		
			Yes	Total	Completing	ITT %	PP %	Yes	Total	%	Yes	Total	%
Nista *et al*[21]	Caucasian	LAR (10 d; L: 500 mg OD)	66	70	70	94.3	94.3	7	70	10.0	0	70	0.0
		Q07	44	70	64	62.9	68.8	15	70	21.4	5	70	7
Perri *et al*[29]	Caucasian	LAP (7 d; L: 500 mg OD)	37	58	56	63.8	66.1	3	58	5.2	1	58	1.7
		Q07	46	55	51	83.6	90.2	17	55	30.9	3	55	5.5
Orsi *et al*[1][38]	Caucasian	LAR (12 d; L: 500 mg OD)	43	50	47	86.0	89	4	47	8.5	NA	NA	NA
		Q07	44	50	44	88.0	91	11	44	25	NA	NA	NA
Bilardi *et al*[39]	Caucasian	LAP (10 d; L: 250 mg BD)	16	23	NA	69.6	NA	-	-	-	1	44	
		Q07	6	17	NA	35.3	NA	-	-	-	1	46	
Nista *et al*[1][35]	Caucasian	LAE (10 d; L: 500 mg OD)	26	30	30	86.7	86.7	-	-	-			
		Q07	25	35	31	71.4	80.6	-	-	-			
Nista *et al*[1][36]	Caucasian	LAR (10 d; L: 500 mg OD)	42	46	46	91.3	91.3	-	-	-			
		LAR (7 d; L: 500 mg OD)	37	50	50	74.0	74.0	-	-	-			
		Q07	34	50	46	68	73.9	-	-	-			
Gisbert *et al*[28]	Caucasian	LAO (7 or 10 d; L: 500 mg BD)	83	112	NA	74	NA	39	112	34.8	NA	NA	NA
		Q07	21	38	NA	55	NA	6	38	15.8	NA	NA	NA
Wong *et al*[1][44]	Asian	LALa (7 d; L: 500 mg BD)	21	33	NA	63.6	NA	-	-	-			
		Q07	22	30	NA	73.3	NA	-	-	-			
Lee *et al*[80]	Asian	LAR (10 d; L: 200 mg BD)	5	9	8	55.6	62.5	-	-	-			
		Q07	4	14	10	28.6	40.0	-	-	-			
Wong *et al*[19]	Asian	LALa (7 d; L: 500 mg BD)	19	31	NA	61.3	NA	18	54[2]	33.3	NA	NA	NA
		Q07	26	30	NA	86.7	NA	21	52[2]	40.4	NA	NA	NA
Zhang *et al*[43]	Asian	LAE (7 d; L: 500 mg OD)	42	49	NA	85.7	NA						
		Q07	30	44	NA	68.2	NA						
Zhang *et al*[37]	Asian	LAE (7 d; L: 500 mg OD)	42	48	46	87.5	91.3	7	48				
		Q07	33	47	34	70.2	97.0	15	47				
Jung *et al*[42]	Asian	LAP (7 d; L: 300 mg BD)	16	31	30	51.6	53.3	3	30	10.0	0	31	0.0
		Q07	22	45	35	48.9	62.9	11	35	31.4	1	45	2.2
Kuo *et al*[41]	Asian	LAE (7 d; L: 500 mg OD)	58	83	77	69.9	75.3	10	80	12.5	1	83	
		Q07	53	83	63	63.9	84.1	25	71	35.2	5	83	

[1]Data arisen from abstract publication; [2]side effects calculated on the entire study population (not stratified for number of failed previous therapy). L: Levofloxacin; OD: Once daily; BD: Twice daily; LA/La: Levofloxacin/Lansoprazole; ITT: Intention-to-treat eradication rates; PP: Per-protocol; NA: Not available; LAR: Levofloxacin/amoxicillin/rabeprazole; LAO: Levofloxacin/amoxicillin/omeprazole; LAE: Levofloxacin/amoxicillin/esomeprazole; LAP: Levofloxacin/amoxicillin/pantoprazole.

