original article

Wien Klin Wochenschr (2009) 121: ■–■
DOI 10.1007/s00508-008-1122-2
Printed in Austria

Wiener klinische Wochenschrift
The Middle European Journal of Medicine

Second-line treatment for *Helicobacter* pylori infection based on moxifloxacin triple therapy: a randomized controlled trial

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Received June 3, 2008, accepted after revision November 27, 2008

Moxifloxacin-basierte Triple-Therapie zur second-line Behandlung einer *Helicobacter pylori* Infektion: eine randomisierte, kontrollierte Studie

Zusammenfassung. *Hintergrund der Studie:* Die Standard-Quadruple-Second-Line-Therapie zur Eradikation einer Helicobacter pylori (Hp) Infektion, bestehend aus einem Protonenpumpen-Hemmer (PPI), Bismuth, Metronidazol und Tetracyclin versagt häufig, wobei die Patienten oft eine schlechte Compliance bei dieser Therapie zeigen. Ziel der vorliegenden Studie war es, die Wirksamkeit und Verträglichkeit einer Moxifloxacin-basierten Triple Therapie als alternatives Second-Line-Protokoll zu untersuchen.

Methoden: 160 Patienten, bei denen die initiale Standard PPI-Triple-Therapie zur Eradikation einer Infektion mit Hp versagt hatte, wurden in die Studie aufgenommen. Der ursprüngliche Hp-Status wurde durch den C13-Urea-Atemtest erhoben. Die Patienten wurden zu folgenden 7-Tages Therapieschemata randomisiert: 1) „OMM": Omeprazol 20 mg 2 x tgl., Moxifloxacin 400 mg/Tag, Metronidazol 500 mg 3 x tgl; 2) „OBMT": Omeprazol 20 mg 2 x tgl., kolloidales Bismuth Subzitrat 120 mg 4 x tgl., Metronidazol 500mg 3 x tgl., Tetrazyklin 500 mg 4 x tgl. Eine Woche nach Ende der Therapie wurde durch Pillenzählen die Compliance überprüft und nach Nebenwirkungen gefragt. Der HpStatus wurde durch den C13-Urea-Atemtest 6 Wochen nach Ende der Therapie reevaluiert.

Ergebnisse: Folgende Eradikationsraten wurden erhoben:

Für die mit dem OMM-Schema behandelten Patienten: 73,2% (60/82 – intention to treat) bzw. 78,9% (60/76 per-Protokoll-Analyse).

Für die mit dem OBMT-Schema behandelten Patienten: 53,8% (42/78 intention to treat; p = 0.018 im Vergleich zu OMM) bzw. 64,6% (42/65 per Protokoll, p = 0.088 im Vergleich zu OMM)

Nebenwirkungen und/oder Unverträglichkeit wurden von 12 der 82 OMM Patienten bzw. von 18 der 78 OBMT Patienten angegeben. Die Compliance betrug 92,7% in der OMM Gruppe und 83,3% in der OBMT Gruppe.

Schlussfolgerungen: Die Moxifloxacin-basierte Triple-Therapie ist eine sehr wirksame second-line Behandlung zur Eradikation einer Hp Infektion. Auf Grund der hochgradigen Sicherheit und guten Verträglichkeit stellt dieses Protokoll eine adäquate Alternative zur bisherigen Bismuth-basierten Standard-Therapie dar.

Summary. *Background:* In eradication of *Helicobacter pylori* infection, standard quadruple second-line therapy consisting of proton pump inhibitor (PPI), bismuth, metronidazole and tetracycline often fails and shows poor patient compliance. The aim of our study was to evaluate the efficacy and tolerability of moxifloxacin-based triple therapy as an alternative second-line protocol.

Methods: A total of 160 patients, in whom the initial standard PPI triple therapy had failed to eradicate *H. pylori* infection, were included in the study. The initial *H. pylori* status was assessed using the ^{13}C-urea breath test. Patients were randomized to one of the following 7-day treatment regimens: (1) OMM: omeprazole 20 mg twice a day, moxifloxacin 400 mg/day, metronidazole 500 mg three times a day; and (2) OBMT: omeprazole 20 mg twice a day, colloidal bismuth subcitrate 120 mg four times a day, metronidazole 500 mg three times a day, tetracycline 500 mg four times a day. Patient compliance and adverse events were evaluated one week after completion of therapy. *H. pylori* status was re-assessed with the ^{13}C-urea breath test six weeks after the end of therapy.

