World Journal of Gastroenterology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.3748/wjg.v20.i27.8947

*World J Gastroenterol* 2014 July 21; 20(27): 8947-8956
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
© 2014 Baishideng Publishing Group Inc. All rights reserved.

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (6): *Helicobacter pylori*

# Fluoroquinolone-based protocols for eradication of *Helicobacter pylori*

Antonio Rispo, Pietro Capone, Fabiana Castiglione, Luigi Pasquale, Matilde Rea, Nicola Caporaso

Antonio Rispo, Pietro Capone, Fabiana Castiglione, Matilde Rea, Nicola Caporaso, Division of Gastroenterology, Department of Clinical Medicine and Surgery - University "Federico Ⅱ" of Naples, 80131 Napoli, Italy
Luigi Pasquale, Division of Gastroenterology, P.O. "Sant'Ottone Frangipane", Ariano Irpino, 80131 Napoli, Italy
Author contributions: Rispo A wrote the article; Capone P and Rea M identified the articles by Medline search; Castiglione F and Pasquale L reviewed the papers; Caporaso N contributed to critical revision of the manuscript.
Correspondence to: Antonio Rispo, MD, Division of Gastroenterology, Department of Clinical Medicine and Surgery - University "Federico Ⅱ" of Naples, Via S. Pansini 5, 80131 Napoli, Italy. antoniorispo@email.it
Telephone: +39-81-7463849 Fax: +39-81-5465649
Received: September 4, 2013 Revised: February 10, 2014
Accepted: April 1, 2014
Published online: July 21, 2014

## Abstract

*Helicobacter pylori* (*H. pylori*) is a widespread pathogen infecting about 40% of people living in urban areas and over 90% of people living in the developing regions of the world. *H. pylori* is well-documented as the main factor in the pathogenesis of peptic ulcer disease, chronic gastritis, and gastric malignancies such as cancer and mucosa-associated lymphoid tissue-lymphoma; hence, its eradication is strongly recommended. The Maastricht Ⅳ consensus, which focused on the management of *H. pylori* infection, set important new strategies in terms of treatment approaches, particularly with regards to first- and second-line treatment protocols and led to improved knowledge and understanding of *H. pylori* resistance to antibiotics. In recent years, various fluoroquinolone-based protocols, mainly including levofloxacin, have been proposed and effectively tested at all therapeutic lines for *H. pylori* eradication. The aim of the present paper is to review the scientific literature focused on the use of fluoroquinolones in eradicating *H. pylori*.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words:** *Helicobacter pylori*; Eradication; Fluoroquinolone; Therapy

**Core tip:** The Maastricht Ⅳ consensus, which focused on the management of *Helicobacter pylori* (*H. pylori*) infection, set important new strategies in terms of treatment approaches, particularly with regards to first- and second-line treatment protocols and led to improved knowledge and understanding of *H. pylori* resistance to antibiotics. In recent years, various fluoroquinolone-based protocols, mainly including levofloxacin, have been proposed and effectively tested at all therapeutic lines for *H. pylori* eradication. The aim of the present invited paper is to review the scientific literature focused on the use of fluoroquinolones in eradicating *H. pylori*.

Rispo A, Capone P, Castiglione F, Pasquale L, Rea M, Caporaso N. Fluoroquinolone-based protocols for eradication of *Helicobacter pylori*. *World J Gastroenterol* 2014; 20(27): 8947-8956 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i27/8947.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i27.8947

## INTRODUCTION

Nalidixic acid, the precursor of all fluoroquinolones, was developed and marketed during the 1960s for the oral treatment of urinary tract infections and is still prescribed with this indication. Several fluoroquinolones were developed since; however, the role of new molecules only became significant when it was demonstrated that substitutions at the Carbon atoms in C-6 and C-7 positions

**Table 1 Current recommendations for *Helicobacter pylori* eradication**

| Treatment | Region with low clarithromycin prevalence | Region with high clarithromycin prevalence |
|---|---|---|
| First line | PPI - clarithromycin - amoxicillin/metronidazole or bismuth quadruple | Bismuth quadruple[1]. If not available: non-bismuth quadruple (either sequential or concomitant) |
| Second line | Bismuth quadruple[1] or PPI - levofloxacin/amoxicillin | PPI - levofloxacin/amoxicillin |
| Third line | Based on susceptibility testing only. Besides clarithromycin and levofloxacin, rifabutin is another candidate that may be used | |

[1]PPI + tetracyclines + bismuth + metronidazole. PPI: Proton pump inhibitors.

improved both antibacterial activity and pharmacological features. From that point onwards, fluoroquinolones were tested and used in the treatment of urinary, respiratory, gastrointestinal, urogenital, and intra-abdominal infections in the context of several pathological conditions[1-5].

*Helicobacter pylori* (*H. pylori*) is a widespread pathogen infecting about 40% of people living in urban areas and over 90% of people living in the developing regions of the world[6,7]. *H. pylori* is well-documented as the main factor in the pathogenesis of peptic ulcer disease, chronic gastritis, and gastric malignancies such as cancer and mucosa-associated lymphoid tissue-lymphoma. Hence, its eradication is strongly recommended[8-13]. The Maastricht Ⅲ consensus proposed that triple therapy protocols containing clarithromycin and metronidazole should be used as first-line treatment for *H. pylori* infection, in view of their high efficacy and safety[14]. However, more recent data show that these antibiotics have lost some efficacy because of increased primary/secondary drug resistance, so that they permit *H. pylori* eradication in only a maximum of 70% of the affected patients (a percentage significantly lower than the one that can be expected for the treatment of an infectious disease - about 90% at per-protocol analysis). Thus, antibiotics different from clarithromycin and metronidazole have been proposed for eradicating *H. pylori*[15,16]. The Maastricht Ⅳ consensus generated important new information with regard to the treatment of *H. pylori* infection. In particular, it proposed the prescription of three antibiotics together with a proton pump inhibitor (PPI; non-bismuth sequential or quadruple therapy) as first-line treatment for *H. pylori* infection in areas of high clarithromycin resistance[17-21].

In recent years, various fluoroquinolone-based protocols, mainly including levofloxacin, have been proposed and tested at all therapeutic lines for *H. pylori* eradication. The aim of this paper is to review the scientific literature focused on the use of fluoroquinolones in eradicating *H. pylori*.

Studies providing information on the use of levofloxacin-based anti-*H. pylori* protocols were identified through systematic searches in the MEDLINE and EMBASE databases. Various combinations of the terms "*H. pylori*", "fluoroquinolone", "levofloxacin", "ciprofloxacin", "eradication", "first-line", "second-line" and "rescue" were used for the searches. Additionally, references of retrieved articles were screened to identify additional relevant studies (cross-referencing). We also performed a manual search of all review articles, recently published editorials, and retrieved original studies presented at the 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 up to August 1, 2013 were included. Searches were limited to randomized controlled trials and studies comparing fluoroquinolone-based protocols to other treatment regimens. Two investigators (Dr Capone and Dr Rea) independently extracted data from the included studies by using a structured form. Only data from patients undergoing fluoroquinolone-based eradication protocols were included in the analysis. There was a > 95% agreement in data extraction between the two investigators.

## CURRENT RECOMMENDATIONS FOR ERADICATING *H. PYLORI*

As mentioned above, the Maastricht Ⅳ consensus introduced important changes to the treatment of *H. pylori* infection (Table 1)[17].