(33%) was observed in the 14-d QT group, although the same scheme administered for 7 d was well tolerated. Dropouts and severe adverse events were observed exclusively in the quadruple regimen[21]. The same authors compared two 10-d levofloxacin-based (500 mg OD) triple schemes in combination with either amoxicillin or azithromycin with the standard QT regimen. Eradication rates of levofloxacin-based groups were higher, even if not significantly, compared with standard QT (86.6% and 71.4%, respectively), but incidence of side effects was significantly lower (26.6% *vs* 60%). Dropouts occurred only in the QT group[35,36].

In terms of duration of treatment, the same researchers compared efficacy and tolerability of 7 d and 10 d levofloxacin/amoxicillin-based treatment to 7 d QT, demonstrating a higher cure rate for the triple 10-d levofloxacin regimen (91.3%) compared to both the 7-d levofloxacin-based or QT regimen (74% and 68%, respectively), with optimal tolerability[35,36]. Zhang *et al*[37] also confirmed similar results.

Orsi *et al*[38] have studied efficacy of a 12-d treatment course by comparing the levofloxacin/amoxicillin-based regimen with QT. Both regimens were equally effective (86% *vs* 88%) but the triple regimen was better tolerated (incidence of side effects: 8.6% *vs* 24%).

A drastic difference in eradication rates were observed in another Italian study in which the levofloxacin-based triple and quadruple regimens achieved an eradication rate of 70% *vs* 35%, respectively, in second-line, even if patients were given a full-dose course of PPI for 1 wk prior to bismuth therapy. Interestingly, levofloxacin-based triple regimen was successful in most patients with both metronidazole- and clarithromycin-resistant strains, whereas QT was less effective, particularly when metronidazole resistance occurred[39].

Bilardi *et al*[39] used LA-based triple therapy both in first- and second-line compared to standard first-line triple and quadruple second-line regimens, respectively. In first-line, eradication rate of levofloxacin-based and standard triple regimen was 69.8% and 74%, respectively, while as rescue regimen, levofloxacin-based therapy achieved an eradication rate of 62.5% compared to 40% for the standard QT regimen.

Gisbert e*t al*[40] compared 7-d levofloxacin-based therapy with a quadruple ranitidine bismuth citrate-based regimen and reported an identical eradication rate of

68% for both regimens, with similar incidence of side effects (38% *vs* 36%, respectively). Nevertheless, the antisecretory activity of ranitidine might have contributed to the eradication rate in the QT regimen. Conversely, dose of levofloxacin (500 mg BD) and duration (7 d) of treatment might have affected efficacy (shorter treatment) and tolerance (high dosage) in the triple regimen[40].

In the study by Kuo *et al*[41], levofloxacin triple regimen and QT eradication rates were 69.9% *vs* 63.9%, respectively, and although compliance was similar, incidence of side effects was 12.6% in the LA *vs* 35.2% in the QT groups. In this study, levofloxacin resistance was analyzed and was a crucial predictor for eradication failure (21.2% of patients).

In a Korean trial, 7 d levofloxacin-based therapy and standard QT achieved comparable but low cure rates (51.6% *vs* 48.9%), even if the triple regimen was better tolerated (adverse events incidence: 10% *vs* 31.4%)[42]. Another Asian trial confirmed the high cure rate of levofloxacin-based therapy for 7 d (85.7%)[43].

Finally, few studies have demonstrated superiority of the recommended QT regimen compared with the levofloxacin triple regimen. QT was superior to levofloxacin-based regimen for persistent *H. pylori* infection in the study conducted by Perri *et al*[29] (eradication rate: 63% in the levofloxacin group). In this trial bismuth- and ranitidine/bismuth citrate-based QT regimens achieved a cure rate of 83% and 85%, respectively, although a higher incidence of side effects was observed in the bismuth-treated group (30.9% *vs* 5.1%). Conversely, adverse events occurred in 3.3% of patients treated with levofloxacin.