Results: The eradication rates were 73.2% (60/82) and 78.9% (60/76) with moxifloxacin-based triple therapy, and 53.8% (42/78) and 64.6% (42/65) with bismuth-

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based quadruple therapy, by intention-to-treat (P = 0.018) and per-protocol (P = 0.088) analyses, respectively. Adverse events/intolerability were described in 12/82 patients in the OMM group and 18/78 patients in the OBMT group. Compliance with treatment was 92.7% in the OMM group and 83.3% in the OBMT group.

Conclusion: Moxifloxacin-based triple therapy is a highly effective second-line eradication treatment in *H. pylori* infection. Because of its high levels of safety and tolerability, this protocol represents an adequate alternative to the standard bismuth-based quadruple therapy.

Key words: *Helicobacter pylori*, moxifloxacin, second-line therapy, quadruple therapy, triple therapy.

Introduction

Helicobacter pylori plays an important role in the pathogenesis of chronic active gastritis, peptic ulcers and gastric malignancies [1]. Its successful eradication is therefore essential and strongly recommended in diagnosed patients and first-degree relatives of patients with gastric cancer. According to current European guidelines, triple therapy consisting of a proton-pump inhibitor (PPI), clarithromycin, and either amoxicillin or metronidazole is recommended as the first-line treatment [2, 3]; nevertheless, the most successful treatment regimens have achieved eradication rates below 95% [4, 5].

Failure of first-line therapy is mostly a consequence of antibiotic resistance [6–8] and the resulting persistent *H. pylori* infection therefore requires a second-line treatment. The European guidelines recommend quadruple therapy consisting of a PPI, bismuth, metronidazole and tetracycline for that purpose [2, 3]; however, in the most recent update of the guidelines antimicrobial susceptibility-based rescue treatment is also recommended in certain cases [3].

Great variability of eradication rates (<60%–100%, mean 75.8%) has been found in studies using a bismuth-based quadruple therapy as rescue treatment [9]. Major causes of such variability included differing prevalences of primarily resistant *H. pylori* strains in different geographic regions, variation in acquisition of secondary resistance ascribed to different initial therapy regimens, and differences in patient compliance with different treatment regimens. Bacterial resistance to metronidazole has a negative impact on the effectiveness of quadruple therapy, but it is possible to overcome this by increasing the duration of treatment [10]. In contrast, resistance to clarithromycin excludes the possibility of its further use, and probably also that of other macrolides, in rescue protocols [10, 11]. Resistance to amoxicillin and tetracycline is generally very low or even absent and is thus clinically insignificant [11]. Poor patient compliance with quadruple therapy is mainly due to the complicated dosing schedules and frequent, though mild, side-effects [10].

Several studies have shown that pretreatment antimicrobial susceptibility testing can significantly improve the eradication of *H. pylori* [12–15]. However, routine susceptibility testing is time-consuming and new methods based on molecular biology [16] are expensive, therefore there is still a need for safe and effective empirical protocols, although it is difficult to establish a generally recognized optimal rescue treatment.

Moxifloxacin is a second-generation fluoroquinolone widely used to treat respiratory and skin infections [17]. It is rapidly absorbed after oral administration, penetrates tissues well, and its half-life of 9–16 hours allows a single daily dose. The drug is well tolerated, with only mild gastrointestinal disturbances as the most common side-effects. Recent reports have shown that moxifloxacin-based triple regimens provide excellent first-line treatment for *H. pylori* eradication [18–20]; such regimens have also achieved high eradication rates as second-line treatment [21, 22] and were significantly superior to the standard bismuth-based quadruple regimen in terms of side-effects and compliance with treatment.

The aim of this study was to compare the efficacy and tolerability of moxifloxacin-based triple therapy and bismuth-based quadruple therapy, as rescue protocols, in a Croatian study population.

Patients, materials and methods

The study was conducted between March 2005 and December 2007 as a single-blinded, randomized comparative clinical trial in parallel groups of patients.

Before recruitment into the study each patient reviewed and signed an informed consent form approved by the local ethics committee. Standards of Good Clinical Practice and The Declaration of Helsinki were followed.

Patients

Consecutive patients of either sex and at least 18 years of age, suffering from non-ulcer dyspepsia and in whom the initial standard PPI triple therapy had failed to eradicate *H. pylori* infection, were included in the study.

