

# Second-line and Rescue Therapies for *Helicobacter pylori* Eradication in Clinical Practice

Angelo Zullo<sup>1</sup>, Vincenzo De Francesco<sup>2</sup>, Gianpiero Manes<sup>3</sup>, Giuseppe Scaccianoce<sup>4</sup>, Francesca Cristofari<sup>1</sup>, Cesare Hassan<sup>1</sup>

1) Gastroenterology and Digestive Endoscopy, "Nuovo Regina Margherita" Hospital, Rome; 2) Gastroenterology Unit, "Riuniti" Hospital, Foggia; 3) Department of Gastroenterology, University Hospital "L. Sacco", Milan; 4) Digestive Endoscopy, "Umberto I" Hospital, Altamura, Bari, Italy

## Abstract

**Background & Aims.** A levofloxacin-based triple therapy and a rifabutin-based regimen are advised as second-line and rescue therapies in the current Italian guidelines for *H. pylori* eradication. However, no data are available for the efficacy of these treatments in clinical practice. **Methods.** A total of 86 consecutive patients who failed a standard, first-line, triple therapy for *H. pylori* infection were treated with a 10-day triple therapy including omeprazole 20 mg, amoxicillin 1 g, and levofloxacin 250 mg or 500 mg, each given twice daily. Eradication failure patients received a 10-day rescue therapy with omeprazole 20 mg, amoxicillin 1 g, and rifabutin 150 mg, each given twice daily. A further therapeutic attempt was performed with a 14-day, high-dose dual therapy (esomeprazole 40 mg and amoxicillin 1 g, each thrice daily). **Results.** Following the second-line therapy, *H. pylori* infection was cured in 76.4% (95% CI = 67.8-85.0) and 79.5% (95% CI = 70.8-88.2) at intention-to-treat (ITT) and per-protocol (PP) analysis, respectively. After the rescue therapy, bacterial eradication was achieved in 84.6% (95% CI = 65-100). Two patients with persistent infection were successfully cured with the high-dose dual therapy. **Conclusion.** The efficacy of levofloxacin-based second-line therapy seems to be decreasing, whilst rescue therapy with rifabutin would appear a valid third-line therapy, and a high-dose dual therapy may be used as a further rescue therapy.

## Keywords

*Helicobacter pylori* – levofloxacin – rifabutin – rescue therapy.

## Introduction

*Helicobacter pylori* infection is a widespread disease causing a significant morbidity and mortality, thus requiring an appropriate therapeutic approach [1, 2]. Indeed, such a bacterium is recognised as an important factor involved in non-ulcer dyspepsia, peptic ulcer disease, and gastric MALT-lymphoma [2]. In addition, it is classified as a definite carcinogenetic factor for gastric cancer development [3]. *H. pylori* treatment still remains a challenge for physicians, no current first-line therapies being able to cure the infection in all treated patients. A triple therapy, comprising a proton pump inhibitor, clarithromycin and amoxicillin or metronidazole, is the first-line treatment suggested in the International guidelines [4-7]. However, two very large meta-analysis studies showed that standard 7-14 days triple therapies fail to eradicate *H. pylori* infection in up to 20-25% of patients [8, 9]. Therefore, several patients require further treatment to cure the infection in clinical practice. Both US and European guidelines suggest the use of a quadruple therapy for these patients [4, 5], whilst a 10-day levofloxacin-based triple therapy is endorsed by the Italian guidelines [6]. Indeed, meta-analysis studies found higher eradication rates following a levofloxacin-based therapy as compared to the quadruple regimen [10, 11], high efficacy of such a therapy being also observed as third-line regimen [12, 13]. Nevertheless, some recent studies would suggest that the efficacy of levofloxacin-based triple re-treatment is decreasing [14-16], most likely due to an increased primary levofloxacin resistance [17]. In the event of therapy failure after the second-line regimen, a rescue therapy should be tailored according to the antibiotic susceptibility tested at culture [5] or by empirically using a rifabutin-based triple therapy [6]. However, data on the efficacy of a rifabutin-based triple rescue therapy are still scanty and conflicting.

The present study aimed to assess in clinical practice the efficacy of a second-line levofloxacin-based triple therapy and that of a rifabutin-based rescue therapy for *H. pylori* eradication, as suggested in the current Italian guidelines [6].

Received: 27.11.2009 Accepted: 25.03.2010

J Gastrointest Liver Dis

June 2010 Vol.19 No 2, 131-134

Address for correspondence:

Angelo Zullo  
Ospedale Nuovo Regina Margherita  
Gastroenterologia ed Endoscopia  
Digestiva  
Rome, Italy  
Email: zullo66@yahoo.it

## Methods

### Patients

Consecutive outpatients who failed a standard, first-line, triple therapy (proton pump inhibitor, clarithromycin and amoxicillin) for *H. pylori* infection were invited to participate in the present study. Consenting patients were enrolled if >18 years old, irrespective of the initial endoscopic and histological diagnosis (non-ulcer dyspepsia, peptic ulcer, gastric MALT-lymphoma). Pregnant women, those with known antibiotic allergy, and those with severe comorbidity (hepatic impairment, kidney failure, etc.) were not enrolled. Assessment of *H. pylori* infection was performed by using a standard <sup>13</sup>C urea breath test (UBT) at least 4 weeks following therapy.

