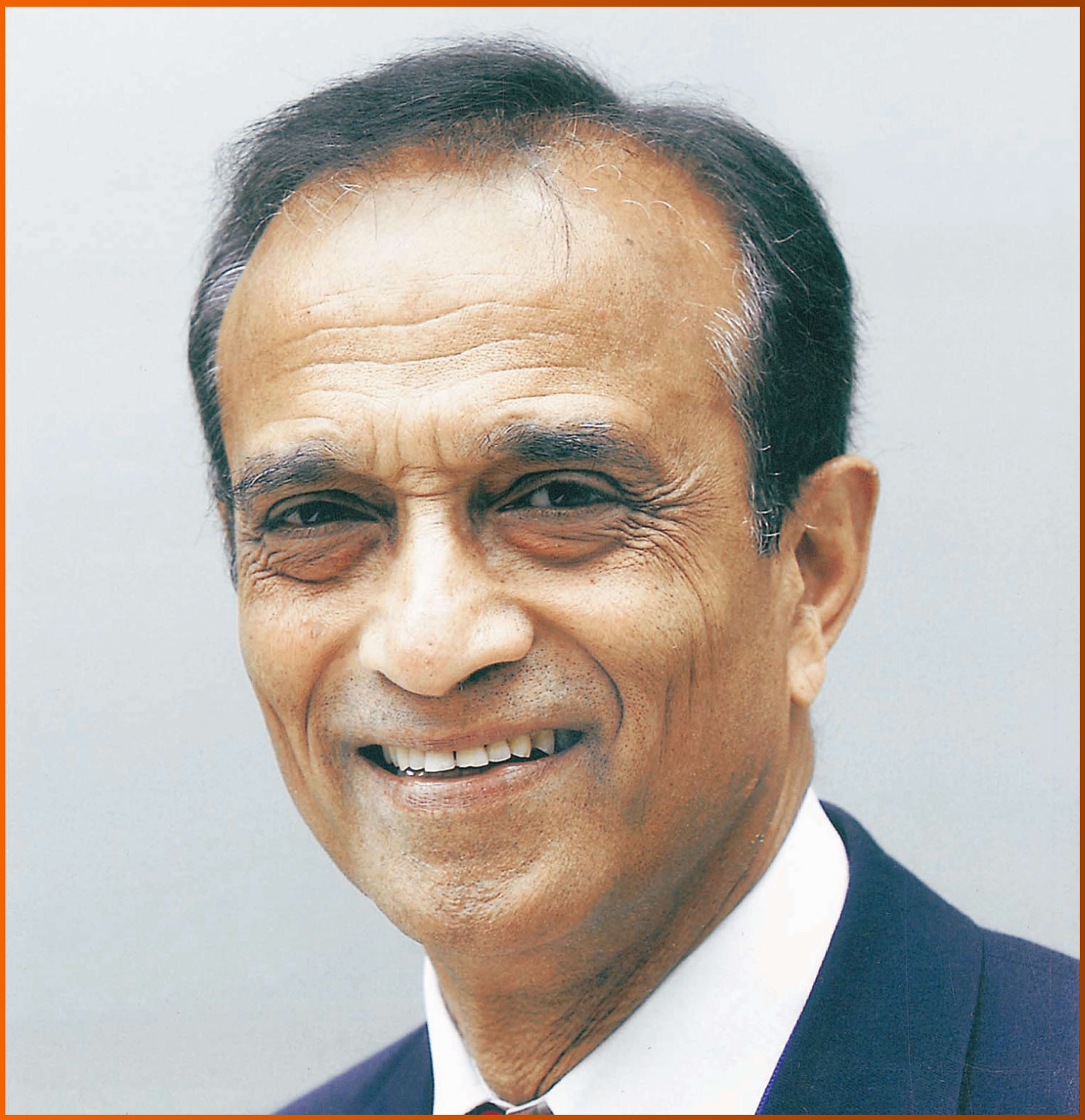
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2018 August 7; 24(29): 3201-3312



Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

Contents

Weekly Volume 24 Number 29 August 7, 2018

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Rakesh Kumar Tandon, FRCP (Hon), MD, PhD, Doctor, Professor, Department of Gastroenterology, Pushpawati Singhania Research Institute for Liver, Renal and Digestive Diseases, Sheikh Sarai-Phase II, New Delhi 110017, Delhi, India

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 642 experts in gastroenterology and hepatology from 59 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2018 edition of Journal Citation Reports® cites the 2017 impact factor for *WJG* as 3.300 (5-year impact factor: 3.387), ranking *WJG* as 35th among 80 journals in gastroenterology and hepatology (quartile in category Q2).

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

EDITORIAL OFFICE
Ze-Mao Gong, Director
World Journal of Gastroenterology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
August 7, 2018

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Gastroenterology

Submit a Manuscript: http://www.f6publishing.com

World J Gastroenterol 2018 August 7; 24(29): 3302-3312

DOI: 10.3748/wjg.v24.i29.3302

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

META-ANALYSIS

Fourth-generation quinolones in the treatment of *Helicobacter pylori* infection: A meta-analysis

Ying An, Ya Wang, Shuang Wu, You-Hua Wang, Xing Qian, Zhen Li, Ying-Jun Fu, Yong Xie

Ying An, Ya Wang, Shuang Wu, You-Hua Wang, Xing Qian, Yong Xie, Department of Gastroenterology, the First Affiliated Hospital of Nanchang University, Key Laboratory of Digestive Diseases of Jiangxi, Nanchang 330000, Jiangxi province, China

Ying An, Ya Wang, Ying-Jun Fu, School of Pharmacy, Nanchang University, Nanchang 330000, Jiangxi province, China

Zhen Li, Medical College, Nanchang University, Nanchang 330000, Jiangxi province, China

ORCID number: Ying An (0000-0003-2332-3825); Ya Wang (0000-0001-6644-2993); Shuang Wu (0000-0002-2849-6437); You-Hua Wang (0000-0002-0157-0721); Xing Qian (0000-0002-5209-0584); Zhen Li (0000-0002-2227-7612); Ying-Jun Fu (0000-0001-8884-7860); Yong Xie (0000-0002-5290-5579).

Author contributions: Fu YJ and Xie Y designed the research; An Y, Wang Y, and Wu S performed the research; Wang YH, Qian X, and Li Z contributed to analytic tools; An Y and Wang Y analyzed data; An Y and Wang Y wrote the paper.

Supported by the Graduate Innovation Project of Nanchang University, No. CX2017213 and No. CX2017251; the National Natural Science Foundation of China, No. 81460115; and the Science and Technology Projects of Jiangxi Province, No. 2014BBG70019.

Conflict-of-interest statement: The authors deny any conflict of interest.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Manuscript source: Unsolicited manuscript

Correspondence to: Yong Xie, MD, PhD, Professor, Department of Gastroenterology, the First Affiliated Hospital of Nanchang University, Key Laboratory of Digestive Diseases of Jiangxi, Nanchang 330000, Jiangxi Province, China. xieyong_tfahoncu@163.com
Telephone: +86-791-88692507

Received: April 4, 2018
Peer-review started: April 4, 2018
First decision: April 19, 2018
Revised: May 12, 2018
Accepted: June 16, 2018
Article in press: June 16, 2018
Published online: August 7, 2018

Abstract

AIM

To assess the efficacy and safety of fourth-generation quinolones for *Helicobacter pylori* (*H. pylori*) eradication, we conducted this systematic review and meta-analysis of randomized clinical trials.

METHODS

Major literature databases (PubMed, EMBASE and the Cochrane Central Register of Controlled Trials) were searched for relevant articles published prior to February 2018. We performed a meta-analysis of all randomized clinical trials that examined the efficacy of *H. pylori* eradication therapies and included fourth-generation quinolones in the experimental arm. Subgroup analyses by regions and different types of fourth-generation quinolones were also performed.

RESULTS

Ten studies including a total of 2198 patients were assessed. A meta-analysis of randomized controlled trials showed that the eradication rate of therapies containing non-fourth-generation quinolones was significantly lower

than that of therapies containing fourth-generation quinolones by intention-to-treat (ITT) analysis [75.4% *vs* 81.8%; odds ratio (OR) = 0.661; 95% confidence interval (CI): 0.447-0.977; *P* = 0.038]. This analysis also showed that the eradication rate of the therapies containing non-fourth-generation quinolones was inferior to that of therapies containing fourth-generation quinolones by per-protocol analysis (79.1% *vs* 84.7%; OR = 0.663; 95%CI: 0.433-1.016; *P* = 0.059). Moreover, the occurrence of side effects was significantly different between the control and experimental groups by ITT analysis (30.6% *vs* 19.5%; OR = 1.874; 95%CI: 1.120-3.137; *P* = 0.017). The sub-analyses also showed significant differences in moxifloxacin therapies *vs* other fourth-generation quinolone therapies (84.3% *vs* 71.9%) and in Asian *vs* European groups (76.7% *vs* 89.1%).