Wong *et al*[44] reported an eradication rate of 73% and 64% in second-line for QT and levofloxacin-based regimens, respectively. Similarly, in a study conducted in Hong Kong, second-line 7-d triple levofloxacin-based therapy achieved an eradication rate of 61% *vs* 87% with QT, due to resistance to levofloxacin (18% of patients)[19]. However, the study included a small sample of refractory patients and eradication rate was superior in subjects in the LA group with dual resistance to metronidazole and clarithromycin respect to antibiotics resistant patients in Q group (79% *vs* 65%, respectively). However, treatment choice was based on antibiotic susceptibility testing and might not reflect common clinical practice[19].

Results of our meta-analysis are summarized in Figure 1. Overall eradication rate (pooled data) with levofloxacin was 76.5% (95% CI: 54.4%-97.6%). When exclusively 7-d regimens were included, cure rate was 70.6% (95% CI: 40.2%-99.1%), whereas for the 10-d regimen, eradication rate was significantly higher (88.7%; 95% CI: 56.1%-109.9%; $P < 0.05$). Mean eradication rate for QT was 67.4% (95% CI: 42.4%-91.6%).

The meta-analysis showed a trend indicating superiority of any LA regimens (7, 10 or 12 d) to QT (OR: 1.59; 95% CI: 0.98-2.58; $P = 0.06$; Figure 1A). Both 7-d LA and QT regimens showed comparable efficacy (OR: 1.09; 95% CI: 0.63-1.87; $P = 0.40$; Figure 1B), whereas the 10-d LA regimen was significantly more effective (OR: 5.05; 95% CI: 2.74-9.31; $P < 0.00\,001$; Figure 1C).

No differences were reported in QT eradication rates between Asian and European studies, whereas LA regimens were more effective in Caucasians (78.3% *vs* 67.7%; $P = 0.05$). Of note, if data on comparison between LA and QT regimens were stratified by ethnicity (Figure 1A), any levofloxacin regimen was more effective in the Caucasian population ($P = 0.09$). Those findings were not confirmed when only 7-d levofloxacin regimens were included (Figure 1B). No data were available on 10-d levofloxacin regimens in Asian populations (Figure 1C).

Mean incidence of side effects (pooled data) was lower in LA regimens (13.7%, 95% CI: 12%-24%) compared with standard QT (27.2%, 95% CI: 24%-34%). The OR for this comparison was 0.39 (95% CI: 0.18-0.85; $P = 0.02$) at meta-analysis (Figure 2). When incidence of side effects (pooled data) was stratified by ethnicity, no differences were registered between the two geographical areas for the levofloxacin regimens (14.8% *vs* 12.1%, respectively in Europe and Asia), whereas a slightly higher rate was reported in the Asian population treated with QT (32.5% *vs* 23.3%, $P = 0.09$). Moreover, the lower risk of occurrence of side effects in the levofloxacin arms overall was mainly due to the Asian studies contribution.

DISCUSSION

Antibiotic resistance is the main cause of failure in curing *H. pylori* infection[45-49]. Other factors determining eradication rate are: *H. pylori* strain, patient compliance, and properties of drugs administered[2].