The consensus led to abandoning the use of clarithromycin-containing triple therapy in regions where clarithromycin resistance rate is over 15%-20% - for example, many areas of Europe and North America - if susceptibility testing cannot be carried out[16,22]. However, in areas of known low clarithromycin resistance, clarithromycin-containing protocols are still recommended for the first-line empirical treatment of *H. pylori* infection. In these areas of low clarithromycin resistance bismuth-containing quadruple treatment protocols are considered an effective alternative, whilst in regions with high clarithromycin resistance, they are the recommended protocols for first-line empirical treatment of *H. pylori* infection[23-25]. In countries where a bismuth-based regimen is not easily available, sequential treatment or a non-bismuth quadruple treatment is recommended as first-line eradication protocol[26-29].

With regard to the role of fluoroquinolones for *H. pylori* eradication, current recommendations stress their efficacy as a second-line treatment option. In particular, either bismuth-containing quadruple therapy or levofloxacin-containing triple therapy is recommended after failure of a regimen containing PPI-clarithromycin. In areas of low fluoroquinolone resistance, a levofloxacin-containing regimen (together with a PPI and clarithromycin) can prove an effective second-line alternative in the presence of penicillin allergy[30-35]. However, when considering a

treatment approach including fluoroquinolones, clinicians should be aware of the rising rates of levofloxacin resistance, particularly in Europe and North America.

## DRUG RESISTANCE IN THE TREATMENT OF *H. PYLORI* INFECTION

The success of treatment protocols for the eradication of *H. pylori* is currently being compromised by the increase in antimicrobial resistance[36,37].

Clarithromycin resistance in particular has a major negative impact on the efficacy of the recommended first-line triple therapy and a progressive increase in its prevalence may limit its use. The almost two-fold increase (from 9.8% to 17.5%) of the prevalence of clarithromycin resistance over the past 10 years (in specific areas of Southern Europe it is higher than 30%) could have been anticipated on the grounds of the genetic basis of this resistance. By contrast, metronidazole resistance, although highly prevalent (particularly in Mediterranean Africa), can be partly overcome and is therefore of secondary importance. As for amoxicillin, all the surveys performed so far have reported a resistance rate lower than 1%, indicating that resistance to this drug is not yet a clinical concern[38-42].

At present, it is well known that fluoroquinolones are the only class of antibiotics for clinical use that directly inhibit bacterial DNA synthesis. Fluoroquinolones inhibit DNA gyrase and topoisomerase Ⅳ, two bacterial enzymes which have essential and distinct roles in DNA replication. Resistance to fluoroquinolones occurs mainly by means of a mutation in the chromosomal genes for gyrase and topoisomerase Ⅳ. Miyachi *et al*[43] showed that primary levofloxacin resistance, found in approximately 15% of *H. pylori* strains, was related to point mutations in gyrA at Asn-87 or Asp-91 in 84% of cases; only 14% of the susceptible strains had gyrA mutations. The difference in occurrence of gyrA mutations between levofloxacin-resistant and -susceptible strains was significant. Other mechanisms that can determine bacterial resistance to fluoroquinolones could be microbial SOS response, auto-induction of resistance and plasmid-mediated resistance, with the latter being more frequent for other kind of urinary, pulmonary and intestinal infections. In contrast to other bacteria, resistant *H. pylori* strains show no spread of resistance through horizontal transfer of mobile genetic elements (*e.g.* plasmids)[44]. As a consequence, the low transmission rate of *H. pylori* and the lack of expansion of specific clones in the community imply that antibiotic resistance in *H. pylori* is caused by previous and direct exposure to antibiotics in infected patients. *H. pylori* infection is an example of long-lasting infection and it should be highlighted that the exposure to antibiotics for this microbe may be much longer than that for most other pathogens.

A recent paper by Mégraud *et al*[37] focused on the antibiotic resistance of *H. pylori*. The study by these authors included more than 2000 patients with *H. pylori* infection and showed resistance rates of 14.1% for levofloxacin, 17.5% for clarithromycin, and 34.9% for metronidazole, with significantly higher fluoroquinolone resistance in Western/Central and Southern Europe (> 20%) than in Northern European countries (< 10%). The results of this paper correlate well with those reported by O'Connor *et al*[45] in Ireland. These authors encountered a rate of levofloxacin resistance of 2.6 % in the under-45 age group, compared to 19.1% in patients above 45 years of age. In keeping with the suggested mechanisms of *H. pylori* resistance to fluoroquinolones, a significant association was found between fluoroquinolone use among outpatients and the proportion of levofloxacin resistance.

Carothers *et al*[46] have already shown how *H. pylori* resistance to fluoroquinolones and its impact on treatment outcomes are influenced by previous use of this class of antibiotics. In their study, resistance rates appeared to be significantly associated with any prior fluoroquinolone assumption over the previous 10 years and with the total number of courses prescribed. For patients who have previously undergone treatment with fluoroquinolones, a treatment protocol not comprising levofloxacin should be suggested.

However, previous use of fluoroquinolones for therapeutic purposes is not the only mechanism through which resistance to the drug occurs. A recent paper from Germany demonstrated that about 85% of all antibiotics used in general practice is administered in food animals; animal manure waste is spread onto agricultural land and will influence ecosystem compartments. Antibiotics such as fluoroquinolones and tetracyclines are not biodegradable; they can persist in soil for long periods and/or in high concentrations and can be detected in soil and water[47]. Antibiotic resistance pre-dates the use of antibiotics because resistance determinants have been circulating within the microbial genome for millennia[48]. Ongoing non-therapeutic use of antibiotics in food animals will increase the pool and occurrence rate of resistance genes in many bacterial species, thus having dramatic public health consequences. The Maastricht Ⅳ consensus recommendations relating to the rising rate of levofloxacin resistance are therefore extremely relevant for every-day clinical practice[17,5,49].

## FLUOROQUINOLONE-BASED PROTOCOLS IN THE FIRST-LINE TREATMENT OF *H. PYLORI* INFECTION

Fluoroquinolones - levofloxacin being the main representative of this class of molecules - are antibacterial agents with a wide spectrum of activity against Gram-positive and -negative bacteria, including *in vitro* activity against *H. pylori* and atypical pathogens. Levofloxacin is widely used for the rescue treatment of resistant *H. pylori* infections. Recent meta-analyses have underlined its better efficacy and tolerability profile in the second-line treatment of *H. pylori* infection when compared with the

**Table 2 Randomized controlled trials containing levofloxacin in first-line triple therapy of *Helicobacter pylori***

| Ref. | Year | Nation | Patients | Therapy | Posology | Duration | Comparator | ITT |
|---|---|---|---|---|---|---|---|---|
| Shah *et al*[53] | 2013 | India | 131 | LTE | 500 | 7 | | 85.0% |
| Qian *et al*[54] | 2012 | China | 345 | LAE | 500 | 7 | SEQ-L | 78.1% |
| Cuadrado-Lavín *et al*[61] | 2012 | Spain | 250 | LAO | 500 | 10 | CAO | 82.8% |
| Pan *et al*[62] | 2010 | China | 199 | LAE | 500 | 7 | NAR | 87.1% |
| Chen *et al*[63] | 2010 | Taiwan | 189 | LCE | 500 | 7 | CAE | 78.9% |
| Assem *et al*[64] | 2010 | Egypt | 450 | LAE | 500 | 7 | CLE/CAE | 84.7% |
| Erçin *et al*[65] | 2010 | Turkey | 91 | LAL | 500 | 14 | LAL (7) | 72.0% |
| Liou *et al*[66] | 2010 | Taiwan | 432 | LAL | 500 | 7 | CAL | 74.0% |
| Chen *et al*[63] | 2010 | China | 300 | LAL | 500 | 7 | CAL | 74.0% |
| Molina-Infante *et al*[69] | 2010 | Spain | 460 | LAO | 500 | 10 | SEQ-L | 82.6% |
| Castro-Fernández *et al*[59] | 2009 | Spain | 135 | LAO | 500 | 10 | | 71.8% |
| Gisbert *et al*[55] | 2007 | Spain | 64 | LARBIS | 500 | 10 | | 84.4% |
| Rispo *et al*[52] | 2007 | Italy | 130 | LAE | 500 | 7 | CAE | 90.8% |
| Nista *et al*[51] | 2006 | Italy | 300 | CLE | 500 | 7 | CME/CAE | 87.0% |
| Lee *et al*[56] | 2006 | South Korea | 267 | LAE | 500 | 7 | CAE | 69.8% |
| Cammarota[50] | 2004 | Italy | 100 | CLR | 500 | 7 | CLR (250) | 84.0% |