CONCLUSION

Therapies containing fourth-generation quinolones achieved a poor eradication rate in the treatment of *H. pylori* infection. Such regimens might be useful as a rescue treatment based on antimicrobial susceptibility testing. Different antibiotics should be chosen in different regions.

Key words: *Helicobacter pylori*; Fourth-generation quinolones; Eradication; Systematic review; Meta-analysis

Core tip: With the increase in the *Helicobacter pylori* (*H. pylori*) resistance rate, eradication is becoming increasingly challenging. This is the first meta-analysis comprehensively focused on fourth-generation quinolones for the treatment of *H. pylori* infection. Additionally, we found that fourth-generation quinolones had a higher eradication rate (81.8%) and a lower rate of incidence of side effects (19.5%). These findings will provide a specific basis for the clinical use of fourth-generation quinolones for *H. pylori* eradication.

An Y, Wang Y, Wu S, Wang YH, Qian X, Li Z, Fu YJ, Xie Y. Fourth-generation quinolones in the treatment of *Helicobacter pylori* infection: A meta-analysis. *World J Gastroenterol* 2018; 24(29): 3302-3312 Available from: URL: http://www.wjgnet.com/1007-9327/full/v24/i29/3302.htm DOI: http://dx.doi.org/10.3748/wjg.v24.i29.3302

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection plays a crucial role in the pathogenesis of gastrointestinal diseases, such as gastritis, non-ulcer dyspepsia, peptic ulcer diseases, and gastric cancer[1]. *H. pylori* infection affects approximately 50% of the population worldwide[2]. Its prevalence is approximately 70% in developing nations and approximately 20%-30% in developed nations[3]. Eradication of *H. pylori* facilitates peptic ulcer healing, reduces ulcer relapse rates, and prevents gastric cancer[4]. In the past, the recommended treatment for eradicating *H. pylori* was 7 d of standard triple therapy (STT) consisting of a proton pump inhibitor (PPI) with clarithromycin (CAM) and amoxicillin (AMPC)[5]. However, with the wide use of the STT regimen, the eradication rate of *H. pylori* has declined to unacceptable levels over the last decade (< 80%) due to high resistance to metronidazole and clarithromycin[6]. A recent study on *H. pylori* resistance to antimicrobial agents reported that clarithromycin resistance has rapidly increased in many countries over the past decade, with resistance rates of approximately 18% in Europe, 30% in Japan, 40% in Turkey, and 50% in China; limited data are available for the United States[7-10]. The prevalence of *H. pylori* resistance to metronidazole is 33% in Europe and 40% in the United States, with a high resistance rate (50%-80%) in developing countries[10]. To overcome these difficulties, there is a need to evaluate novel regimens and antibiotics to identify effective alternative treatment strategies. Levofloxacin-based therapy is recommended by the Maastricht Ⅳ[11] and Maastricht Ⅴ Consensus Reports[12]. Nonetheless, according to studies, the resistance rate to levofloxacin is approximately 22.1% in Italy and 36.9% in China; a recent study surprisingly reported a resistance rate of 31.9% in the United States[13-15]. Jeong *et al*[16] reported that the eradication rate was 57.1% when levofloxacin was used. Fourth-generation quinolones, including moxifloxacin, sitafloxacin, gemifloxacin, and gatifloxacin, which have broad-spectrum antibacterial activity, are active against a variety of gram-negative and gram-positive bacteria[17]. Recent studies have shown that fourth-generation quinolones can increase drug penetration into bacterial cells, improve the strength of activity and have better bioavailability. This group of drugs inhibits the metabolism of bacterial cells by inhibiting DNA replication and therefore enhances antibacterial activity[18]. Furthermore, treatment with fourth-generation quinolones has achieved a high *H. pylori* eradication rate and has been recommended in some studies[19-22]. Nevertheless, Chung *et al*[23] reported that the eradication rate was not satisfactory when using fourth-generation quinolones.

To evaluate the efficacy and safety of therapies containing fourth-generation quinolones, we conducted a systematic review and meta-analysis of the available data. The primary outcome measures we assessed were eradication rates, side effects, and compliance of the therapies containing fourth-generation quinolones compared with those of therapies containing non-fourth-generation quinolones. Our outcomes will provide useful evidence for clinical practice[24].

MATERIALS AND METHODS

Literature sources

We searched the PubMed (to February 2018), EMBASE (to February 2018), and Cochrane Central Register of Controlled Trials (Issue 2, 2018) databases. The

following search terms were used for all databases: (*"Helicobacter pylori" OR H. pylori*) AND (Moxifloxacin OR Sitafloxacin OR Gemifloxacin OR Gatifloxacin); the search terms varied slightly among these databases. This meta-analysis was conducted according to the Preferred Reporting Item for Systematic Reviews and Meta-Analyses (PRISMA)[25].

Inclusion criteria

Articles eligible for inclusion in the meta-analysis met the following criteria: (1) randomized controlled trial (RCT) conducted; (2) methods used for the diagnosis of *H. pylori*, including the urea breath test (UBT), the rapid urease test (RUT), bacterial culture, histology, and/or fecal antigen test; (3) eradication rate made available; (4) eradication testing with UBT and/or histology performed at least 4 wk after the completion of therapy; and (5) eradication regimens in the experimental arm included fourth-generation quinolones.

Exclusion criteria

Studies were excluded under the following circumstances: (1) eradication data could not be confirmed; (2) articles and abstracts were written in a language other than English; (3) fourth-generation quinolones were included in two treatment arms; and (4) the experimental group and the control group included more than one variable (for example, the comparison of triple therapy and quadruple therapy; antibiotics and duration were different in both groups).

Data extraction

Three authors (An Y, Wang Y, and Wu S) independently extracted data from the selected studies. Any disagreements were resolved by consensus.

The extracted data included the following: the study design; number of enrolled patients in each treatment arm; diagnostic methods for confirming *H. pylori* infection before enrolling and re-checking strategies after completing the eradication study; publication time; name of the authors; location of the trial; drug regimens; duration of treatment; eradication rates by intention-to-treat (ITT) analysis and per-protocol (PP) analysis; number of successful and failed eradications; and percentage of adverse effects.

To avoid duplication of data, if a trial was repeatedly published by the same authors or institutions, only the most recently published or most informative study was included.

Risk of bias

The quality of RCTs with available full text was assessed using the risk of bias assessment tool developed by the Cochrane Handbook for Systematic Reviews of Interventions[26]. Two independent reviewers assessed the risk of bias through six domain-based evaluations, including selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias. Each indicator was scored by low risk of bias, unclear risk of bias, and high risk of bias. Any disagreement was discussed and decided by a third reviewer. We also employed a funnel plot and Egger's test to assess the presence of publication bias.

Statistical analysis

The statistical analysis was performed using the meta-analysis software STATA12.0 (StataCorp LP, College Station, TX, United States). The primary outcomes of the meta-analysis were the *H. pylori* eradication rate and therapy-related side effects among the trials comparing the control and experimental groups based on ITT analysis. For each trial, we calculated the odds ratio (OR) for the primary measure. The ORs were presented with 95% confidence intervals (CIs); in addition, a P-value < 0.05 was considered significant. The degree of heterogeneity among the trial results was estimated using the χ^2 statistic (P-value < 0.10 considered significant) and the I^2 test (0%-25%, 25%-50%, 50%-75%, and > 75% represented insignificant, low, moderate, and high heterogeneity, respectively). If significant heterogeneity (P < 0.10 or I^2 > 50%) was achieved, we employed the random effects model to combine the effect sizes of the included studies. When no significant heterogeneity was found, we used fixed effects to pool the data. Additionally, subgroup analyses were performed based on the location and different types of fourth-generation quinolones.