Patients with duodenal or gastric ulcers, gastrointestinal bleeding or contraindication to any of the study medication were excluded from the study. Patients using non-steroidal anti-inflammatory drugs, anti-coagulants, corticosteroids or gold-based drugs, and patients who had been recently treated with other antimicrobials were also excluded. Further exclusion criteria were the presence of a severe concurrent disease (cardiorespiratory, renal, hepatic, neurological, pulmonary, metabolic, hematological or endocrine, and suspected or confirmed malignancy), a condition associated with poor compliance (alcohol or drug abuse), pregnancy or breastfeeding.

Study design

The *H. pylori* status was assessed before the study (i.e. six weeks after the end of the first treatment attempt) by means of the ^{13}C-urea breath test (Helicobacter test ^{13}C-urea, INFAI - Institute for biomedical analytics and NMR imaging, Bochum, Germany). If the test was positive, the first-line treatment was considered a failure, and the patients were randomized to one of the following 7-day treatment regimens:

OMM: omeprazole 20 mg twice a day, moxifloxacin 400 mg/day, metronidazole 500 mg three times a day;

OBMT: omeprazole 20 mg twice a day, colloidal bismuth subcitrate 120 mg four times a day, metronidazole 500 mg three times a day, tetracycline 500 mg four times a day.

Table 1. Baseline demographic characteristics of enrolled patients

	OMM	OBMT
Included in ITT analysis (n)	82	78
Age (mean ± SD)	50 ± 12	48 ± 15
Male/female (n)	42/40	41/37
Smokers (n)	28	24

ITT intention-to-treat; *SD* standard deviation; *OMM* omeprazole + moxifloxacin + metronidazole; *OBMT* omeprazole + bismuth + metronidazole + tetracycline.

One week after completion of treatment, drug compliance was evaluated by a physician, both by questioning and by pill counting. Compliance was considered successful if drug intake was >80%. Patients were asked about adverse events at the same interview.

H. pylori status was re-assessed with the ^{13}C-urea breath test six weeks after the end of treatment. Eradication was considered successful if the test was negative.

Diagnostic procedures

Primary diagnosis of *H. pylori* infection in patients suffering from non-ulcer dyspepsia was obtained prior to this study, using methods previously described [20].

The ^{13}C-urea breath test was performed after an overnight fast and collection of a baseline exhaled-breath sample. A glass of orange juice (200 ml) was given to delay gastric emptying; this was followed by 75 mg of ^{13}C-urea dissolved in 30 ml of water administered orally. The second breath sample was collected 30 minutes later. Breath samples were analyzed in an isotope-ratio mass spectrometer (IRMS, Wagner Analysen Technik, Bremen, Germany). An increase of $^{13}CO_2$ exceeding the baseline value by more than 4‰ indicated the presence of *H. pylori*.

Statistics

Efficacy of *H. pylori* eradication was assessed by both intention-to-treat (ITT) and per-protocol (PP) analyses. All patients enrolled in the study were included in ITT evaluation, whereas PP evaluation considered only those patients who complied with the study protocol (>80% of the prescribed drugs taken). All treatment results were expressed as percentages, with 95% confidence intervals provided. The chi-squared test was used to analyze categorical variables (eradication rates, side-effect rates, compliance with therapy), and $P < 0.05$ was considered statistically significant.

Statistica 7 software (Statistica for Windows, Version 7.0, StatSoft Inc., Tulsa, OK, USA) was used for the analyses.

Results

Enrollment of patients

A total of 160 patients were enrolled in the study; of these, 82 were randomized to the OMM group and 78 to the OBMT group. The two groups did not differ in their baseline demographic characteristics (Table 1). All the patients were included in the ITT analysis; 19 patients (6 from the OMM group, 13 from the OBMT group) were excluded from PP analysis for one of the following reasons: loss from follow-up (1 patient from the OMM group, 1 from the OBMT group), discontinuation of treatment due to adverse events (4 patients from the OMM group,