Levofloxacin, a second-generation fluoroquinolone, with a broad spectrum of activity against Gram-positive and Gram-negative bacteria[50-52], is a recognized antimicrobial alternative to the standard antibiotics used to treat *H. pylori* infection. Levofloxacin is mainly indicated to treat infections of respiratory and genitourinary tract, skin and skin structures[33,51,53-55]. In recent years, its role has been successfully extended to treatment of *H. pylori* infection and has been included as treatment of choice in guidelines[15,33,56]. Its optimal tolerance spectrum, with the most frequent adverse events being nausea and diarrhea, makes it a safe alternative[57]. Only a few cases of QTc prolongation, seizures, glucose disturbances and tendonitis have been reported[33,51,56]. Although primary resistance is infrequent, resistance to quinolones is easily acquired in areas of high consumption[58]. In Asian countries, levofloxacin resistance has recently increased[59,60]. In particular, in Hong Kong, Korea and Japan, estimated *H. pylori* resistance rates for levofloxacin are 11.5%, 21.5% and 15% respectively[61,62]. In the Chinese adolescent population, all *H. pylori* strains were found to be resistant to levofloxacin[63,64]. In Europe, such as Spain, France, Netherlands, Austria and Portugal, fluoroquinolone resistance is less than 10%[65-69]. However, despite a reported levofloxacin resistance rate of 18%, Italian guidelines recommend levofloxacin regimens for second-line therapy, with optimal results[16]. Moreover, antibiotic

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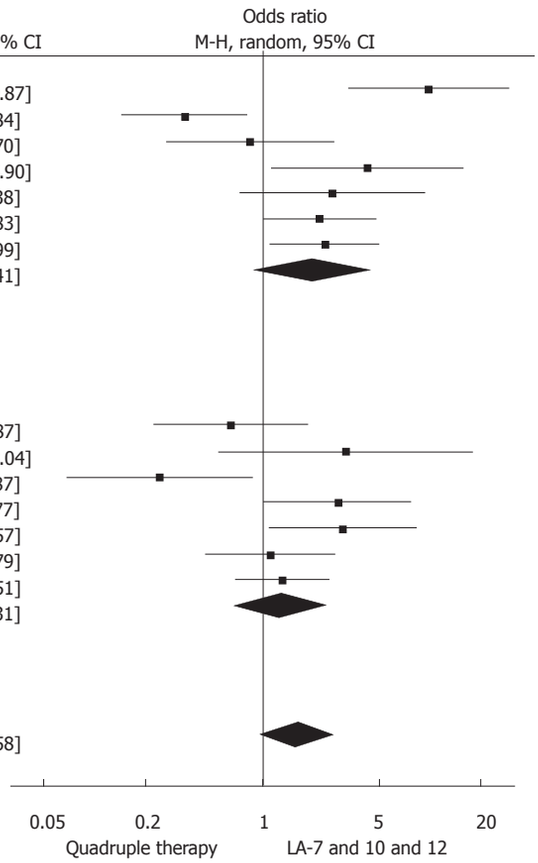
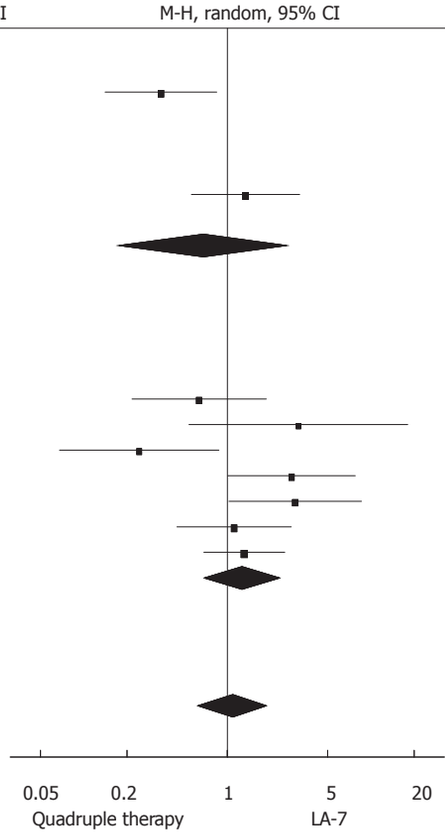
Study or subgroup	LA 7 and 10 and 12 Events	Total	Quadruple therapy Events	Total	Weight	Odds ratio M-H, random, 95% CI
1.4.1 Caucasian						
Nista *et al*[21]	66	70	44	70	6.9%	9.75 [3.18, 29.87]
Perri *et al*[29]	37	58	46	55	8.0%	0.34 [0.14, 0.84]
Orsi *et al*[38]	43	50	44	50	6.7%	0.84 [0.26, 2.70]
Bilardi *et al*[39]	16	23	6	17	6.0%	4.19 [1.10, 15.90]
Nista *et al*[35]	26	30	25	35	6.2%	2.60 [0.72, 9.38]
Nista *et al*[36]	79	96	34	50	8.4%	2.19 [0.99, 4.83]
Gisbert *et al*[28]	83	112	21	38	8.6%	2.32 [1.08, 4.99]
Subtotal (95% CI)		439		315	50.7%	1.99 [0.90, 4.41]
Total events	350		220			
Heterogeneity: Tau^2 = 0.87; χ^2 = 26.07, df = 6 (P = 0.0002); I^2 = 77%						
Test for overall effect: Z = 1.69 (P = 0.09)						
1.4.2 Asian						
Wong *et al*[44]	21	33	22	30	7.1%	0.64 [0.22, 1.87]
Lee *et al*[80]	5	9	4	14	4.5%	3.13 [0.54, 18.04]
Wong *et al*[19]	19	31	26	30	6.2%	0.24 [0.07, 0.87]
Zhang *et al*[43]	42	49	30	44	7.3%	2.80 [1.01, 7.77]
Zhang *et al*[37]	42	48	33	47	7.2%	2.97 [1.03, 8.57]
Jung *et al*[42]	16	31	22	45	7.8%	1.12 [0.45, 2.79]
Kuo *et al*[41]	58	83	53	83	9.1%	1.31 [0.69, 2.51]
Subtotal (95% CI)		284		293	49.3%	1.27 [0.70, 2.31]
Total events	203		190			
Heterogeneity: Tau^2 = 0.35; χ^2 = 13.88, df = 6 (P = 0.03); I^2 = 57%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		723		608	100.0%	1.59 [0.98, 2.58]
Total events	553		410			
Heterogeneity: Tau^2 = 0.57; χ^2 = 41.66, df = 13 (P < 0.0001); I^2 = 69%						
Test for overall effect: Z = 1.86 (P = 0.06)						
Test for subgroup differences: χ^2 = 0.77, df = 1 (P = 0.38); I^2 = 0%						