RESULTS

Description of the studies

The bibliographical search yielded a total of 548 studies from PubMed, Embase, and the Cochrane Central Register of Controlled Trials. Among these articles, we excluded 144 due to duplication and 175 that were unrelated. We selected 229 potential studies for detailed assessment, among which 68 were excluded because there was no control group. We also excluded 67 review articles, comments, or letters. Thirty-three articles were excluded because of the inclusion of fourth-generation quinolones in two regimens, 14 articles were non-RCTs, 11 articles were excluded due to an inappropriate drug regimen, and 19 articles had data that could not be determined. Then, 17 articles were selected for further evaluation. Five articles were excluded because the data repeated those in other studies, one study did not state the methods for diagnosis of *H. pylori,* and one study was published in Japanese. Ultimately, 10 studies (two abstracts and eight full-text articles) met the inclusion criteria and were included in the systematic review and meta-analysis (Figure 1). These 10 studies[27-36] are summarized in Table 1 based on our meta-analysis. The quality assessment is reported in Table 2.

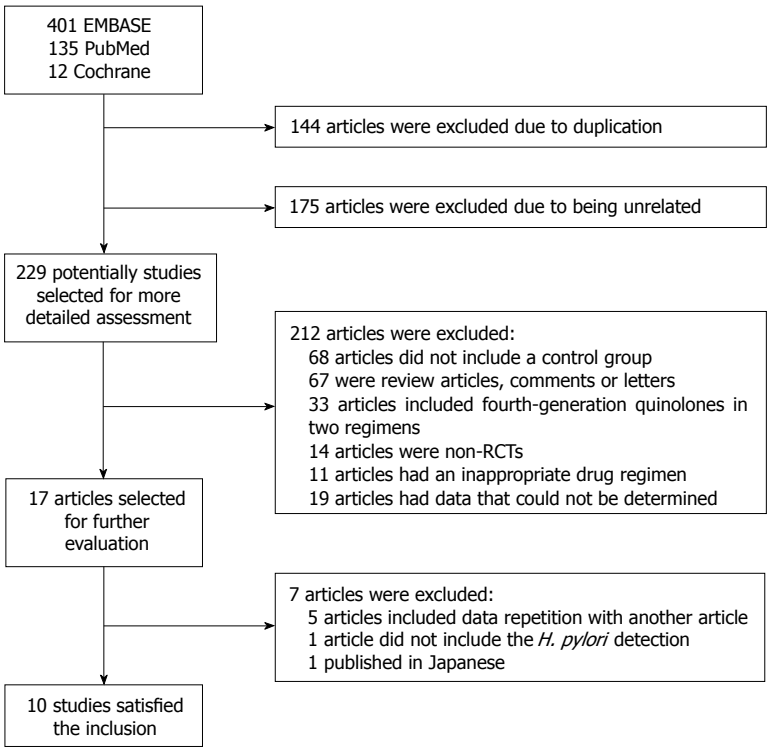


Figure 1 Flow diagram of the identified and selected trials.

Efficacy of H. pylori eradication

There were 10 studies with a total of 2198 patients in our meta-analysis; of these patients, 1107 received therapy without fourth-generation quinolone and 1091 received therapy with fourth-generation quinolone. The pooled eradication rates were 75.4% (835/1107) in the control group and 81.8% (892/1091) in the experimental group by ITT analysis. The pooled OR was 0.661 (95%CI: 0.447-0.977; P = 0.038) using the random effects model (I^2 = 66.2%, P = 0.000; Figure 2).

Moreover, the pooled eradication rates were 79.1% (835/1055) in the control group and 84.7% (892/1053) in the experimental group by PP analysis. The pooled OR was 0.663 (95%CI: 0.433-1.016; P = 0.059) using the random effects model (I^2 = 64.4%, P = 0.000).

The results of ITT showed that the eradication rates of therapies containing non-fourth-generation quinolones was significantly lower than those of therapies containing fourth-generation quinolones.

Subgroup analyses

Additional subgroup analyses for the meta-analysis were performed due to heterogeneity. We analyzed different types of fourth-generation quinolones, covering seven moxifloxacin trials and three other trials (including 1 sitafloxacin and 2 gemifloxacin). In the moxifloxacin subgroup, the pooled eradication rates were 77.3% (689/891) in the control group and 84.3% (733/870) in the experimental group (OR = 0.614, 95%CI: 0.403-0.935; P = 0.023; Figure 3) by ITT analysis, and the rates were 81.3% (689/847) in the control group and 87.3% (689/891) in the experimental group by PP analysis (OR = 0.614, 95%CI: 0.395-0.956; P = 0.031). In the other subgroup, the pooled eradication rates were 67.6% (146/216) in the control group and 71.9% (159/221) in the experimental group (OR = 0.846, 95%CI: 0.274-2.614; P = 0.772; Figure 3) by ITT analysis, and the rates were 70.2% (146/208) in the control group and 74.6% (159/213) in the experimental group by PP analysis (OR = 0.860, 95%CI: 0.239-3.091; P = 0.817). This subgroup analysis showed that the regimen with moxifloxacin achieved a higher eradication rate than the regimen without moxifloxacin. However, there was no significant difference in the eradication rate in the other subgroup.

We also conducted subgroup analysis by region (seven trials in Asia and three trials in Europe). In the Asian subgroup, the pooled eradication rates of the control group and the experimental group were 76.5% (488/638) and 76.7% (493/643), respectively, by ITT analysis (OR = 1.051; 95%CI: 0.671-1.646; P = 0.827; Figure 4) and 79.6% (488/613) and 80.0% (493/616), respectively, by PP analysis (OR = 1.072; 95%CI: 0.627-1.833; P = 0.800). In the European subgroup, the pooled eradication rates of the control group and the experimental group were 74.0% (347/469) and 89.1% (399/448), respectively, by ITT analysis (OR = 0.661; 95%CI: 0.447-0.977; P = 0.000; Figure 4) and 78.5% (347/442) *vs* 91.3% (399/437), respectively, by PP analysis (OR = 0.361; 95% CI: 0.240-0.544; P = 0.000). The results showed that therapies containing fourth-generation quinolones may not be advisable treatments for *H. pylori* infection in Asia. However, the use of fourth-generation quinolones in Europe can

Table 1 Characteristics of studies included in the meta-analysis

Year-Author	Location	*H. pylori* infection initial diagnosis/re-checking	Control group -Day	Fourth-generation quinolone group-Day	Eradication rate (ITT) (control group/fourth- generation quinolone group)	Eradication rate (PP) (control group/fourth- generation quinolone group)	Compliance	Side effects
2017-Mansour Ghanaei, F	Iran	14C-UBT or histology	BPAC-10	BPAG-10	89% (81/91)/77% (70/91)	91% (81/90)/77.8% (70/90)		
2015-Masoodi, M	Iran	13C-UBT, RUT pathology test	OBAC-10	OBAG-10	61.6% (37/60)/66.6% (40/60)	67.2% (37/55)/72.7% (40/55)	97.1%/98.3%	37/19
2014-Rakici, H	Turkey	pistology, stool antigen test	LanAL-10	LanAM-10	89.4% (92/103)/87.8% (93/106)	92% (92/100)/91.8% (93/102)	96%/95.1%	-
2013-Murakami, K	Japan	culture method, RUT, UBT	LanAL-7	LanAS-7	43.1% (28/65)/70% (49/70)	43.7% (28/84)/72.1% (49/68)	98.4%/94.1%	11/11
2012-Zeng, Z	China	14C-UBT	EAC-7	EAM-7	78.9% (180/228)/79.4% (181/228)	82.9% (180/217)/84.2% (181/215)	-	-
2009-Lu, NH	China	14C-UBT	EAC-7	EAM-7	90.3% (28/31)/85.7% (24/28)	-	-	-
2008-Kilic, ZM	Turkey	gastroscopy, histology, RUT, 13C-UBT	RBCAC-14	RBCAM-14	76.7% (23/30)/66.7% (20/30)	76.7% (23/30)/66.7% (20/30)	100%/100%	11/13
			EAC-14	EAM-14	63.3% (19/30)/53.3% (16/30)	63.3% (19/30)/53.3% (16/30)	100%/100%	17/21
2007-Bago, P	Croatia	RUT, histology, culture test, 13C-UBT	LanMetC-7	LanMetM-7	70.4% (50/71)/93.5% (58/62)	75.8% (50/66)/96.7% (58/60)	-	
			LanAC-7	LanAM-7	78.2% (61/78)/86.4% (57/66)	80.2% (61/76)/90.5% 57/63)		
2005-Kist, M	Germany	13C-UBT	EAC-7	EAM-7	72.5% (58/80)/87.5% (70/80)	78% (58/74)/89% (70/79)	-	-
			ETC-7	ETM-7	75% (60/80)/90% (72/80)	79% (60/76)/92% (72/78)		
2005-Nista, EC	Italy	Histological examination, 13C-UBT	ETC-7	ETM-7	75% (60/80)/90% (72/80)	78.9% (60/76)/92.3% (72/78)	-	29/11
			EAC-7	EAM-7	72.5% (58/80)/87.5% (70/80)	78.4% (58/74)/88.6% (70/79)		26/10

A: Amoxicillin; B: Bismuth; C: Clarithromycin; E: Esomeprazole G: Gemifloxacin; Lan: Lansoprazole; L: Levofloxacin; M: Moxifloxacin; Met: Metronidazole; O: Omeprazole; P: Pantoprazole; S: Sitafloxacin; RBC: Ranitidine bismuth citrate; -: Not reported.

significantly improve the eradication rate.