LTE: Levofloxacin + tinidazole + esomeprazole; LAE: Levofloxacin + amoxicillin + esomeprazole; SEQ-L: Standard sequential therapy or levofloxacin-containing sequential therapy; LAO: Levofloxacin + amoxicillin + omeprazole; CAO: Clarithromycin + amoxicillin + omeprazole; LCE: Levofloxacin + clarithromycin + esomeprazole; CAE: Clarithromycin + amoxicillin + esomeprazole; CLE: Clarithromycin + levofloxacin + esomeprazole; LAL: Levofloxacin + amoxicillin + lansoprazole; CAL: Clarithromycin + amoxicillin + lansoprazole; LARBIS: Levofloxacin + amoxicillin + ranitidine bismuth citrate; CLR: Clarithromycin + levofloxacin + rifabutin; ITT: Intention-to-treat.

quadruple protocol comprising bismuth (which we discuss shortly).

Since 2006, several clinical trials have tested the efficacy of levofloxacin in the first-line treatment of *H. pylori*. The majority of authors utilised levofloxacin as part of a triple drug regimen including a PPI and another antibiotic agent (frequently amoxicillin). The first experience by Cammarota *et al*[50] in a trial including 100 patients with *H. pylori* infection treated with levofloxacin (500 mg/d), clarithromycin and rabeprazole showed an eradication rate of 84%. An analogous rate of *H. pylori* eradication (87%) was reported by Nista *et al*[51], who treated 300 infected patients with levofloxacin, clarithromycin and esomeprazole. Drawing upon this existing research, our team carried out a study to evaluate the efficacy of a triple therapy including levofloxacin in the first-line treatment of *H. pylori* infection when compared to the conventional protocol containing clarithromycin. We prospectively randomized 130 consecutive outpatients with histological first diagnosis of *H. pylori* infection in two treatment groups: the LAE group (65 patients) was treated with levofloxacin 250 mg *bid*, amoxicillin 1 g *bid*, esomeprazole 20 mg *bid*; and the CAE group (65 patients) with clarithromycin 500 mg *bid*, amoxicillin 1 g *bid*, and esomeprazole 20 mg *bid*. The success rate was assessed by means of $^{13}$C urea breath test, which showed *H. pylori* eradication in 90.8% of patients in the LAE group, compared to 76.9% of those in the CAE group ($P < 0.01$; NNT = 7). In our experience the eradication rate was unrelated to the baseline characteristics of the patients and their underlying gastro-duodenal disease[52].

However, subsequent trials, mainly conducted in Spain and Asia, did not confirm our remarkable results. In effect, almost all recent papers coming from Spain, Northern Africa, and Asia highlighted that the rate of *H. pylori* eradication achieved by means of levofloxacin-based triple protocols is less noteworthy than expected (about 85%), probably as a result of the increased rate of *H. pylori* resistance to fluoroquinolones (Table 2). Indeed, these quite rather inadequate eradication rates are likely to be related to a higher prevalence of levofloxacin resistant *H. pylori* strains in that particular geographical areas in which the studies were carried out. Furthermore, not only has fluoroquinolone resistance readily increased over the last decade, but regional differences within the same country can be significant; this appears clearly and particularly true for Spain and China[53-66].

More recently, levofloxacin has been effectively used in first-line sequential and quadruple protocols. Romano *et al*[67] carried out a randomised trial aimed at evaluating the efficacy of a levofloxacin-containing sequential regimen compared to a clarithromycin containing sequential therapy in the eradication of *H. pylori* infection in patients from Southern Italy, a geographical area with > 15% prevalence of clarithromycin resistance. Eradication rates in these authors' intention-to-treat analyses were: 80.8% with clarithromycin sequential treatment; 96.0% with levofloxacin-250 sequential treatment; and 96.8% with levofloxacin-500 sequential treatment. The levofloxacin-250 sequential treatment appeared to be cost-saving compared to the clarithromycin sequential therapy. Two years after this study, the same authors performed a non-inferiority randomized trial to determine whether a 5-d treatment course of levofloxacin-containing quadruple concomitant regimen was as safe and effective as the 10-d course of sequential regimen in eradicating *H. pylori* in previously untreated patients. The intention-to-treat analysis showed similar eradication rates for concomitant (92.2%) and sequential regimens (93.3%). In addition, the authors showed that the concomitant regimen cost $9

less than the sequential one[67,68]. However, once again the remarkable results of using levofloxacin as the first-line eradication drug were not similarly satisfying in different geographical areas. The trials by Molina-Infante *et al*[69] (Spain) and by Qian *et al*[54] (China), using a modified levofloxacin-based quadruple sequential protocol, showed an eradication rate of 80%-85%, highlighting once again the importance of geographical differences in terms of *H. pylori* resistance to antibiotics[70].

We agree with all the experts who emphasise that susceptibility testing may help to identify the most suitable treatment protocol and to therefore use only the antibiotic agent that works well locally.

## FLUOROQUINOLONE-BASED PROTOCOLS IN THE SECOND-LINE TREATMENT OF *H. PYLORI* INFECTION

With regard to the role of fluoroquinolones in *H. pylori* eradication, current recommendations underline their efficacy as a second-line option, in particular as levofloxacin containing triple therapy. Levofloxacin has been widely used for the rescue treatment of resistant infection, and a meta-analysis by Gisbert *et al*[34] has highlighted its better efficacy and tolerability profile in the second-line treatment of *H. pylori* infection compared to the quadruple protocol comprising bismuth. More specifically, this meta-analysis - which included 14 trials with a total of 977 patients - showed that the mean eradication rate with levofloxacin-based regimens was 80%, with 10-d regimens appearing to be more effective than 7-d combinations (81% *vs* 73%; $P < 0.01$). The meta-analysis also showed better results with levofloxacin than with the quadruple combination (81% *vs* 70%; OR = 1.80), and a better safety profile for levofloxacin than for the quadruple regimen, both overall (19% *vs* 44%) and in terms of severe adverse effects (0.8% *vs* 8.4%).

More recently, Di Caro *et al*[71] updated Gisbert *et al*[72], s meta-analysis by comparing the effectiveness of levofloxacin/amoxicillin-based schemes to that of quadruple regimens for the eradication of *H. pylori* in second-line treatment. In total, 10 articles and four abstracts were identified; the analysis, including 14 trials with a total of 677 patients, showed an overall eradication rate of 76.5% in the group treated with levofloxacin-amoxicillin and of 67.4% in that treated with quadruple regimen, with a cure rate of 70.6% for 7-d regimens and 88.7% for 10-d combinations. Interestingly, even though the 7-d levofloxacin-amoxicillin and quadruple protocols showed comparable efficacy, the 10-d fluoroquinolone-based regimen was significantly more effective than the quadruple regimen (OR = 0.5). No differences were reported in quadruple protocol-based eradication rates among Asian and European studies, whereas levofloxacin-amoxicillin regimens were more effective in European populations (78.3% *vs* 67.7%; $P = 0.05$). The incidence of side effects was lower in the levofloxacin-amoxicillin treatment group than in the quadruple regiment group (OR = 0.39; 95%CI: 0.18-0.85; $P = 0.02$). Consequently, the meta-analysis supported the use of 10-d levofloxacin-amoxicillin regimens as a second-line treatment for the eradication of *H. pylori* with excellent tolerability and eradication rates[71].