B

Study or subgroup	LA-7 Events	Total	Quadruple therapy Events	Total	Weight	Odds ratio M-H, random, 95% CI
1.1.1 Caucasian						
Nista *et al*[21]	0	0	44	70		Not estimable
Perri *et al*[29]	37	58	46	55	12.4%	0.34 [0.14, 0.84]
Orsi *et al*[38]	0	0	44	50		Not estimable
Bilardi *et al*[39]	0	0	6	17		Not estimable
Nista *et al*[35]	0	0	25	35		Not estimable
Nista *et al*[36]	37	50	34	50	12.6%	13.34 [0.56, 3.19]
Gisbert *et al*[28]	0	0	21	38	24.9%	Not estimable
Subtotal (95% CI)		108		315		0.68 [0.18, 2.58]
Total events	74		220			
Heterogeneity: Tau^2 = 0.72; χ^2 = 4.57, df = 1 (P = 0.03); I^2 = 78%						
Test for overall effect: Z = 0.56 (P = 0.57)						
1.1.2 Asian						
Wong *et al*[44]	21	33	22	30	10.7%	0.64 [0.22, 1.87]
Lee *et al*[80]	5	9	4	14	6.3%	3.13 [0.54, 18.04]
Wong *et al*[19]	19	31	26	30	9.1%	0.24 [0.07, 0.87]
Zhang *et al*[43]	42	49	30	44	11.2%	2.80 [1.01, 7.77]
Zhang *et al*[37]	42	48	33	47	10.9%	2.97 [1.03, 8.57]
Jung *et al*[42]	16	31	22	45	12.1%	1.12 [0.45, 2.79]
Kuo *et al*[41]	58	83	53	83	14.7%	1.31 [0.69, 2.51]
Subtotal (95% CI)		284		293	75.1%	1.27 [0.70, 2.31]
Total events	203		190			
Heterogeneity: Tau^2 = 0.35; χ^2 = 13.88, df = 6 (P = 0.03); I^2 = 57%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		392		608	100.0%	1.09 [0.63, 1.87]
Total events	277		410			
Heterogeneity: Tau^2 = 0.41; χ^2 = 21.29, df = 8 (P = 0.006); I^2 = 62%						
Test for overall effect: Z = 0.31 (P = 0.75)						
Test for subgroup differences: χ^2 = 0.70, df = 1 (P = 0.40); I^2 = 0%						