Side effects

Of the 10 studies, four studies provided data regarding side effects. The results showed that common symptoms included nausea, diarrhea, black stool, and taste disturbance. The occurrence of total side effects in the control group was significantly higher than that in the experimental group by ITT analysis (30.6% *vs* 19.5%, OR = 1.874; 95%CI: 1.120-3.137; $P = 0.017$; Figure 5).

Compliance

Four studies included in the meta-analysis provided information about compliance. The results showed high compliance (> 95%), and there were no significant differences between the study groups.

Risk of bias in publication

Egger's regression test suggested that there was no significant bias ($P = 0.725$) in the ITT analysis, while the funnel plot showed a slightly asymmetrical distribution (Figure 6).

DISCUSSION

H. pylori infection is marked by a vast prevalence and strong association with various gastric diseases[37]. Therapeutic regimens range from STT to the present novel regimens,

Table 2 Risk assessment of included studies

Year-Author	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
2017-Mansour Ghanaei, F	L	H	H	L	L	L	L
2015-Masoodi, M	L	L	L	H	L	L	L
2014-Rakici, H	L	H	H	H	L	U	L
2013-Murakami, K	L	H	L	H	L	L	L
2012-Zeng, Z	U	U	U	U	L	U	U
2009-Lu, NH	U	U	U	U	L	U	U
2008-Kilic, ZM	L	H	H	H	L	L	U
2007-Bago, P	L	L	L	H	L	L	L
2005-Kist, M	H	H	H	H	L	H	L
2005- Nista, EC	L	H	H	H	L	L	L

L: Low risk of bias; H: High risk of bias; U: Unclear risk of bias.

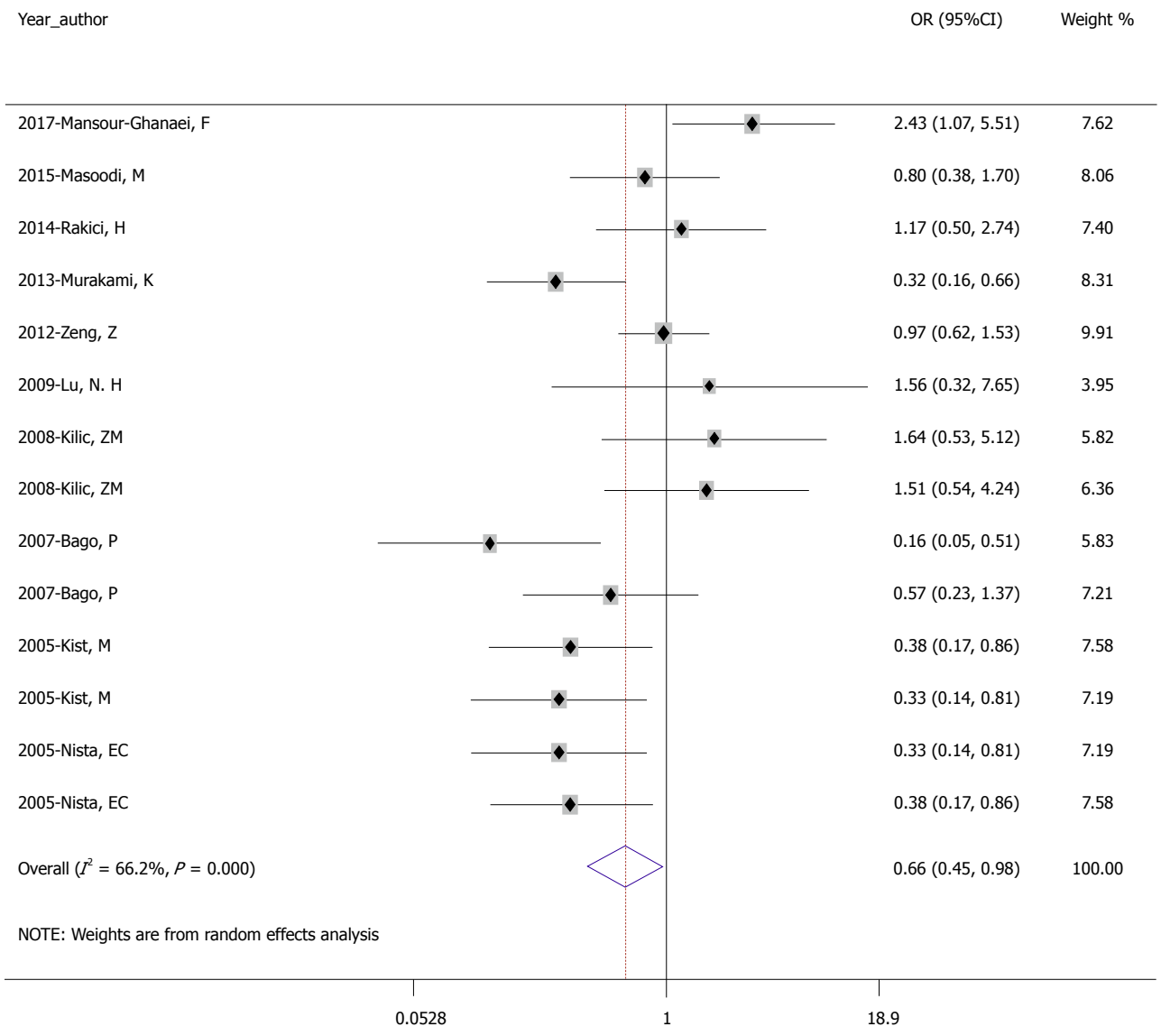


Figure 2 Forest plot of eradication rate of the therapies containing non-fourth-generation quinolones *vs* that of the therapies containing fourth-generation quinolones (intention-to-treat analysis).

such as quadruple therapy with bismuth, sequential treatment, concomitant therapy, and hybrid therapy[38,39]. However, the treatment effects are still not ideal due to bacterial antibiotic resistance[40]. Thus, it is necessary to evaluate novel regimens or antibiotics[41]. With the resistance rate to the third-generation quinolone