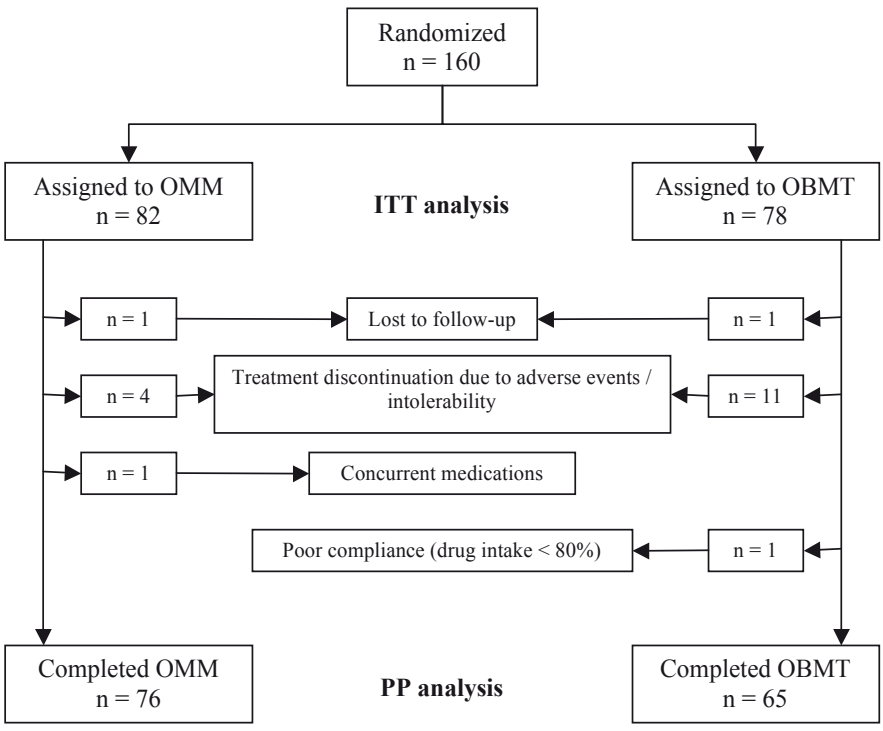

Fig. 1. Flow diagram of the patients enrolled in the study. *ITT* intention-to-treat; PP per-protocol; OMM omeprazole + moxifloxacin + metronidazole; OBMT omeprazole + bismuth + metronidazole + tetracycline

11 from the OBMT group), intake of concurrent disapproved medications (1 patient from the OMM group), or intake of study drugs <80% (1 patient from the OBMT group). Thus, 141 patients (76 in the OMM group and 65 in the OBMT group) completed the protocol and were included in the PP analysis. The allocation of all patients in the study is summarized in Fig. 1.

Helicobacter pylori eradication

The eradication rates of *H. pylori* based on ITT and PP analyses, with their respective 95% confidence intervals, are shown in Table 2. Based on the ITT analysis, the eradication rates were significantly higher in the OMM group than in the OBMT group (χ^2 = 5.65, P = 0.018). Eradication rates were also higher in the OMM group by PP analysis, although statistical significance was not reached (χ^2 = 2.92, P = 0.088).

Adverse events and compliance

Adverse events/intolerability were described in 12/82 patients (14.6%) in the OMM group and 18/78 patients (23.1%) in the OBMT group (Table 3). The rate of side-effects was lower in the OMM group than in the OBMT group, but without statistical significance (χ^2 = 1.36, P = 0.244). Most adverse events were mild-to-moderate in intensity. Fifteen patients discontinued the treatment due to adverse events; of these, four (2 with epigastric discomfort, 2 with diarrhea) were in the OMM group and 11 (9 with epigastric discomfort, 2 with nausea/vomiting) in the OBMT group.

Compliance with treatment (drug intake >80%) was 92.7% (76/82 patients) in the OMM group and 83.3% (65/78 patients) in the OBMT group. Although numerically higher in the former group, there was no significant difference between the two groups (χ^2 = 2.51, P = 0.114).

Discussion

Selection of appropriate second-line therapy for the treatment of *H. pylori* infection is still a challenging issue. According to the European guidelines, bismuth-containing quadruple treatments remain the best choice if available [3]. Whether antibiotic susceptibility testing should be performed after the first eradication failure is still a matter of debate, because although such testing is known to improve eradication rates its high cost means that it is not always easily available. It is generally considered unnecessary in the majority of cases [23, 24]. Safe and effective empirical protocols are therefore still needed. However, the European guidelines [3] also recommend bismuth-containing quadruple treatments as the alternative first-line therapy in populations with a high prevalence of antibiotic resistance. Clearly, if the quadruple protocol fails as first- or second-line therapy, the rescue treatment will have to be based on antimicrobial susceptibility testing.