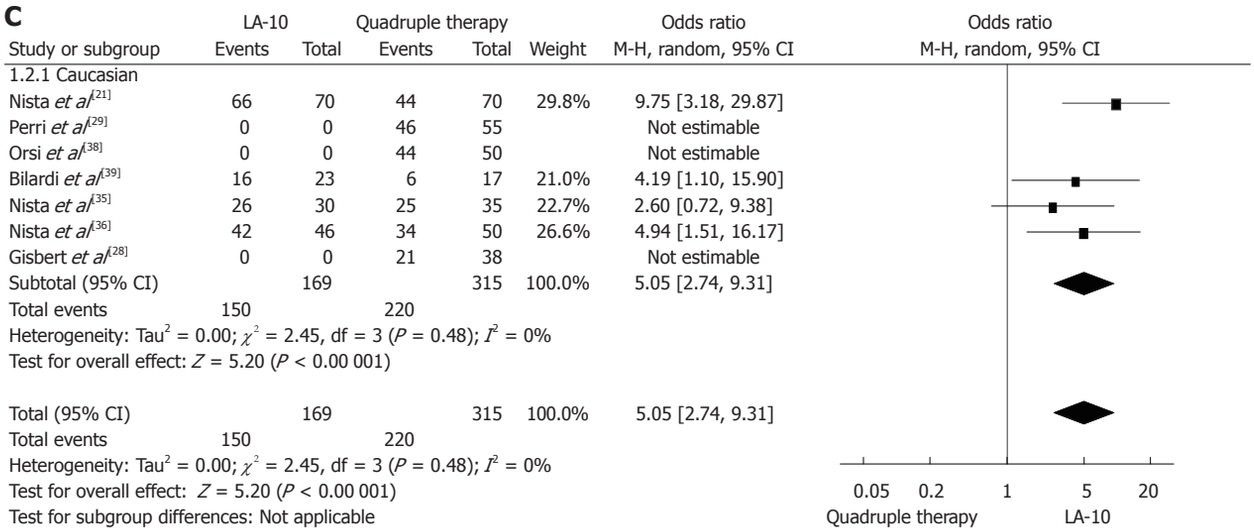


Figure 1 Meta-analysis comparing the efficacy of anti-*Helicobacter pylori* levofloxacin/amoxicillin-based triple therapy *vs* quadruple therapy 7-10 or 12 d (A), 7 d (B), 10 d (C) levofloxacin/amoxicillin regimens were considered. CI: Confidence interval; LA: Levofloxacin/amoxicillin.

resistance testing is not routinely performed to guide prescription. Therefore, even if widely used, published data on levofloxacin-based regimens for *H. pylori* eradication are extremely heterogeneous. Differences in dosages, length of treatment, drug combination, patients' demographic characteristics, and previous courses of therapy, preclude a definitive conclusion.

The present study included only studies comparing cure rate and tolerability of standard QT regimen to 7 or 10 d combination of LA-based triple therapy in second-line, to provide guidance in clinical practice. In accordance with previous reports[70-72], our data showed that 7 d LA-based triple regimen and QT achieved similar efficacy results, whereas LA-based regimen administered for 10 d was more effective than QT. Thus, tolerability was optimal in LA-based triple therapy and patients experienced a lower rate of adverse events compared to patients treated with standard QT, with the exception of a single discordant study[28]. However, in a multicenter study, the same author reported remarkably superior tolerability using a 10-d levofloxacin-based regimen[38,40].