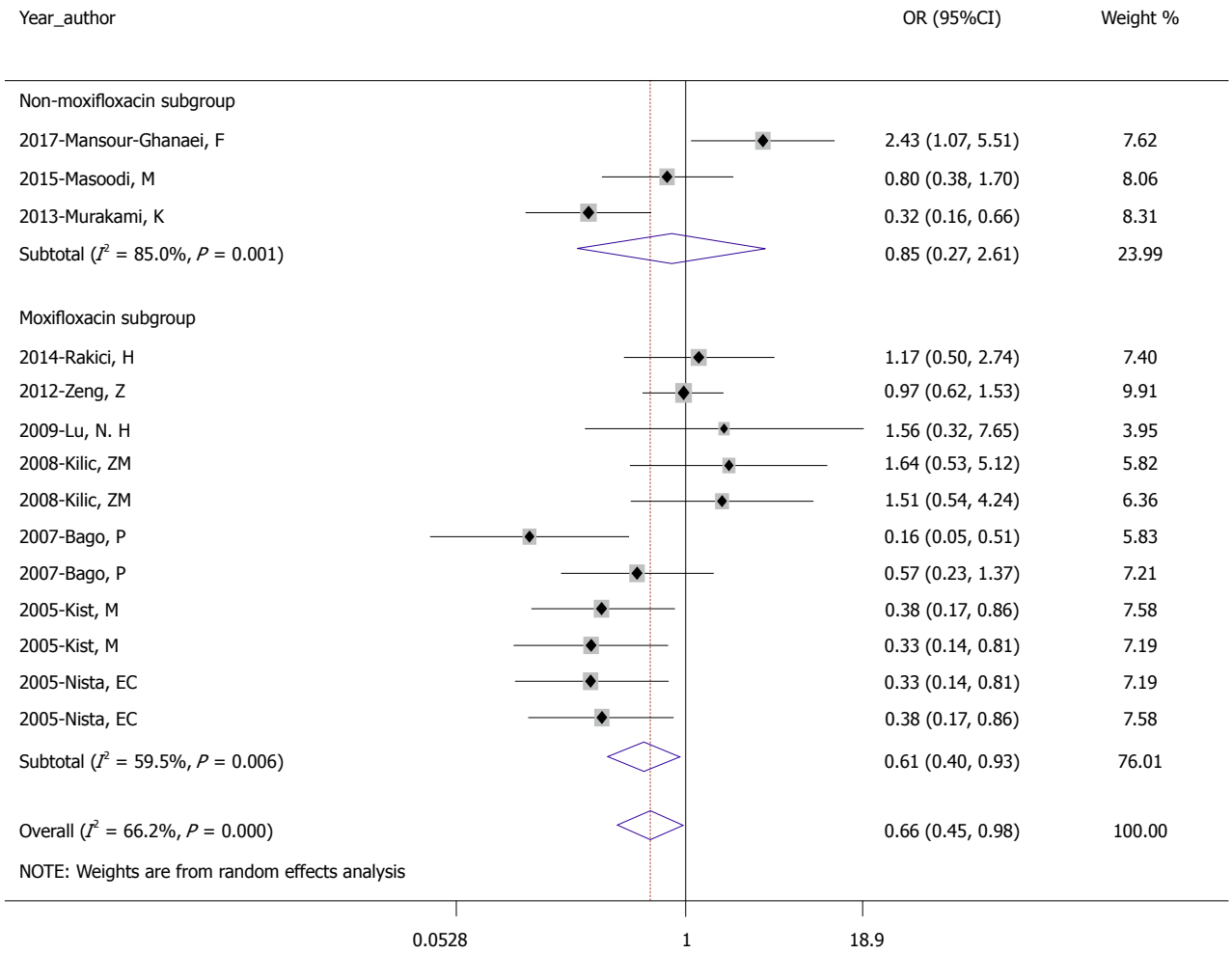


Figure 3 Forest plot of the sub-analysis according to types of fourth-generation quinolone (intention-to-treat analysis).

levofloxacin continuing to increase, resulting in a low eradication rate[16], therapies containing fourth-generation quinolones might be suitable for the treatment of *H. pylori* infection.

This meta-analysis indicated that therapies containing fourth-generation quinolones had a higher clearance rate than other therapies by ITT and PP analyses. The mechanism of action of fourth-generation quinolones against *H. pylori* is to inhibit bacterial DNA gyrase, thus interfering with bacterial DNA replication[42]. These fourth-generation quinolones embed in the broken DNA chain and form complexes to inhibit nicking and closing activity, achieving a bactericidal effect[43]. However, according to Graham, who had given a report card to grade *H. pylori* therapy by ITT, the eradication rate is still poor (grade D, 81%-84%)[44]. This may be related to the low compliance of patients[27,33]. The choice of fourth-generation quinolones, the duration of treatment, and the difference in PPI also influenced the pooled eradication rates of therapies containing fourth-generation quinolones.

The subgroup analyses of antibiotic species conducted in this study demonstrated that regimens containing moxifloxacin were superior to those not containing moxifloxacin (84.3% *vs* 71.9%). This finding might be consistent with a previous systematic review[45], but the eradication rate was still less than 85% by ITT analysis. The main reason was that the resistance rate of *H. pylori* to moxifloxacin was higher, even reaching up to 27.0% when analyzed by the E-test[31]. This phenomenon reminds us that it is best to conduct a susceptibility test to choose antibiotics reasonably.

We also conducted subgroup analysis by region. The eradication rate of fourth-generation quinolone treatments in Europe was much higher than that in Asia (89.1% *vs* 76.7%). This difference may be due to the low utilization rate of antibiotics in Europe[8]. In Asia, the abuse of antibiotics is very common, which leads to a high drug resistance rate of *H. pylori.* According to a multiregion prospective 7-year study by Liu *et al*[46], the prevalence of *H. pylori* after moxifloxacin treatment was 17.2%. Resistance to moxifloxacin was reported to be similar to that of levofloxacin, ranging from 14.9% to 20.0% in Turkey[29]. The increasing antibiotic resistance rate makes the eradication of *H. pylori* more difficult.

The rate of incidence of adverse events in the control groups was higher than that in the experimental groups. The pooled OR (1.874) indicated that the use of fourth-generation quinolones in the treatment of *H. pylori* infection can reduce the incidence of adverse

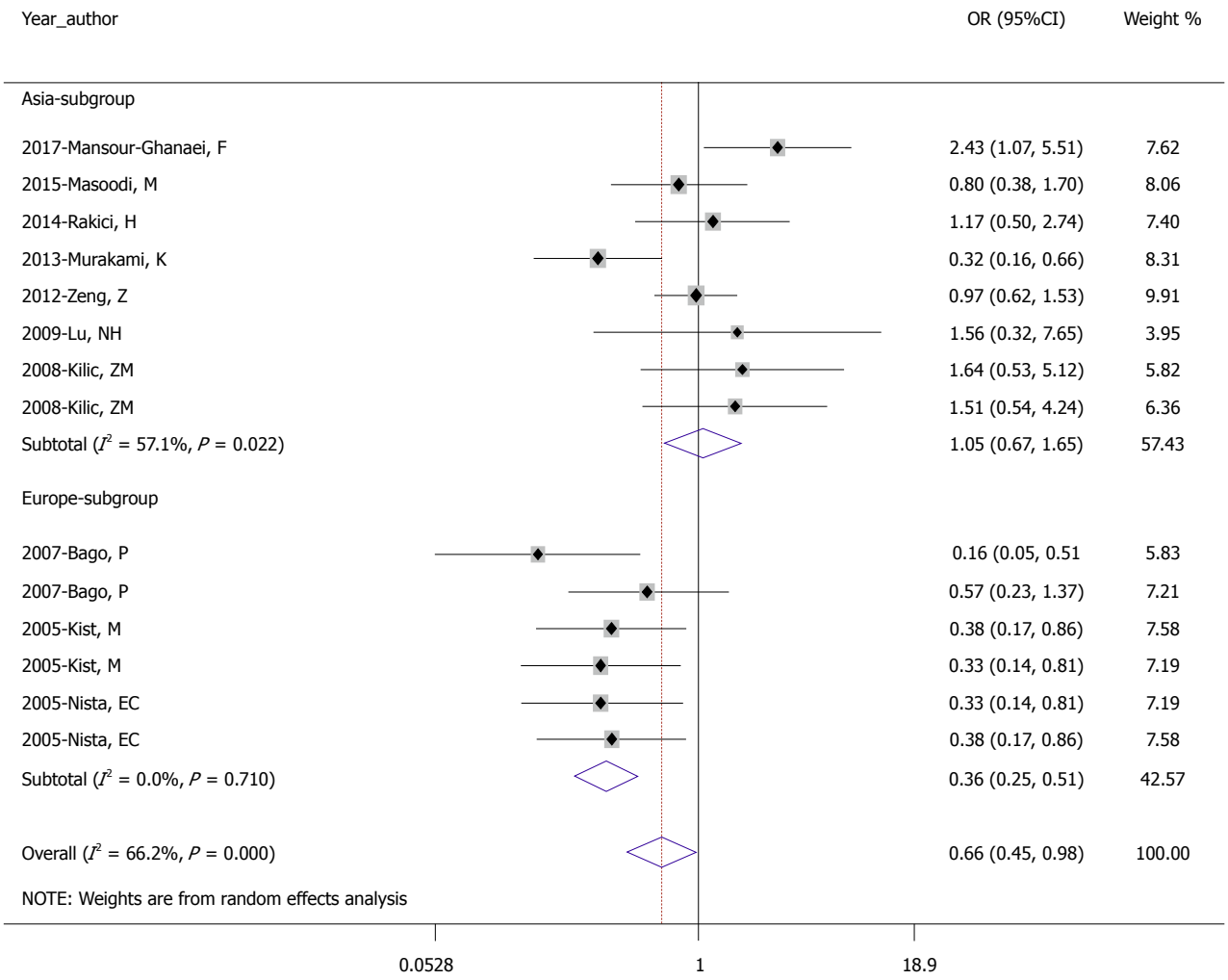


Figure 4 Forest plot of the sub-analysis according to region (intention-to-treat analysis).

reactions. This result indicates that therapies containing fourth-generation quinolones are safer.