The failure of bismuth-containing quadruple protocols to eradicate *H. pylori* is associated with bacterial resistance to antibiotics and poor compliance with treatment regimens [10, 12]. Primary resistance to metronidazole varies between 20% and 40% across Europe [25, 11] and in our previous study was found to be 33% in the Croatian population [26]. The considerable side-effects and complicated dosing schedules of quadruple therapies result in poor patient compliance [10]. Although it is possible to overcome metronidazole resistance by increasing the duration of treatment [10], the prolongation of treatment can further decrease patient compliance.

Several regimens that overcome bacterial resistance to standard antibiotics and reduce the incidence of side-effects have been evaluated in recent years. Fluoroquinolone-based schemes have been investigated, as either first-line or rescue therapies. Because of low eradication rates, first-generation fluoroquinolones (norfloxacin, pefloxacin) were not satisfactory [27, 28]; however, second-generation fluoroquinolones (levofloxacin, moxifloxacin) have proved effective in different protocols. Levofloxacin-based triple therapies achieved eradication rates up to 90% in first-line treatments [29, 30]. Eradication rates were even higher with moxifloxacin-based triple regimens [18–20].

Moxifloxacin has several advantages in terms of safety and simplicity of dosing schedules. Moreover, *in*

Table 2. *Helicobacter pylori* eradication rates

	OMM	OBMT	P value
ITT analysis			
Eradication rate	73.2% (60/82)	53.8% (42/78)	0.018
95% CI	64.3–82.1%	43.8–63.8%	
PP analysis			
Eradication rate	78.9% (60/76)	64.6% (42/65)	0.088
95% CI	70.7–87.1%	55.0–74.2%	

ITT intention-to-treat; *PP* per-protocol; *CI* confidence interval; *OMM* omeprazole + moxifloxacin + metronidazole; *OBMT* omeprazole + bismuth + metronidazole + tetracycline.

Table 3. Adverse events/intolerability

	OMM	OBMT
Epigastric discomfort	2	9
Nausea/vomiting	1	4
Diarrhea	2	0
Constipation	0	5
Metallic taste	5	0
Headache	1	0
Pruritus	1	0
Total	12	18

OMM omeprazole + moxifloxacin + metronidazole; *OBMT* omeprazole + bismuth + metronidazole + tetracycline.

vitro studies have shown excellent susceptibility of *H. pylori* strains to this antibiotic [18, 31, 21]. Data on primary resistance to moxifloxacin (5.9%) from our previous study [20] are consistent with these findings.

With this background, we hypothesized that moxifloxacin-based triple therapy could be an equally or more effective and tolerable second-line eradication protocol for *H. pylori*, in comparison with conventional bismuth-based quadruple therapy. We therefore compared *H. pylori* eradication rates, adverse events and patients' compliance with treatment in the two protocols, after failure of first-line eradication. The eradication rates with triple therapy were higher than those with quadruple therapy by both ITT and PP analyses, although the difference was significant only in the ITT analysis, and different dropout rates might further lessen the significance. Adverse events and treatment discontinuation due to adverse events/intolerability were less frequent with the triple therapy than with the quadruple therapy. Compliance with treatment was also better with the triple therapy. The most likely reason for the difference in compliance between the two protocols is the complexity of the dosing scheme: with the triple therapy a patient has to take only nine pills each day (omeprazole 2 x 1, moxifloxacin 1 x 1, metronidazole 3 x 2), whereas with the quadruple therapy 20 pills have to be taken every day (omeprazole 2 x 1, bismuth 4 x 1, metronidazole 3 x 2, tetracycline 4 x 2).

Overall, our results suggest that moxifloxacin-based triple therapy is at least equally effective and is better tolerated as a second-line eradication treatment of *H. pylori* infection, in comparison with the standard bismuth-based quadruple therapy. Our findings are in complete agreement with those of a study in Korea [21], where moxifloxacin-based triple therapy (moxifloxacin, esomeprazole, amoxicillin) was compared with bismuth-based quadruple therapy (esomeprazole, tripotassium dicitrate bismuthate, metronidazole, tetracycline) as 7-day second-line protocols. The triple therapy in that study [21] included amoxicillin as the second antibiotic, because of the high resistance rate of *H. pylori* to metronidazole in Korea. In contrast, our triple therapy (and the quadruple therapy) included metronidazole, thus the final difference in eradication rates between the two protocols can be ascribed solely to the effect of moxifloxacin.