In previous studies, dose of quinolone appeared the crucial factor influencing the incidence of side effects[70,71,73]. In most studies included in the analysis, levofloxacin has been administered at a dosage of 500 mg daily. Interestingly, a higher incidence of side effects was registered in one of the trials using 1 g in two divided doses[28].

Statistical comparison of side effects experienced in 7-d *vs* 10-d groups was not consistent due to the structure of the selected studies. With the exception of the study by Gisbert *et al*[28], tolerability was excellent in all other trials using levofloxacin-based regimens for 10 d or longer. Probably, acceptance of LA therapy depends on the simplicity of the therapeutic regimen itself. Although a new preparation of single three-in-one capsules containing bismuth subcitrate potassium, metronidazole, and tetracycline has been recently proposed in first-line[74], QT still consists of a complex scheme (12 pills/d), and bismuth salts are no longer available in many countries. On the contrary, levofloxacin-based therapy appears simple (5 pills/d), effective (10-d regimen eradication rate: 88.7%) and safe (overall side effects incidence: 13.7%). Duration of treatment appeared the unique factor influencing the efficacy[75].

Nevertheless, considering that the ideal for *H. pylori* infection might differ between areas, countries and races[76-78], we performed an additional analysis on efficacy in different parts of the world.

In a sub-analysis comparing Asian and European trials, QT was equally effective, while LA-based regimens were more effective in the European population. Differences in efficacy rates between Asian and European populations using LA-based schemes might be explained with primary antibiotic resistance and/or genetic background. The meta-analysis showed that the LA-based regimen was more effective in Caucasians only when any regimen was included. However, 10-d levofloxacin-based treatment has never been tested in Asian countries and efficacy increases with duration of treatment, therefore, it is difficult to establish whether differences reported depended on ethnicity or duration of therapy.

Regarding incidence of side effects, ethnicity appeared to affect tolerability of QT compared with LA-based therapy in Asian populations. However, the single outlier among European trials might bias this finding.

Apart from levofloxacin, other regimens containing fluoroquinolones have been proposed both in first- and second-line *H. pylori* treatment. Among these, moxifloxacin-based regimens appear interesting (eradication rate up to 90% and 70%, respectively in first and second-line[72,75,79]. With respect to levofloxacin, moxifloxacin has been relatively more recently introduced on the market, with a consequent possibly lower rate of antibiotic resistance. However, it is more expensive. Nevertheless, no conclusive recommendations can be issued on which