The main limitation of this meta-analysis is potential biases. On the one hand, the largest number of studies was conducted using moxifloxacin; only one study used sitafloxacin, and two used gemifloxacin. This selection had a certain effect on the pooled eradication rate and may also be a particularly important issue in the use of a single antibiotic to eradicate *H. pylori* for clinical treatment. On the other hand, all included studies were performed in Europe and Asia, with no studies conducted in Africa or America. Because *H. pylori* infection occurs worldwide, our results may not be appropriate for global generalization. These two factors lead to the bias of conclusion. In addition, most of the studies in our meta-analysis had problems with concealment of allocation and blinding, which caused the selection bias. The restrictions on the language of publication also imply other bias, and thus our meta-analysis may not reflect all the outcomes.

Our analysis also implied other limitations. Most articles reporting a control arm were conducted using clarithromycin; our analysis is therefore especially lacking detailed data on levofloxacin. Two of the 10 included studies were abstracts, generating concerns regarding the data extraction and quality assessment of these studies and affecting the reliability of our results.

In conclusion, this meta-analysis indicates that therapies containing fourth-generation quinolones can achieve a higher eradication rate of *H. pylori* infection, but the eradication rate remains poor. In the absence of other drug options or in cases of patient allergy to penicillin, such regimens might be considered as a rescue treatment based on antimicrobial susceptibility testing. Further investigation is necessary to draw more solid conclusions about the use of fourth-generation quinolones in the treatment of *H. pylori* infection. In addition, we will study more effective therapies for *H. pylori* infection if necessary.

ARTICLE HIGHLIGHTS

Research background

The resistance of *Helicobacter pylori* (*H. pylori*) to antibiotics is increasing and often leads to the failure of eradication treatment. Recent studies have reported that therapies containing fourth-generation quinolones remain effective against antibiotic-resistant *H. pylori*. However, the efficacy and safety of these therapies require further study. This is the first meta-analysis comparing the curative

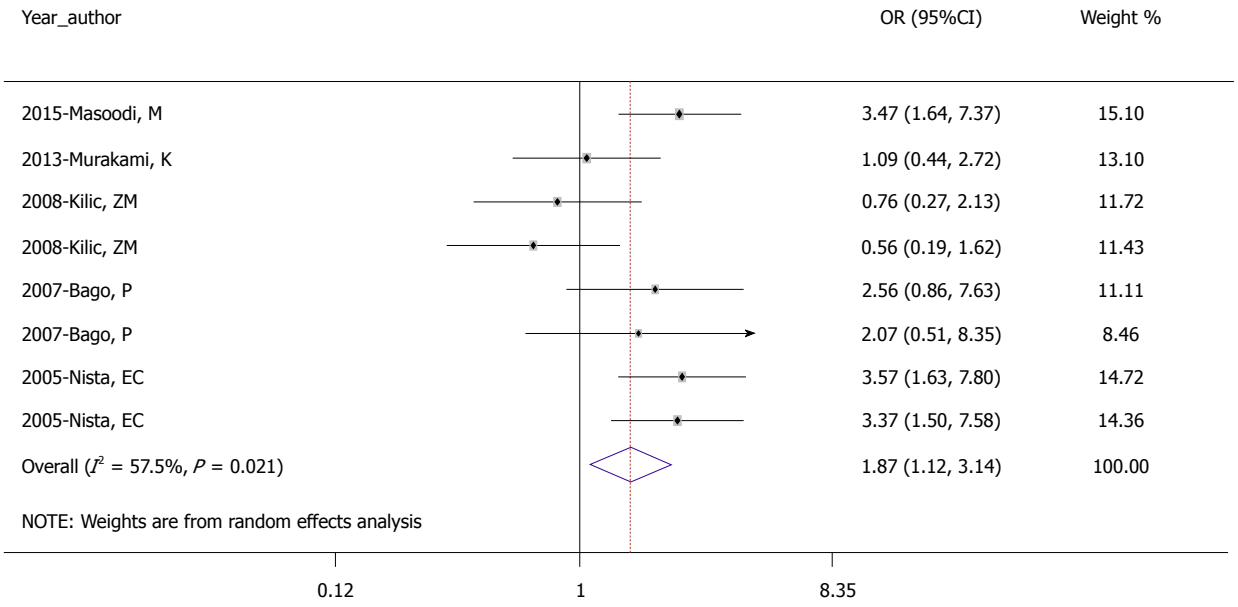


Figure 5 Forest plot of the side effects of the therapies containing fourth-generation quinolones *vs* the therapies containing non-fourth-generation quinolones.

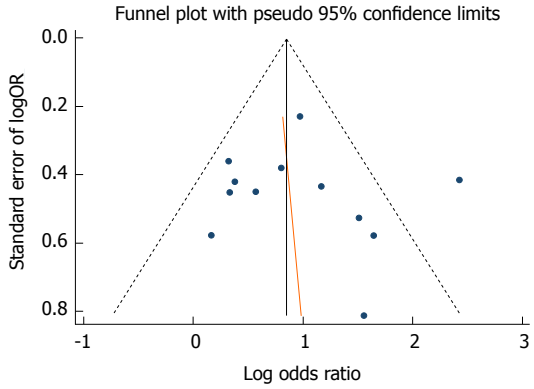


Figure 6 Funnel plot of the therapies containing non-fourth-generation quinolones *vs* the therapies containing fourth-generation quinolones (intention-to-treat analysis).

effect of fourth-generation quinolones with that of other therapies in regard to eradicating *H. pylori*.

Research motivation

In the Maastricht Ⅳ and Maastricht Ⅴ Consensus Reports, levofloxacin-based therapy is recommended when the first treatment fails. Therapies containing fourth-generation quinolones are not mentioned. Our meta-analysis focused on eradication rates, side effects and compliance of therapies containing fourth-generation quinolones when compared with therapies using non-fourth-generation quinolones.

Research objectives

This meta-analysis aimed to clarify the effect of fourth-generation quinolones on the eradication of *H. pylori* infection and provide some evidence for clinical practice.

Research methods

The meta-analysis was conducted according to the PRISMA criteria. We searched the PubMed, EMBASE, and Cochrane Library databases. The outcome was to calculate the pooled eradication rate and therapy-related side effects among the trials, comparing the control and experimental groups. We calculated the odds ratio of each trial for the primary measure. The odds ratios were presented with 95% confidence intervals, and a *P*-value < 0.05 was considered significant. This methodology was also performed for subgroup analysis.

Research results

Available data from 10 studies showed that treatment with a fourth-generation quinolone could achieve a higher *H. pylori* eradication rate and decrease the side effects, but the eradication rate is less than acceptable. Fourth-generation quinolones can significantly improve the eradication rate in Europe but not in Asia.

Research conclusions

Quinolone resistance increases with age and duration of use. It is essential for practitioners to use quinolone antibiotics in the clinic reasonably. This study comprehensively analyzed the role of fourth-generation quinolone in the treatment of *H. pylori* infection. Our results suggested that fourth-generation quinolones are not ideal for eradication of *H. pylori*. Treatment based on antibiotic susceptibility testing might be more valid and obtain a higher rate of eradication of *H. pylori* infection, particularly in areas where resistance to antibiotics develops rapidly.

Research perspectives

According to reports that mutations at positions 87 and 91 of gyrA are the main cause of *H. pylori* resistance to fourth-generation quinolones, we will continue to pay attention to the resistance rate to fourth-generation quinolones globally. We will also focus on rapid genotyping methods, such as detecting gyrA mutations in *H. pylori*. Further studies of sitafloxacin, gemifloxacin, and gatifloxacin are imperative to draw more solid conclusions about the use of fourth-generation quinolones for the eradication of *H. pylori* infection.