One limitation of our study was the absence of evaluation of antibiotic resistance and investigation of its relation to eradication rates. The low primary resistance to moxifloxacin found in our previous study [20] indicates that, at least for the time being, satisfactory results can be expected with moxifloxacin-based treatments. However, extensive use of moxifloxacin for respiratory and skin infections, as well as in eradication failure in *H. pylori* infections, can potentially increase the resistance of the bacterium. It will therefore be necessary to monitor primary and secondary *H. pylori* resistance to moxifloxacin in the future. A second limitation of the study was the use of a single laboratory test to assess eradication, which could have produced false positive results. However, with the known sensitivity and specificity of the ^{13}C-urea breath test we considered the risk of overestimation acceptable.

In conclusion, 7-day moxifloxacin-based triple therapy (omeprazole, moxifloxacin, metronidazole) is a highly effective second-line eradication treatment for *H. pylori* infection. The high safety and tolerability of this protocol make it an adequate alternative to the standard bismuth-based quadruple therapy. Further studies that include data on antibiotic resistance are needed before final recommendations can be made.

References

1. Suerbaum S, Michetti P (2002) *Helicobacter pylori* infection. N Engl J Med 347: 1175–1186
2. Malfertheiner P, Megraud F, O'Morain C, Hungin AP, Jones R, Axon A, et al (2002) Current concepts in the management of *Helicobacter pylori* infection – The Maastricht 2-2000 Consensus Report. Aliment Pharmacol Ther 16: 167–180
3. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al (2007) Current concepts in the management of *Helicobacter pylori* infection: The Maastricht III Consensus Report. Gut 56: 772–781
4. Bazzoli F, Zagari M, Pozzato P, Varoli O, Fossi S, Ricciardiello L, et al (1998) Evaluation of short-term low-dose triple therapy for the eradication of *Helicobacter pylori* by factorial design in a randomized, double-blind, controlled study. Aliment Pharmacol Ther 12: 439–445
5. Vergara M, Vallve M, Gisbert JP, Calvet X (2003) Meta-analysis: comparative efficacy of different proton-pump inhibitors in triple therapy for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 18: 647–654
6. Graham DY (1998) Antibiotic resistance in *Helicobacter pylori:* implications for therapy. Gastroenterology 115: 1272–1277
7. Megraud F, Doermann HP (1998) Clinical relevance of resistant strains of *Helicobacter pylori:* a review of current data. Gut 43 [Suppl 1]: S61–S65
8. Ducons JA, Santolaria S, Guirao R, Ferrero M, Montoro M, Gomollon F (1999) Impact of clarithromycin resistance on the effectiveness of a regimen for *Helicobacter pylori*: a prospective study of one week lansoprazole, amoxicillin and clarithromycin in active peptic ulcer. Aliment Pharmacol Ther 13: 775–780
9. Hojo M, Miwa H, Nagahara A, Sato N (2001) Pooled analysis on the efficacy of the second-line treatment regimens for *Helicobacter pylori* infection. Scand J Gastroenterol 36: 690–700
10. Megraud F, Lamouliatte H (2003) Review article: the treatment of refractory *Helicobacter pylori* infection. Aliment Pharmacol Ther 17: 1333–1343
11. Megraud F (2004) *H. pylori* antibiotic resistance: prevalence, importance, and advances in testing. Gut 53: 1374–1384
12. Houben MHMG, van de Beek D, Hensen EF, de Craen AJM, Rauws EAJ, Tytgat GNJ (1999) A systematic review of *Helicobacter pylori* eradication therapy – the impact of antimicrobial resistance on eradication rates. Aliment Pharmacol Ther 13: 1047–1055
13. Toracchio S, Cellini L, Di Campli E, Cappello G, Malatesta mg, Ferri A, et al (2000) Role of antimicrobial susceptibility testing on efficacy of triple therapy in *Helicobacter pylori* eradication. Aliment Pharmacol Ther 14: 1639–1643
14. Romano M, Marmo R, Cuomo A, De Simone T, Mucherino C, Iovene MR, et al (2003) Pretreatment antimicrobial susceptibility testing is cost saving in the eradication of