More recently, Gisbert *et al*[72] have re-assessed this issue in 100 consecutive patients in whom a non-bismuth quadruple regimen, administered either sequentially (PPI + amoxicillin for 5 d followed by PPI plus clarithromycin plus metronidazole for 5 more days) or concomitantly (PPI plus amoxicillin plus clarithromycin plus metronidazole for 10 d) had previously failed. At the end of the study the per-protocol and intention-to-treat *H. pylori* eradication rates were 75.5% and 74%. Intention-to-treat eradication rates achieved with levofloxacin in the "sequential" and "concomitant" failed regimen groups were 74.4% and 71.4%, respectively. A rate of *H. pylori* eradication of approximately 75% obtained using levofloxacin-based triple protocol as a second-line regimen was confirmed also by Manfredi *et al*[73] in Italy. Furthermore, the efficacy of levofloxacin-based protocols and their value over time were explored by a Spanish multicenter study. The study sample comprised 1000 consecutive patients who had not responded to previous treatment with the standard clarithromycin-based triple protocol. It showed per-protocol and intention-to-treat eradication rates of 75.1% and 73.8%, respectively. The treatment (intention-to-treat) efficacy was 76% in year 2006; 68% in year 2007; 70% in year 2008; 76% in year 2009; 74% in year 2010; and 81% in year 2011, underlying the fact that the efficacy of levofloxacin-based protocols tends to remain stable over time[74].

However, once again, different results in terms of efficacy were reported from Eastern countries. Moon *et al*[75] evaluated the efficacy and safety of triple therapy with levofloxacin, metronidazole, and lansoprazole as a second-line treatment, compared to those of quadruple therapy. According to the intention-to-treat analysis, the infection was eradicated in 38 of the 56 patients (67.9%) treated with triple therapy and in 48 of the 57 (84.2%) treated with quadruple therapy ($P = 0.042$). Per-protocol analysis showed successful eradication in 38 of 52 patients (73.1%) from the triple protocol group and 48 of 52 patients (92.3%) from the quadruple protocol group ($P = 0.01$). Even though the choice of metronidazole instead of amoxicillin could partially explain the results of this study, geographical differences in terms of *H. pylori* resistance to fluoroquinolones should not be ignored.

More recently, levofloxacin has been used in a non-bismuth quadruple second-line protocol. Calhan *et al*[76] designed a study aiming to investigate the efficacy of two levofloxacin-containing second-line treatment protocols for *H. pylori* infection. The patients were randomized consecutively to two treatment groups: 73 patients were assigned to the levofloxacin-containing sequential regimen and 75 to the levofloxacin-containing quadruple regimen group. The first group received pantoprazole 40 mg and amoxicillin 1000 mg twice daily for 5 d followed

by pantoprazole 40 mg twice daily and metronidazole 500 mg three times daily and levofloxacin 500 mg once daily for 7 d. The second group received pantoprazole 40 mg twice daily, tetracycline 500 mg four times daily, bismuth subcitrate 300 mg four times daily and levofloxacin 500 mg once daily for 10 d. The intention-to-treat analysis showed eradication rates of 82.2% and 90.6%, respectively, for the two treatment groups, with no statistically significant difference.

On the basis of these studies and findings, the role of levofloxacin (and the modalities of its use) in the second-line treatment of *H. pylori* infection is well defined by Statement 14 of the Maastricht Ⅳ Consensus. According to these recommendations, after failure of a PPI- and clarithromycin-containing treatment, either a bismuth-containing quadruple protocol or a levofloxacin-containing triple protocol is recommended, although the rising rates of levofloxacin resistance should be taken into account.

## FLUOROQUINOLONE-BASED PROTOCOLS IN THE THIRD-LINE TREATMENT OF *H. PYLORI* INFECTION

The Maastricht Ⅳ consensus clearly states that after failure of second-line treatment, the therapeutic approach should be guided by antimicrobial susceptibility testing whenever possible. The work by Cammarota *et al*[77] assessed the efficacy of a third-line, culture-guided treatment approach for the eradication of *H. pylori* infection. Patterns of resistance to antibiotics were analysed in *H. pylori* isolates from 94 consecutive patients in whom the infection had persisted after two eradication protocols. Using the *E*-test, susceptibility analysis was performed for amoxicillin, clarithromycin, metronidazole, tetracycline and levofloxacin. Patients were then treated with a culture-guided, third-line regimen: 89 patients with a 1-wk quadruple regimen including omeprazole, bismuth, doxycycline and amoxicillin, and 5 patients with a 1-wk triple regimen containing omeprazole, amoxicillin and levofloxacin or clarithromycin. The study showed that 94 patients (100%) were resistant to metronidazole, 89 (95%) to clarithromycin, 29 (31%) to levofloxacin and 5 (5%) to tetracycline. No resistance to amoxicillin was found. The overall eradication rate was 90%. The quadruple regimen was effective in 91% of patients (ITT). Four patients (80%, both per protocol and intention-to-treat analyses) were *H. pylori* negative after the triple regimen.

Regrettably, antimicrobial susceptibility testing is not widely and promptly available, being performed almost exclusively at third-level centres. In view of these limitations, a number of studies have assessed the effectiveness of empirical third-line *H. pylori* eradicating protocols, which frequently included levofloxacin. Gisbert *et al*[78] reported on a prospective multicentre study which focused on this type of treatment. The authors included in their study 100 patients for whom a first treatment with omeprazole-clarithromycin-amoxicillin and a second with omeprazole-bismuth-tetracycline-metronidazole (or ranitidine bismuth citrate with these antibiotics) had failed in eradicating the *H. pylori* infection. These patients were treated with a 10-d third-line eradication protocol comprising levofloxacin (500 mg *bid*), amoxicillin (1 g *bid*), and omeprazole (20 mg *bid*). Per-protocol and intention-to-treat eradication rates were 66% and 60%, respectively. A prospective study carried out in Spain evaluated the efficacy of different "rescue" treatments empirically prescribed over the course of 10 years to 500 (consecutive) patients for whom at least one eradication regimen had failed to cure the *H. pylori* infection. The 'rescue' regimens included: quadruple therapy with omeprazole-bismuth-tetracycline-metronidazole; ranitidine bismuth citrate-tetracycline-metronidazole; omeprazole-amoxicillin-levofloxacin; and omeprazole-amoxicillin-rifabutin. Antibiotic susceptibility was unknown (rescue regimens were chosen empirically). Overall, *H. pylori* eradication rates with the second-, third- (mostly levofloxacin-based), and fourth-line rescue regimens were 70%, 74%, and 76%, respectively. Cumulative *H. pylori* eradication rate with four successive treatments was 99.5%[32].

A levofloxacin-based third-line *H. pylori* eradicating protocol was also compared to the rescue treatment based on rifabutin. Forty patients were randomised to receive a 10-d treatment course with either rifabutin (150 mg b.d.) or levofloxacin (500 mg b.d.), plus amoxicillin (1 g b.d.) and omeprazole (20 mg b.d.). At the end of the study, per-protocol eradication rates were 45% in the rifabutin group and 81% in the levofloxacin group ($P < 0.05$). Intention-to-treat eradication rates were 45% and 85%, respectively ($P < 0.01$)[79]. However, bearing in mind the efficacy of levofloxacin compared to rifabutin, regional differences in *H. pylori* resistance to antibiotics should be carefully considered. A study by Jeong *et al*[80] from South Korea compared rifabutin and levofloxacin rescue regimens in patients with first- and second-line *H. pylori* eradication failures. These patients received treatment with either rifabutin or levofloxacin, plus amoxicillin (1 g b.d) and standard dose PPI. Eradication rates were 71.4% in the rifabutin group, and 57.1% in the levofloxacin group. Although there was no significant difference in *H. pylori* eradication rates between the two groups ($P = 0.656$), the rifabutin based regimen showed a relatively higher eradication rate in that geographical region. Once again the choice of antibiotics should be based on available data on regional *H. pylori* antibiotic resistance and susceptibility.