REFERENCES

1 **Liou JM**, Lin JT, Chang CY, Chen MJ, Cheng TY, Lee YC, Chen CC, Sheng WH, Wang HP, Wu MS. Levofloxacin-based and clarithromycin-based triple therapies as first-line and second-line treatments for Helicobacter pylori infection: a randomised comparative trial with crossover design. *Gut* 2010; **59**: 572-578 [PMID: 20427390 DOI: 10.1136/gut.2009.198309]

2 **Molina-Infante J,** Romano M, Fernandez-Bermejo M, Federico A, Gravina AG, Pozzati L, Garcia-Abadia E, Vinagre-Rodriguez G, Martinez-Alcala C, Hernandez-Alonso M , Miranda A,

Iovene MR, Pazos-Pacheco C, Gisbert JP. Optimized nonbismuth quadruple therapies cure most patients with Helicobacter pylori infection in populations with high rates of antibiotic resistance. Gastroenterology 2013; **145**: 121-128.e1 [PMID: 23562754 DOI: 10.1053/j.gastro.2013.03.050]

3 **Song M**, Ang TL. Second and third line treatment options for Helicobacter pylori eradication. *World J Gastroenterol* 2014; **20**: 1517-1528 [PMID: 24587627 DOI: 10.3748/wjg.v20.i6.1517]

4 **Wang B**, Lv ZF, Wang YH, Wang H, Liu XQ, Xie Y, Zhou XJ. Standard triple therapy for Helicobacter pylori infection in China: a meta-analysis. *World J Gastroenterol* 2014; **20**: 14973-14985 [PMID: 25356059 DOI: 10.3748/wjg.v20.i40.14973]

5 **Malfertheiner P**, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of Helicobacter pylori infection: the Maastricht Ⅲ Consensus Report. *Gut* 2007; **56**: 772-781 [PMID: 17170018 DOI: 10.1056/NEJMcp1001110]

6 **Molina-Infante J**, Pazos-Pacheco C, Vinagre-Rodriguez G, Perez-Gallardo B, Dueñas-Sadornil C, Hernandez-Alonso M, Gonzalez-Garcia G, Mateos-Rodriguez JM, Fernandez-Bermejo M, Gisbert JP. Nonbismuth quadruple (concomitant) therapy: empirical and tailored efficacy versus standard triple therapy for clarithromycin-susceptible Helicobacter pylori and versus sequential therapy for clarithromycin-resistant strains. *Helicobacter* 2012; **17**: 269-276 [PMID: 22759326 DOI: 10.1111/j.1523-5378.2012.00947.x]

7 **Mitui M**, Patel A, Leos NK, Doern CD, Park JY. Novel Helicobacter pylori sequencing test identifies high rate of clarithromycin resistance. *J Pediatr Gastroenterol Nutr* 2014; **59**: 6-9 [PMID: 25222804 DOI: 10.1097/MPG.0000000000000380]

8 **Megraud F**, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, Andersen LP, Goossens H, Glupczynski Y; Study Group participants. Helicobacter pylori resistance to antibiotics in Europe and its relationship to antibiotic consumption. *Gut* 2013; **62**: 34-42 [PMID: 22580412 DOI: 10.1136/gutjnl-2012-302254]

9 **Horiki N**, Omata F, Uemura M, Suzuki S, Ishii N, Iizuka Y, Fukuda K, Fujita Y, Katsurahara M, Ito T, Cesar GE, Imoto I, Takei Y. Annual change of primary resistance to clarithromycin among Helicobacter pylori isolates from 1996 through 2008 in Japan. *Helicobacter* 2009; **14**: 86-90 [PMID: 19751432 DOI: 10.1111/j.1523-5378.2009.00714.x]

10 **Thung I**, Aramin H, Vavinskaya V, Gupta S, Park JY, Crowe SE, Valasek MA. Review article: the global emergence of Helicobacter pylori antibiotic resistance. *Aliment Pharmacol Ther* 2016; **43**: 514-533 [PMID: 26694080 DOI: 10.1111/apt.13497]

11 **Malfertheiner P**, Megraud F, O'Morain CA, Atherton J, Axon AT, Bazzoli F, Gensini GF, Gisbert JP, Graham DY, Rokkas T, El-Omar EM, Kuipers EJ; European Helicobacter Study Group. Management of Helicobacter pylori infection--the Maastricht Ⅳ/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

12 **Malfertheiner P**, Megraud F, O'Morain CA, Gisbert JP, Kuipers EJ, Axon AT, Bazzoli F, Gasbarrini A, Atherton J, Graham DY, Hunt R, Moayyedi P, Rokkas T, Rugge M, Selgrad M, Suerbaum S, Sugano K, El-Omar EM; European Helicobacter and Microbiota Study Group and Consensus panel. Management of Helicobacter pylori infection-the Maastricht Ⅴ/Florence Consensus Report. *Gut* 2017; **66**: 6-30 [PMID: 27707777 DOI: 10.1136/gutjnl-2016-312288]

13 **Saracino IM**, Zullo A, Holton J, Castelli V, Fiorini G, Zaccaro C, Ridola L, Ricci C, Gatta L, Vaira D. High prevalence of primary antibiotic resistance in Helicobacter pylori isolates in Italy. *J Gastrointestin Liver Dis* 2012; **21**: 363-365 [PMID: 23256118]

14 **Gao W**, Cheng H, Hu F, Li J, Wang L, Yang G, Xu L, Zheng X. The evolution of Helicobacter pylori antibiotics resistance over 10 years in Beijing, China. *Helicobacter* 2010; **15**: 460-466 [PMID: 21083752 DOI: 10.1111/j.1523-5378.2010.00788.x]

15 **Shiota S**, Reddy R, Alsarraj A, El-Serag HB, Graham DY. Antibiotic Resistance of Helicobacter pylori Among Male United States Veterans. *Clin Gastroenterol Hepatol* 2015; **13**: 1616-1624 [PMID: 25681693 DOI: 10.1016/j.cgh.2015.02.005]

16 **Jeong MH**, Chung JW, Lee SJ, Ha M, Jeong SH, Na S, Na BS, Park SK, Kim YJ, Kwon KA, Ko KI, Jo Y, Hahm KB, Jung HY. [Comparison of rifabutin- and levofloxacin-based third-line rescue therapies for Helicobacter pylori]. *Korean J Gastroenterol* 2012; **59**: 401-406 [PMID: 22735872 DOI: 10.4166/kjg.2012.59.6.401]

17 **Mah FS**. Fourth-generation fluoroquinolones: new topical agents in the war on ocular bacterial infections. *Curr Opin Ophthalmol* 2004; **15**: 316-320 [PMID: 15232471 DOI: 10.1097/00055735-200408000-00007]

18 **Kłosińska-Szmurło E**, Grudzień M, Betlejewska-Kielak K, Pluciński F, Biernacka J, Mazurek AP. Physicochemical properties of lomefloxacin, levofloxacin, and moxifloxacin relevant to the biopharmaceutics classification system. *Acta Chim Slov* 2014; **61**: 827-834 [PMID: 25551723]

19 **Hirata Y**, Serizawa T, Shichijo S, Suzuki N, Sakitani K, Hayakawa Y, Yamada A, Koike K. Efficacy of triple therapy with esomeprazole, amoxicillin, and sitafloxacin as a third-line Helicobacter pylori eradication regimen. *Int J Infect Dis* 2016; **51**: 66-69 [PMID: 27590563 DOI: 10.1016/j.ijid.2016.08.019]

20 **Mahmoudi L**, Farshad S, Seddigh M, Mahmoudi P, Ejtehadi F, Niknam R. High efficacy of gemifloxacin-containing therapy in Helicobacter Pylori eradication: A pilot empirical second-line rescue therapy. *Medicine* (Baltimore) 2016; **95**: e4410 [PMID: 27759625 DOI: 10.1097/MD.0000000000004410]

21 **Sugimoto M**, Sahara S, Ichikawa H, Kagami T, Uotani T, Furuta T. High Helicobacter pylori cure rate with sitafloxacin-based triple therapy. *Aliment Pharmacol Ther* 2015; **42**: 477-483 [PMID: 26075959 DOI: 10.1111/apt.13280]

22 **Gisbert JP**, Romano M, Molina-Infante J, Lucendo AJ, Medina E, Modolell I, Rodríguez-Tellez M, Gomez B, Barrio J, Perona M, Ortuño J, Ariño I, Domínguez-Muñoz JE, Perez-Aisa Á, Bermejo F, Domínguez JL, Almela P, Gomez-Camarero J, Millastre J, Martin-Noguerol E, Gravina AG, Martorano M, Miranda A, Federico A, Fernandez-Bermejo M, Angueira T, Ferrer-Barcelo L, Fernández N, Marín AC, McNicholl AG. Two-week, high-dose proton pump inhibitor, moxifloxacin triple Helicobacter pylori therapy after failure of standard triple or non-bismuth quadruple treatments. *Dig Liver Dis* 2015; **47**: 108-113 [PMID: 25454706 DOI: 10.1016/j.dld.2014.10.009]

23 **Chung KH**, Dong HL, Kim N, Shin CM, Jin HH, Sang HL, Lee D, Hong SO, Jin EH. Su1696 Efficacy of Second-Line Treatment for *Helicobacter pylori* Infection: Moxifloxacin-Containing Triple Therapy *vs*. Bismuth-Containing Quadruple Therapy. *Gastroenterology* 2012; **142**: S-483-S-484 [DOI: 10.1016/S0016-5085(12)61839-3]