Helicobacter pylori. Clin Gastroenterol Hepatol 1: 273–278
15. Lamouliatte H, Megraud F, Delchier JC, Bretagne JF, Courillon-Mallet A, de Korwin JD, et al (2003) Second-line treatment for failure to eradicate *Helicobacter pylori:* a randomized trial comparing four treatment strategies. Aliment Pharmacol Ther 18: 791–797
16. Oleastro M, Menard A, Santos A, Lamouliatte H, Monteiro L, Barthelemy P, et al (2003) Real-time PCR assay for rapid and accurate detection of point mutations conferring resistance to clarithromycin in *Helicobacter pylori*. J Clin Microbiol 41: 397–402
17. Keating GM, Scott LJ (2004) Moxifloxacin: a review of its use in the management of bacterial infections. Drugs 64: 2347–2377
18. Di Caro S, Ojetti V, Zocco MA, Cremonini F, Bartolozzi F, Candelli M, et al (2002) Mono, dual and triple moxifloxacin-based therapies for *Helicobacter pylori* eradication. Aliment Pharmacol Ther 16: 527–532
19. Nista EC, Candelli M, Zocco MA, Cazzato IA, Cremonini F, Ojetti V, et al (2005) Moxifloxacin-based strategies for first-line treatment of *Helicobacter pylori* infection. Aliment Pharmacol Ther 21: 1241–1247
20. Bago P, Vcev A, Tomic M, Rožankovic M, Marušić M, Bago J (2007) High eradication rate of *H. Pylori* with moxifloxacin-based treatment: a randomized controlled trial. Wien Klin Wochenschr 119: 372–378
21. Cheon JH, Kim N, Lee DH, Kim JM, Kim JS, Jung HC, et al (2006) Efficacy of moxifloxacin-based triple therapy as second-line treatment for *Helicobacter pylori* infection. Helicobacter 11: 46–51
22. Kang JM, Kim N, Lee DH, Park YS, Kim YR, Kim JS, et al (2007) Second-line treatment for *Helicobacter pylori* infection: 10-day moxifloxacin-based triple therapy versus 2-week quadruple therapy. Helicobacter 12: 623–628
23. Gisbert JP, Pajares JM (2002) Review article: *Helicobacter pylori* "rescue" regimen when proton pump inhibitor-based triple therapies fail. Aliment Pharmacol Ther 16: 1047–1057
24. Gisbert JP, Gisbert JL, Marcos S, Olivares D, Pajares JM (2008) Empirical rescue therapy after *Helicobacter pylori* treatment failure: a 10-year single-centre study of 500 patients. Aliment Pharmacol Ther 22: 1041–1046
25. Teare L, Peters T, Saverymuttu S, Owen R, Tiwari I (1999) Antibiotic resistance in *Helicobacter pylori*. Lancet 353: 242
26. Bago J, Belošić Halle Ž, Strinić D, Kućišec N, Jandrić D, et al (2002) The impact of primary antibiotic resistance on the efficacy of ranitidine bismuth citrate vs. omeprazole-based one-week triple therapies in *H. Pylori* eradication – a randomized controlled trial. Wien Klin Wochenschr 114: 448–453
27. Gupta VK, Dhar A, Srinivasan S, Rattan A, Sharma MP (1997) Eradication of *H. pylori* in a developing country: comparison of lansoprazole versus omeprazole with norfloxacin, in a dual-therapy study. Am J Gastroenterol 92: 1140–1142
28. Ahuja V, Dhar A, Bal C, Sharma MP (1998) Lansoprazole and secnidazole with clarithromycin, amoxycillin or pefloxacin in the eradication of *Helicobacter pylori* in a developing country. Aliment Pharmacol Ther 12: 551–555
29. Cammarota G, Cianci R, Cannizzaro O, Cuoco L, Pirozzi G, Gasbarrini A, et al (2000) Efficacy of two one-week rabeprazole/levofloxacin-based triple therapies for *Helicobacter pylori* infection. Aliment Pharmacol Ther 14: 1339–1343
30. Di Caro S, Zocco MA, Cremonini F, Candelli M, Nista EC, Bartolozzi F, et al (2002) Levofloxacin based regimens for the eradication of *Helicobacter pylori*. Eur J Gastroenterol Hepatol 14: 1309–1312
31. Kim JM, Kim JS, Kim N, Jung HC, Song IS (2005) Distribution of fluoroquinolone MICs in *Helicobacter pylori* strains from Korean patients. J Antimicrob Chemother 56: 965–967