## CONCLUSION

Even the most effective regimens for the treatment of *H. pylori* infection are likely to fail to eradicate *H. pylori* in more than 20% of affected patients. At present, clinicians need to have solid up-to-date knowledge of the first-line eradication regimens - including the more recent quadruple and sequential (bismuth-including or not) protocols -

and to be prepared to face treatment failures.

The treatment strategies for the eradication of *H. pylori* have been enriched by the use and diffusion of fluoroquinolones, an effective and safe option in eradicating *H. pylori* infection. However, as highlighted in the current review and in accordance with the Maastricht Ⅳ consensus, the choice of a first or "rescue" treatment based on fluoroquinolones should be based on regional *H. pylori* antibiotic resistance. It follows that clinicians should be aware of the prevalence of *H. pylori* drug resistance in the geographical area in which they operate. As for second and third line protocols, another crucial variable for the selection of the right drugs is the accurate assessment of the treatment/s that was/were previously used.

In summary, current *H. pylori* eradication guidelines recommend the prescription of levofloxacin (a fluoroquinolone) as part of a sequential treatment or a non-bismuth quadruple treatment in first-line eradication protocols in counties where bismuth-based regimens are not easily available. With regard to second-line treatment regimens, levofloxacin-based protocols constitute an encouraging strategy, representing an alternative to quadruple therapy in patients with previous PPI-clarithromycin-amoxicillin failure and offering the advantages of efficacy, simplicity, and safety. Finally, with regards to third-line and "rescue" protocols, the antibiotic choice should be guided by antimicrobial susceptibility testing irrespective of the efficacy of levofloxacin in the empirical eradication strategies. This appears to be the most sensible and effective treatment option[81-83].

## ACKNOWLEDGMENTS

Many thanks to Giovanna Affinito, our endoscopy nurse, for her precious help and contribution.

## REFERENCES


1 **Appelbaum PC**, Hunter PA. The fluoroquinolone antibacterials: past, present and future perspectives. *Int J Antimicrob Agents* 2000; **16**: 5-15 [PMID: 11185413 DOI: 10.1016/S0924-8579(00)00192-8]

2 **Zhanel GG**, Ennis K, Vercaigne L, Walkty A, Gin AS, Embil J, Smith H, Hoban DJ. A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs* 2002; **62**: 13-59 [PMID: 11790155]

3 **Takahashi H**, Hayakawa I, Akimoto T. [The history of the development and changes of quinolone antibacterial agents]. *Yakushigaku Zasshi* 2003; **38**: 161-179 [PMID: 15143768]

4 **Shariff V A AR**, Shenoy M S, Yadav T, M R. The antibiotic susceptibility patterns of uropathogenic Escherichia coli, with special reference to the fluoroquinolones. *J Clin Diagn Res* 2013; **7**: 1027-1030 [PMID: 23905095 DOI: 10.7860/JCDR/2013/4917.3038]

5 **Dalhoff A**. Global fluoroquinolone resistance epidemiology and implictions for clinical use. *Interdiscip Perspect Infect Dis* 2012; **2012**: 976273 [PMID: 23097666 DOI: 10.1155/2012/976273]

6 **Tonkic A**, Tonkic M, Lehours P, Mégraud F. Epidemiology and diagnosis of Helicobacter pylori infection. *Helicobacter* 2012; **17** Suppl 1: 1-8 [PMID: 22958148 DOI: 10.1111/j.1523-5378.2012.00975.x]

7 **Goh KL**, Chan WK, Shiota S, Yamaoka Y. Epidemiology of Helicobacter pylori infection and public health implications. *Helicobacter* 2011; **16** Suppl 1: 1-9 [PMID: 21896079 DOI: 10.1111/j.1523-5378.2011.00874.x]

8 **Rugge M**, Capelle LG, Cappellesso R, Nitti D, Kuipers EJ. Precancerous lesions in the stomach: from biology to clinical patient management. *Best Pract Res Clin Gastroenterol* 2013; **27**: 205-223 [PMID: 23809241 DOI: 10.1016/j.bpg.2012.12.007]

9 **Shiota S**, Mahachai V, Vilaichone RK, Ratanachu-ek T, Tshering L, Uchida T, Matsunari O, Yamaoka Y. Seroprevalence of Helicobacter pylori infection and gastric mucosal atrophy in Bhutan, a country with a high prevalence of gastric cancer. *J Med Microbiol* 2013; **62**: 1571-1578 [PMID: 23831768]

10 **Uemura N**, Okamoto S, Yamamoto S, Matsumura N, Yamaguchi S, Yamakido M, Taniyama K, Sasaki N, Schlemper RJ. Helicobacter pylori infection and the development of gastric cancer. *N Engl J Med* 2001; **345**: 784-789 [PMID: 11556297]

11 **Zhang C**, Yamada N, Wu YL, Wen M, Matsuhisa T, Matsukura N. Helicobacter pylori infection, glandular atrophy and intestinal metaplasia in superficial gastritis, gastric erosion, erosive gastritis, gastric ulcer and early gastric cancer. *World J Gastroenterol* 2005; **11**: 791-796 [PMID: 15682469]

12 **Kapadia CR**. Gastric atrophy, metaplasia, and dysplasia: a clinical perspective. *J Clin Gastroenterol* 2003; **36**: S29-S36; discussion S61-S62 [PMID: 12702963]

13 **Roesler BM**, Costa SC, Zeitune JM. Eradication Treatment of Helicobacter pylori Infection: Its Importance and Possible Relationship in Preventing the Development of Gastric Cancer. *ISRN Gastroenterol* 2012; **2012**: 935410 [PMID: 22778979 DOI: 10.5402/2012/935410]

14 **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]

15 **Mégraud F**. Current recommendations for Helicobacter pylori therapies in a world of evolving resistance. *Gut Microbes* 2013; **4**: 541-548 [PMID: 23929066]

16 **Megraud F**, Coenen S, Versporten A, Kist M, Lopez-Brea M, Hirschl AM, Andersen LP, Goossens H, Glupczynski Y. 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]

17 **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. Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report. *Gut* 2012; **61**: 646-664 [PMID: 22491499 DOI: 10.1136/gutjnl-2012-302084]

18 **Gatta L**, Vakil N, Leandro G, Di Mario F, Vaira D. Sequential therapy or triple therapy for Helicobacter pylori infection: systematic review and meta-analysis of randomized controlled trials in adults and children. *Am J Gastroenterol* 2009; **104**: 3069-3079; quiz 1080 [PMID: 19844205 DOI: 10.1038/ajg.2009.555]

19 **Luther J**, Higgins PD, Schoenfeld PS, Moayyedi P, Vakil N, Chey WD. Empiric quadruple vs. triple therapy for primary treatment of Helicobacter pylori infection: Systematic review and meta-analysis of efficacy and tolerability. *Am J Gastroenterol* 2010; **105**: 65-73 [PMID: 19755966 DOI: 10.1038/ajg.2009.508]

20 **Jafri NS**, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for Helicobacter pylori infection in patients naive to treatment. *Ann Intern Med* 2008; **148**: 923-931 [PMID: 18490667]

21 **Horvath A**, Dziechciarz P, Szajewska H. Meta-analysis: sequential therapy for Helicobacter pylori eradication in children. *Aliment Pharmacol Ther* 2012; **36**: 534-541 [PMID: 22827718 DOI: 10.1111/j.1365-2036.2012.05229.x]

22 **Oleastro M**, Cabral J, Ramalho PM, Lemos PS, Paixão E, Benoliel J, Santos A, Lopes AI. Primary antibiotic resistance of Helicobacter pylori strains isolated from Portuguese children: a prospective multicentre study over a 10 year period.