24 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**: e1000097 [PMID: 19621072 DOI: 10.1371/journal.pmed.1000097]

25 **Moher D**, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; **8**: 336-341 [PMID: 20171303 DOI: 10.1016/j.ijsu.2010.02.007]

26 **Higgins JP**, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011

27 **Mansour-Ghanaei F**, Pedarpour Z, Shafaghi A, Joukar F. Clarithromycin versus Gemifloxacin in Quadruple Therapeutic Regimens for *Helicobacter Pylori* Infection Eradication. *Middle East J Dig Dis* 2017; **9**: 100-106 [PMID: 28638586 DOI: 10.15171/mejdd.2017.58]

28 **Masoodi M**, Talebi-Taher M, Tabatabaie K, Khaleghi S, Faghihi AH, Agah S, Asadi R. Clarithromycin *vs*. Gemifloxacin in Quadruple Therapy Regimens for Empiric Primary Treatment of Helicobacter pylori Infection: A Randomized Clinical Trial. *Middle East J Dig Dis* 2015; **7**: 88-93 [PMID: 26106468]

29 **Rakici H**, Ayaz T, Akdogan RA, Bedir R. Comparison of levofloxacin- and moxifloxacin-based triple therapies with standard treatment in eradication of Helicobacter pylori as first-line therapy. *Digestion* 2014; **90**: 261-264 [PMID: 25547786 DOI: 10.1159/000369788]

30 **Murakami K**, Furuta T, Ando T, Nakajima T, Inui Y, Oshima T, Tomita T, Mabe K, Sasaki M, Suganuma T, Nomura H, Satoh K, Hori S, Inoue S, Tomokane T, Kudo M, Inaba T, Take S, Ohkusa T, Yamamoto S, Mizuno S, Kamoshida T, Amagai K, Iwamoto J, Miwa J, Kodama M, Okimoto T, Kato M, Asaka M; Japan GAST Study Group. Multi-center randomized controlled study to establish the standard third-line regimen for Helicobacter pylori eradication in Japan. *J Gastroenterol* 2013; **48**: 1128-1135 [PMID: 23307042 DOI: 10.1007/s00535-012-0731-8]

31 **Zeng Z**, Lv N, Hu F, Si J, Wu K, Jiang B, Liu W, Zhang J, Chen M, Hu P. Moxifloxacin-based triple therapy for Helicobacter pylori eradication: A multicenter randomized parallel-controlled study. *J Gastroenterol Hepatol* 2012; **27**: 3

32 **Lu NH**, Xie Y, Zhu X, Chen YX, Ma JH, He XX. Eradication therapy for Helicobacter pylori infection in patients with duodenal ulcers based on moxifloxacin triple therapy: a randomized controlled trial. *J Gastroenterol Hepatol* 2009; **24**: A15-A15

33 **Kiliç ZM**, Köksal AS, Cakal B, Nadir I, Ozin YO, Kuran S, Sahin B. Moxifloxacine plus amoxicillin and ranitidine bismuth citrate or esomeprazole triple therapies for Helicobacter pylori infection. *Dig Dis Sci* 2008; **53**: 3133-3137 [PMID: 18465244 DOI: 10.1007/s10620-008-0285-z]

34 **Bago P**, Vcev A, Tomic M, Rozankovic M, Marusić M, Bago J. High eradication rate of H. pylori with moxifloxacin-based treatment: a randomized controlled trial. *Wien Klin Wochenschr* 2007; **119**: 372-378 [PMID: 17634896 DOI: 10.1007/s00508-007-0807-2]

35 **Kist M**. How effective is moxifloxacin for the first-line treatment of patients with Helicobacter pylori infection? *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 450-451 [PMID: 16224475 DOI: 10.1038/ncpgasthep0288]

36 **Nista EC**, Candelli M, Zocco MA, Cazzato IA, Cremonini F, Ojetti V, Santoro M, Finizio R, Pignataro G, Cammarota G, Gasbarrini G, Gasbarrini A. Moxifloxacin-based strategies for first-line treatment of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2005; **21**: 1241-1247 [PMID: 15882245 DOI: 10.1111/j.1365-2036.2005.02412.x]

37 **Thamphiwatana S**, Gao W, Obonyo M, Zhang L. In vivo treatment of Helicobacter pylori infection with liposomal linolenic acid reduces colonization and ameliorates inflammation. *Proc Natl Acad Sci U S A* 2014; **111**: 17600-17605 [PMID: 25422427 DOI: 10.1073/pnas.1418230111]

38 **Apostolopoulos P**, Koumoutsos I, Ekmektzoglou K, Dogantzis P, Vlachou E, Kalantzis C, Tsibouris P, Alexandrakis G. Concomitant versus sequential therapy for the treatment of Helicobacter pylori infection: a Greek randomized prospective study. *Scand J Gastroenterol* 2016; **51**: 145-151 [PMID: 26435055 DOI: 10.3109/00365521.2015.1079646]

39 **Alhooei S**, Tirgar Fakheri H, Hosseini V, Maleki I, Taghvaei T, Valizadeh SM, Bari Z. A Comparison between Hybrid and Concomitant Regimens for *Helicobacter Pylori* Eradication: A Randomized Clinical Trial. *Middle East J Dig Dis* 2016; **8**: 219-225 [PMID: 27698972 DOI: 10.15171/mejdd.2016.24]

40 **Egan BJ**, Marzio L, O'Connor H, O'Morain C. Treatment of Helicobacter pylori infection. *Helicobacter* 2008; **13** Suppl 1: 35-40 [PMID: 18783520 DOI: 10.1111/j.1523-5378.2008.00639.x]

41 **Kwon YH**, Kim N, Lee JY, Choi YJ, Yoon K, Nam RH, Suh JH, Lee JW, Lee DH. Comparison of the efficacy of culture-based tailored therapy for Helicobacter pylori eradication with that of the traditional second-line rescue therapy in Korean patients: a prospective single tertiary center study. *Scand J Gastroenterol* 2016; **51**: 270-276 [PMID: 26452405 DOI: 10.3109/00365521.2015.1095352]

42 **Moore RA**, Beckthold B, Wong S, Kureishi A, Bryan LE. Nucleotide sequence of the gyrA gene and characterization of ciprofloxacin-resistant mutants of Helicobacter pylori. *Antimicrob Agents Chemother* 1995; **39**: 107-111 [PMID: 7695290 DOI: 10.1128/AAC.39.1.107]

43 **Lee JW**, Kim N, Nam RH, Park JH, Kim JM, Jung HC, Song IS. Mutations of Helicobacter pylori associated with fluoroquinolone resistance in Korea. *Helicobacter* 2011; **16**: 301-310 [PMID: 21762270 DOI: 10.1111/j.1523-5378.2011.00840.x]

44 **Graham DY**, Lee YC, Wu MS. Rational Helicobacter pylori therapy: evidence-based medicine rather than medicine-based evidence. *Clin Gastroenterol Hepatol* 2014; **12**: 177-186.e3; Discussion e12-e13 [PMID: 23751282 DOI: 10.1016/j.cgh.2013.05.028]

45 **Zhang G**, Zou J, Liu F, Bao Z, Dong F, Huang Y, Yin S. The efficacy of moxifloxacin-based triple therapy in treatment of Helicobacter pylori infection: a systematic review and meta-analysis of randomized clinical trials. *Braz J Med Biol Res* 2013; **46**: 607-613 [PMID: 23903685 DOI: 10.1590/1414-431X20132817]

46 **Liu DS**, Wang YH, Zeng ZR, Zhang ZY, Lu H, Xu JM, Du YQ, Li Y, Wang JB, Xu SP, Chen Y, Lan CH, Cheng H, Jiang MD, Zhang LX, Huo LJ, Chen SY, Zhang GX, Wu KC, Zhu X, Chen YX, Zhu Y, Shu X, Xie Y, Lu NH. Primary antibiotic resistance of Helicobacter pylori in Chinese patients: a multiregion prospective 7-year study. *Clin Microbiol Infect* 2018; **24**: 780.e5-780.e8 [PMID: 29138101 DOI: 10.1016/j.cmi.2017.11.010]

P- Reviewer: Chmiela M, Slomiany BL, Tongtawee T
S- Editor: Gong ZM **L- Editor**: Filipodia **E- Editor**: Huang Y

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

ISSN 1007-9327