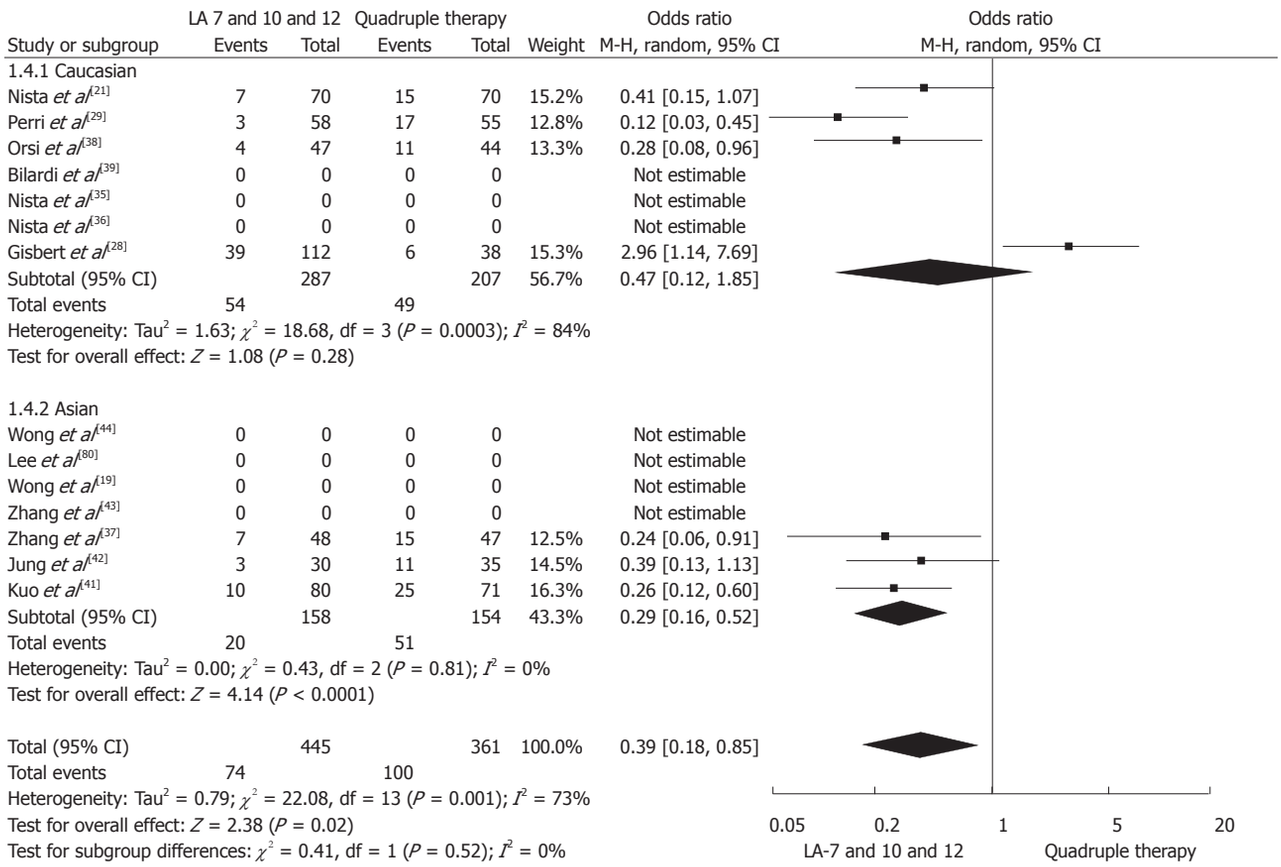


Figure 2 Meta-analysis comparing the incidence of side effects with levofloxacin/amoxicillin-based triple therapy *vs* quadruple therapy for *Helicobacter pylori* eradication. CI: Confidence interval; LA: Levofloxacin/amoxicillin.

fluoroquinolone should be used because there are no trials comparing the two drugs.

Our results are in accordance with previous meta-analyses assessing efficacy and safety of second-generation fluoroquinolones, including levofloxacin and moxifloxacin[13,71,72,79], for *H. pylori* eradication. However, compared to previous studies, our study included the most up to date collection of RCTs and most importantly, compared exclusively second-line treatments and analyzed geographical stratification.

Our meta-analysis had several limitations, mainly due to heterogeneity among trials (different dosing schedules and duration of treatment). Sub-analyses were mainly affected by the small sample size for each category. Finally, the lack of data available on use of 10 d LA-based therapy in Asian populations did not allow a definitive conclusion about the influence of ethnicity on treatment success. Moreover, considering the suboptimal tolerance of QT in Asian populations, alternative strategies, such as 10 d LA-based therapy, and randomized trials in this geographic setting would be desirable.

In our analysis, we selected exclusively RCTs comparing LA-based triple regimens to standard QT to provide practical useful data on a specific treatment to use as rescue regimen of choice due to the rare *H. pylori* resistance to amoxicillin.

In conclusion, this meta-analysis strongly supports the use of 10 d LA-based triple regimen as a simple (5 pills/d) second-line treatment for *H. pylori* eradication, with an excellent eradication rate and tolerability profile in comparison to standard recommended QT in Asian and European countries. Nevertheless, quinolone resistance monitoring in different geographical areas is required.

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