*J Antimicrob Chemother* 2011; **66**: 2308-2311 [PMID: 21764826 DOI: 10.1093/jac/dkr293]
23 **Laine L**, Hunt R, El-Zimaity H, Nguyen B, Osato M, Spénard J. Bismuth-based quadruple therapy using a single capsule of bismuth biskalcitrate, metronidazole, and tetracycline given with omeprazole versus omeprazole, amoxicillin, and clarithromycin for eradication of Helicobacter pylori in duodenal ulcer patients: a prospective, randomized, multicenter, North American trial. *Am J Gastroenterol* 2003; **98**: 562-567 [PMID: 12650788]
24 **O'Morain C**, Borody T, Farley A, De Boer WA, Dallaire C, Schuman R, Piotrowski J, Fallone CA, Tytgat G, Mégraud F, Spénard J. Efficacy and safety of single-triple capsules of bismuth biskalcitrate, metronidazole and tetracycline, given with omeprazole, for the eradication of Helicobacter pylori: an international multicentre study. *Aliment Pharmacol Ther* 2003; **17**: 415-420 [PMID: 12562455]
25 **Malfertheiner P**, Bazzoli F, Delchier JC, Celiński K, Giguère M, Rivière M, Mégraud F. Helicobacter pylori eradication with a capsule containing bismuth subcitrate potassium, metronidazole, and tetracycline given with omeprazole versus clarithromycin-based triple therapy: a randomised, open-label, non-inferiority, phase 3 trial. *Lancet* 2011; **377**: 905-913 [PMID: 21345487 DOI: 10.1016/S0140-6736(11)60020-2]
26 **Gisbert JP**, Calvet X, O'Connor A, Mégraud F, O'Morain CA. Sequential therapy for Helicobacter pylori eradication: a critical review. *J Clin Gastroenterol* 2010; **44**: 313-325 [PMID: 20054285 DOI: 10.1097/MCG.0b013e3181c8a1a3]
27 **Vaira D**, Zullo A, Vakil N, Gatta L, Ricci C, Perna F, Hassan C, Bernabucci V, Tampieri A, Morini S. Sequential therapy versus standard triple-drug therapy for Helicobacter pylori eradication: a randomized trial. *Ann Intern Med* 2007; **146**: 556-563 [PMID: 17438314]
28 **Essa AS**, Kramer JR, Graham DY, Treiber G. Meta-analysis: four-drug, three-antibiotic, non-bismuth-containing "concomitant therapy" versus triple therapy for Helicobacter pylori eradication. *Helicobacter* 2009; **14**: 109-118 [PMID: 19298338 DOI: 10.1111/j.1523-5378.2009.00671.x]
29 **Gisbert JP**, Calvet X. Review article: non-bismuth quadruple (concomitant) therapy for eradication of Helicobater pylori. *Aliment Pharmacol Ther* 2011; **34**: 604-617 [PMID: 21745241 DOI: 10.1111/j.1365-2036.2011.04770.x]
30 **Rokkas T**, Sechopoulos P, Robotis I, Margantinis G, Pistiolas D. Cumulative H. pylori eradication rates in clinical practice by adopting first and second-line regimens proposed by the Maastricht III consensus and a third-line empirical regimen. *Am J Gastroenterol* 2009; **104**: 21-25 [PMID: 19098844 DOI: 10.1038/ajg.2008.87]
31 **Lee JM**, Breslin NP, Hyde DK, Buckley MJ, O'Morain CA. Treatment options for Helicobacter pylori infection when proton pump inhibitor-based triple therapy fails in clinical practice. *Aliment Pharmacol Ther* 1999; **13**: 489-496 [PMID: 10215733]
32 **Gisbert JP**, Gisbert JL, Marcos S, Jimenez-Alonso I, Moreno-Otero R, Pajares JM. Empirical rescue therapy after Helicobacter pylori treatment failure: a 10-year single-centre study of 500 patients. *Aliment Pharmacol Ther* 2008; **27**: 346-354 [PMID: 17999716]
33 **Lee BH**, Kim N, Hwang TJ, Lee SH, Park YS, Hwang JH, Kim JW, Jeong SH, Lee DH, Jung HC, Song IS. Bismuth-containing quadruple therapy as second-line treatment for Helicobacter pylori infection: effect of treatment duration and antibiotic resistance on the eradication rate in Korea. *Helicobacter* 2010; **15**: 38-45 [PMID: 20302588 DOI: 10.1111/j.1523-5378.2009.00735.x]
34 **Gisbert JP**, Morena F. Systematic review and meta-analysis: levofloxacin-based rescue regimens after Helicobacter pylori treatment failure. *Aliment Pharmacol Ther* 2006; **23**: 35-44 [PMID: 16393278]
35 **Saad RJ**, Schoenfeld P, Kim HM, Chey WD. Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent Helicobacter pylori infection: a meta-analysis. *Am J Gastroenterol* 2006; **101**: 488-496 [PMID: 16542284]
36 **Fischbach L**, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for Helicobacter pylori. *Aliment Pharmacol Ther* 2007; **26**: 343-357 [PMID: 17635369]
37 **Mégraud F**. H pylori antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 2004; **53**: 1374-1384 [PMID: 15306603]
38 **Debets-Ossenkopp YJ**, Herscheid AJ, Pot RG, Kuipers EJ, Kusters JG, Vandenbroucke-Grauls CM. Prevalence of Helicobacter pylori resistance to metronidazole, clarithromycin, amoxycillin, tetracycline and trovafloxacin in The Netherlands. *J Antimicrob Chemother* 1999; **43**: 511-515 [PMID: 10350380]
39 **Osato MS**, Reddy R, Reddy SG, Penland RL, Malaty HM, Graham DY. Pattern of primary resistance of Helicobacter pylori to metronidazole or clarithromycin in the United States. *Arch Intern Med* 2001; **161**: 1217-1220 [PMID: 11343444]
40 **Prazeres Magalhães P**, De Magalhães Queiroz DM, Campos Barbosa DV, Aguiar Rocha G, Nogueira Mendes E, Santos A, Valle Corrêa PR, Camargos Rocha AM, Martins Teixeira L, Affonso de Oliveira C. Helicobacter pylori primary resistance to metronidazole and clarithromycin in Brazil. *Antimicrob Agents Chemother* 2002; **46**: 2021-2023 [PMID: 12019131]
41 **Mohammadi M**, Doroud D, Massarrat S, Farahvash MJ. Clarithromycin resistance in Iranian H. pylori strains before introduction of clarithromycin. *Helicobacter* 2003; **8**: 80 [PMID: 12603622]
42 **Teo EK**, Fock KM, Ng TM, Khor CJ, Tan AL. Metronidazole-resistant Helicobacter pylori in an urban Asian population. *J Gastroenterol Hepatol* 2000; **15**: 494-497 [PMID: 10847434]
43 **Miyachi H**, Miki I, Aoyama N, Shirasaka D, Matsumoto Y, Toyoda M, Mitani T, Morita Y, Tamura T, Kinoshita S, Okano Y, Kumagai S, Kasuga M. Primary levofloxacin resistance and gyrA/B mutations among Helicobacter pylori in Japan. *Helicobacter* 2006; **11**: 243-249 [PMID: 16882327]
44 **Cattoir V**, Nectoux J, Lascols C, Deforges L, Delchier JC, Megraud F, Soussy CJ, Cambau E. Update on fluoroquinolone resistance in Helicobacter pylori: new mutations leading to resistance and first description of a gyrA polymorphism associated with hypersusceptibility. *Int J Antimicrob Agents* 2007; **29**: 389-396 [PMID: 17303392]
45 **O'Connor A**, Taneike I, Nami A, Fitzgerald N, Ryan B, Breslin N, O'Connor H, McNamara D, Murphy P, O'Morain C. Helicobacter pylori resistance rates for levofloxacin, tetracycline and rifabutin among Irish isolates at a reference centre. *Ir J Med Sci* 2013; **182**: 693-695 [PMID: 23625165]
46 **Carothers JJ**, Bruce MG, Hennessy TW, Bensler M, Morris JM, Reasonover AL, Hurlburt DA, Parkinson AJ, Coleman JM, McMahon BJ. The relationship between previous fluoroquinolone use and levofloxacin resistance in Helicobacter pylori infection. *Clin Infect Dis* 2007; **44**: e5-e8 [PMID: 17173210]
47 **Wellington EM**, Boxall AB, Cross P, Feil EJ, Gaze WH, Hawkey PM, Johnson-Rollings AS, Jones DL, Lee NM, Otten W, Thomas CM, Williams AP. The role of the natural environment in the emergence of antibiotic resistance in gram-negative bacteria. *Lancet Infect Dis* 2013; **13**: 155-165 [PMID: 23347633 DOI: 10.1016/S1473-3099(12)70317-1]
48 **D'Costa VM**, King CE, Kalan L, Morar M, Sung WW, Schwarz C, Froese D, Zazula G, Calmels F, Debruyne R, Golding GB, Poinar HN, Wright GD. Antibiotic resistance is ancient. *Nature* 2011; **477**: 457-461 [PMID: 21881561 DOI: 10.1038/nature10388]
49 **Dalhoff A**. Resistance surveillance studies: a multifaceted problem--the fluoroquinolone example. *Infection* 2012; **40**: 239-262 [PMID: 22460782 DOI: 10.1007/s15010-012-0257-2]
50 **Cammarota G**, Cianci R, Cannizzaro O, Martino A, Fedeli P, Lecca PG, di Caro S, Cesaro P, Branca G, Gasbarrini G. High-dose versus low-dose clarithromycin in 1-week triple

therapy, including rabeprazole and levofloxacin, for Helicobacter pylori eradication. *J Clin Gastroenterol* 2004; **38**: 110-114 [PMID: 14745283]
51 **Nista EC**, Candelli M, Zocco MA, Cremonini F, Ojetti V, Finizio R, Spada C, Cammarota G, Gasbarrini G, Gasbarrini A. Levofloxacin-based triple therapy in first-line treatment for Helicobacter pylori eradication. *Am J Gastroenterol* 2006; **101**: 1985-1990 [PMID: 16968503]
52 **Rispo A**, Di Girolamo E, Cozzolino A, Bozzi R, Morante A, Pasquale L. Levofloxacin in first-line treatment of Helicobacter pylori infection. *Helicobacter* 2007; **12**: 364-365 [PMID: 17669111]
53 **Shah A**, Javid G, Zargar SA, Teli F, Khan BA, Yattoo GN, Gulzar GM, Sodhi JS, Khan MA, Shoukat A, Saif R. Safety and efficacy of 1-week levofloxacin-based triple therapy in first-line treatment for Helicobacter pylori-related peptic ulcer disease in Kashmir, India. *Indian J Gastroenterol* 2013; **32**: 32-36 [PMID: 23224792 DOI: 10.1007/s12664-012-0285-y]
54 **Qian J**, Ye F, Zhang J, Yang YM, Tu HM, Jiang Q, Shang L, Pan XL, Shi RH, Zhang GX. Levofloxacin-containing triple and sequential therapy or standard sequential therapy as the first line treatment for Helicobacter pylori eradication in China. *Helicobacter* 2012; **17**: 478-485 [PMID: 23067317 DOI: 10.1111/j.1523-5378.2012.00993.x]
55 **Gisbert JP**, Fernández-Bermejo M, Molina-Infante J, Pérez-Gallardo B, Prieto-Bermejo AB, Mateos-Rodríguez JM, Robledo-Andrés P, González-García G. First-line triple therapy with levofloxacin for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2007; **26**: 495-500 [PMID: 17635384]
56 **Lee JH**, Hong SP, Kwon CI, Phyun LH, Lee BS, Song HU, Ko KH, Hwang SG, Park PW, Rim KS, Kim S. [The efficacy of levofloxacin based triple therapy for Helicobacter pylori eradication]. *Korean J Gastroenterol* 2006; **48**: 19-24 [PMID: 16861877]
57 **Gisbert JP**, Bermejo MF, Infante JM, Gallardo BP, Bermejo AB, Rodríguez JM, Andrés PR, García GG. Levofloxacin, Amoxicillin, and Omeprazole as first-line triple therapy for Helicobacter pylori eradication. *J Clin Gastroenterol* 2009; **43**: 384-385 [PMID: 19020466 DOI: 10.1097/MCG.0b013e31816d921c]
58 **Zhang ZF**, Zhao G, Liu LN. [Effectiveness and safety of proton pump inhibitor and levofloxacin based first-line triple therapy in the eradication of Helicobacter pylori: a meta-analysis]. *Zhonghua Yixue Zazhi* 2008; **88**: 2722-2725 [PMID: 19080698]
59 **Castro-Fernández M**, Lamas E, Pérez-Pastor A, Pabón M, Aparcero R, Vargas-Romero J, Larraona JL, Romero-Gómez M. Efficacy of triple therapy with a proton pump inhibitor, levofloxacin, and amoxicillin as first-line treatment to eradicate Helicobacter pylori. *Rev Esp Enferm Dig* 2009; **101**: 395-398, 399-402 [PMID: 19630462]
60 **Gisbert JP**, Pérez-Aisa A, Castro-Fernández M, Barrio J, Rodrigo L, Cosme A, Gisbert JL, Marcos S, Moreno-Otero R. Helicobacter pylori first-line treatment and rescue option containing levofloxacin in patients allergic to penicillin. *Dig Liver Dis* 2010; **42**: 287-290 [PMID: 19632166 DOI: 10.1016/j.dld.2009.06.007]
61 **Cuadrado-Lavín A**, Salcines-Caviedes JR, Carrascosa MF, Dierssen-Sotos T, Cobo M, Campos MR, Ayestarán B, Fernández-Pousa A, González-Colominas E, Aresti-Zárate S, Hernández M, Pascual EL. Levofloxacin versus clarithromycin in a 10 day triple therapy regimen for first-line Helicobacter pylori eradication: a single-blind randomized clinical trial. *J Antimicrob Chemother* 2012; **67**: 2254-2259 [PMID: 22687889 DOI: 10.1093/jac/dks209]
62 **Pan X**, Li Y, Qiu Y, Tang Q, Qian B, Yao L, Shi R, Zhang G. Efficacy and tolerability of first-line triple therapy with levofloxacin and amoxicillin plus esomeprazole or rabeprazole for the eradication of Helicobacter pylori infection and the effect of CYP2C19 genotype: a 1-week, randomized, open-label study in Chinese adults. *Clin Ther* 2010; **32**: 2003-2011 [PMID: 21118735 DOI: 10.1016/j.clinthera.2010.11.005]
63 **Chen LW**, Chien RN, Chang JJ, Fang KM, Chang LC. Comparison of the once-daily levofloxacin-containing triple therapy with the twice-daily standard triple therapy for first-line Helicobacter pylori eradication: a prospective randomised study. *Int J Clin Pract* 2010; **64**: 1530-1534 [PMID: 20846200 DOI: 10.1111/j.1742-1241.2010.02482.x]
64 **Assem M**, El Azab G, Rasheed MA, Abdelfatah M, Shastery M. Efficacy and safety of Levofloxacin, Clarithromycin and Esomeprazol as first line triple therapy for Helicobacter pylori eradication in Middle East. Prospective, randomized, blind, comparative, multicenter study. *Eur J Intern Med* 2010; **21**: 310-314 [PMID: 20603042 DOI: 10.1016/j.ejim.2010.05.011]
65 **Erçin CN**, Uygun A, Toros AB, Kantarcioğlu M, Kilciler G, Polat Z, Bağci S. Comparison of 7- and 14-day first-line therapies including levofloxacin in patients with Helicobacter pylori positive non-ulcer dyspepsia. *Turk J Gastroenterol* 2010; **21**: 12-16 [PMID: 20533106]
66 **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]
67 **Romano M**, Cuomo A, Gravina AG, Miranda A, Iovene MR, Tiso A, Sica M, Rocco A, Salerno R, Marmo R, Federico A, Nardone G. Empirical levofloxacin-containing versus clarithromycin-containing sequential therapy for Helicobacter pylori eradication: a randomised trial. *Gut* 2010; **59**: 1465-1470 [PMID: 20947881 DOI: 10.1136/gut.2010.215350]
68 **Federico A**, Nardone G, Gravina AG, Iovene MR, Miranda A, Compare D, Pilloni PA, Rocco A, Ricciardiello L, Marmo R, Loguercio C, Romano M. Efficacy of 5-day levofloxacin-containing concomitant therapy in eradication of Helicobacter pylori infection. *Gastroenterology* 2012; **143**: 55-61.e1; quize e13-14 [PMID: 22484118 DOI: 10.1053/j.gastro.2012.03.043]
69 **Molina-Infante J**, Perez-Gallardo B, Fernandez-Bermejo M, Hernandez-Alonso M, Vinagre G, Dueñas C, Mateos-Rodriguez JM, Gonzalez-Garcia G, Abadia EG, Gisbert JP. Clinical trial: clarithromycin vs. levofloxacin in first-line triple and sequential regimens for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2010; **31**: 1077-1084 [PMID: 20180787 DOI: 10.1111/j.1365-2036.2010.04274.x]
70 **Molina-Infante J**, Gisbert JP. Levofloxacin in first-line eradication regimens for Helicobacter pylori: better test antibiotic susceptibility before treating. *Gut* 2011; **60**: 1605; author reply 1605-1606 [PMID: 21193443 DOI: 10.1136/gut.2010.233015]
71 **Di Caro S**, Fini L, Daoud Y, Grizzi F, Gasbarrini A, De Lorenzo A, Di Renzo L, McCartney S, Bloom S. Levofloxacin/amoxicillin-based schemes vs quadruple therapy for Helicobacter pylori eradication in second-line. *World J Gastroenterol* 2012; **18**: 5669-5678 [PMID: 23155306 DOI: 10.3748/wjg.v18.i40.5669]
72 **Gisbert JP**, Molina-Infante J, Marin AC, Vinagre G, Barrio J, McNicholl AG. Second-line rescue triple therapy with levofloxacin after failure of non-bismuth quadruple "sequential" or "concomitant" treatment to eradicate H. pylori infection. *Scand J Gastroenterol* 2013; **48**: 652-656 [PMID: 23556551 DOI: 10.3109/00365521.2013.786132]
73 **Manfredi M**, Bizzarri B, de'Angelis GL. Helicobacter pylori infection: sequential therapy followed by levofloxacin-containing triple therapy provides a good cumulative eradication rate. *Helicobacter* 2012; **17**: 246-253 [PMID: 22759323 DOI: 10.1111/j.1523-5378.2012.00945.x]
74 **Gisbert JP**, Pérez-Aisa A, Bermejo F, Castro-Fernández M, Almela P, Barrio J, Cosme A, Modolell I, Bory F, Fernández-Bermejo M, Rodrigo L, Ortuño J, Sánchez-Pobre P, Khorrami S, Franco A, Tomas A, Guerra I, Lamas E, Ponce J, Calvet X. Second-line therapy with levofloxacin after failure of treatment to eradicate helicobacter pylori infection: time trends

in a Spanish Multicenter Study of 1000 patients. *J Clin Gastroenterol* 2013; **47**: 130-135 [PMID: 22647827 DOI: 10.1097/MCG.0b013e318254ebdd]

75 **Moon JY**, Kim GH, You HS, Lee BE, Ryu DY, Cheong JH, Jung JI, Jeong JH, Song CS, Song GA. Levofloxacin, Metronidazole, and Lansoprazole Triple Therapy Compared to Quadruple Therapy as a Second-Line Treatment of Helicobacter pylori Infection in Korea. *Gut Liver* 2013; **7**: 406-410 [PMID: 23898379 DOI: 10.5009/gnl.2013.7.4.406]

76 **Calhan T**, Kahraman R, Sahin A, Senates E, Doganay HL, Kanat E, Ozdil K, Sokmen HM. Efficacy of two levofloxacin-containing second-line therapies for Helicobacter pylori: a pilot study. *Helicobacter* 2013; **18**: 378-383 [PMID: 23601026 DOI: 10.1111/hel.12056]

77 **Cammarota G**, Martino A, Pirozzi G, Cianci R, Branca G, Nista EC, Cazzato A, Cannizzaro O, Miele L, Grieco A, Gasbarrini A, Gasbarrini G. High efficacy of 1-week doxycycline- and amoxicillin-based quadruple regimen in a culture-guided, third-line treatment approach for Helicobacter pylori infection. *Aliment Pharmacol Ther* 2004; **19**: 789-795 [PMID: 15043520]

78 **Gisbert JP**, Castro-Fernández M, Bermejo F, Pérez-Aisa A, Ducons J, Fernández-Bermejo M, Bory F, Cosme A, Benito LM, López-Rivas L, Lamas E, Pabón M, Olivares D. Third-line rescue therapy with levofloxacin after two H. pylori treatment failures. *Am J Gastroenterol* 2006; **101**: 243-247 [PMID: 16454825]

79 **Gisbert JP**, Gisbert JL, Marcos S, Moreno-Otero R, Pajares JM. Third-line rescue therapy with levofloxacin is more effective than rifabutin rescue regimen after two Helicobacter pylori treatment failures. *Aliment Pharmacol Ther* 2006; **24**: 1469-1474 [PMID: 17032282]

80 **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]

81 **Gisbert JP**. Letter: third-line rescue therapy with levofloxacin after failure of two treatments to eradicate Helicobacter pylori infection. *Aliment Pharmacol Ther* 2012; **35**: 1484-1485; author reply 1486 [PMID: 22582841 DOI: 10.1111/j.1365-2036.2012.05117.x]

82 **Gisbert JP**. Rescue Therapy for Helicobacter pylori Infection 2012. *Gastroenterol Res Pract* 2012; **2012**: 974594 [PMID: 22536225 DOI: 10.1155/2012/974594]

83 **Gisbert JP**. "Rescue" regimens after Helicobacter pylori treatment failure. *World J Gastroenterol* 2008; **14**: 5385-5402 [PMID: 18803350]

**P- Reviewers**: Aghakhani A, Buzas GM, Leitman M, Martin-Villa JM, Misra SP, Paulssen EJ, Said ZNA, Zullo A
**S- Editor**: Ma YJ **L- Editor**: Wang TQ **E- Editor**: Wang CH

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

ISSN 1007-9327

© 2014 Baishideng Publishing Group Inc. All rights reserved.