### Therapies

As a second-line therapy, all patients received a 10-day triple therapy with omeprazole 20 mg, amoxycillin 1 g, and either levofloxacin 250 mg or 500 mg, each given twice daily. Proton pump inhibitor was prescribed before breakfast and dinner, whereas all antibiotics after these meals. Patients who failed *H. pylori* eradication were invited to take a 10-day rescue therapy with omeprazole 20 mg, amoxycillin 1 g, and rifabutin 150 mg, each given twice daily. A high-dose, 14-day dual therapy with esomeprazole 40 mg and amoxicillin, each thrice daily, was offered to those patients who failed the rifabutin-based rescue therapy. Such a high-dose dual therapy has been proven to be equally effective as the rifabutin-based regimen as third-line therapy [18]. Patients were asked to return at the end of the treatment to assess the compliance with therapy, and to estimate side-effect incidence. Compliance was defined as consumption of >90% of the prescribed drugs by personal interview at the follow-up visit at the end of the therapy, and side-effects were evaluated using a structured questionnaire. At the end of the rescue therapy with rifabutin, a blood cells count was performed in all patients. All patients gave their informed consent to participate in each study phase.

### Statistics

The eradication rates and their 95% confidence intervals (CI) at both intention-to-treat (ITT) and per protocol (PP) analyses were calculated for each treatment regimen. For all other variables, Fisher's exact test, and t-test were used as appropriate, and p values less than 0.05 were considered significant. The difference between the proportions eradicated was estimated for each centre. Before pooling these estimates, a Fisher's exact test was applied to investigate heterogeneity between the differences.

## Results

### Eradication rates

A total of 86 patients who failed a standard, first-line triple therapy for *H. pylori* were recruited. Following the second-line therapy, 1 patient stopped the treatment within 4 days due to side-effects, whilst 2 patients did not return

for UBT control. Therefore, the final PP population for the second-line therapy consisted of 83 patients. Demographic and clinical characteristics of these patients are provided in Table I.

**Table I.** Demographic and clinical characteristics of patients before first-line therapy

	Patients = 83
Age (mean±SD); years	56.4 ±11.8
Male/Female	39/44
Smoking	23
Family history of gastric cancer	6
Chronic NSAIDs use*	12
Duodenal ulcer	5
Gastric ulcer	3
Non-ulcer dyspepsia	74
MALT-lymphoma	1

\*NSAIDs: non steroidal anti-inflammatory drugs.

Overall, *H. pylori* infection was cured in 66 cases, accounting for an eradication rate of 76.4% (66 of 86; 95% CI = 67.8-85) and 79.5% (66 of 83; 95% CI = 70.8-88.2) at ITT and PP analysis, respectively. No significant differences emerged at ITT analysis between patients who received levofloxacin 500 mg or 250 mg twice daily, the cure rate being 76.9% (30 of 39; 95% CI = 63.7-90.1) and 76.6% (36 of 47; 95% CI = 64.5-88.7), respectively. Thirteen out of 17 eradication failure patients accepted the rifabutin-based rescue therapy (Table II), while 4 patients (all with non-ulcer dyspepsia) refused any further therapy. *H. pylori* eradication was achieved in 11 cases, accounting for an eradication rate of 84.6% (95% CI = 65-100) at both ITT and PP analysis. The remaining 2 patients who failed the rifabutin-based therapy were successfully cured following the high-dose, esomeprazole-amoxycillin dual therapy. Overall, *H. pylori* eradication was achieved in all those patients who accepted to follow the three therapy regimens proposed successively.

**Table II.** Clinical characteristics of patients who took rifabutin-based therapy.

	Patients = 13
Age (mean±SD); years	58.3 ±16.9
Male/Female	6/7
Gastric ulcer	1
MALT-lymphoma	1
Family history of gastric cancer	2
Chronic NSAIDs use*	5
Non-ulcer dyspepsia	4

\*NSAIDs: non steroidal anti-inflammatory drugs.

### Compliance and side-effects

Compliance to the second-line, levofloxacin-based therapy was good in all but one 77-year old male patient who stopped treatment after 4 days due to tendinitis. Overall, 10 (12%) patients complained of side-effects, including mild diarrhoea (4 cases), glossitis (2 cases), vaginal candidiasis

(2 cases), and tendonitis (2 cases). All side-effects were self-limiting, whilst vaginal candidiasis was cured with specific therapy. Compliance to the rescue, rifabutin-based therapy was good in all patients, and no patient interrupted treatment. Overall, 2 (15.4%) patients complained of mild, self-limiting diarrhoea. No significant modification in blood cell count was observed at the end of therapy. Both patients were cured following the high-dose dual therapy and no side-effects were reported.

## Discussion

Therapy for *H. pylori* infection still remains a challenge for physicians, no single therapy regimen being able to cure the infection in all treated patients [1]. Moreover, there is evidence that the efficacy of standard, first-line therapies is decreasing and, consequently, an increasing number of patients require a second or even further therapies in clinical practice. A quadruple regimen is currently advised in the current European guidelines as a second-line therapy in the eradication failure patients [5]. However, this is a quite complex regimen requiring a high number of tablets with possible compliance concerns. Moreover, bismuth salts comprised in this therapy are no longer available in several European countries, including Italy, due to possible toxic effects [19]. In addition, two large meta-analyses found a higher eradication rate of a levofloxacin-based triple second-line therapy as compared to the quadruple regimen [10, 11]. Therefore, current Italian guidelines suggest the use of a 10-day, levofloxacin-amoxicillin triple therapy [6]. The present study found a 76.4% eradication rate following this treatment. Surprisingly, such a success rate would appear no higher than the 83.3% we achieved using the same regimen as third-line regimen in 2003 [12], and similar to 72.6% we observed as second-line regimen in 2007 [15]. Therefore, our data have failed to confirm the 85–90% eradication rate achieved in a recent study following the same 10-day levofloxacin-based regimen [16]. Of note, a cure rate as low as 69.9% has been recently observed in Taiwan [14]. Most likely, the decreasing efficacy of levofloxacin-based re-treatments depends on the increasing levofloxacin resistance. Indeed, we recently observed a primary levofloxacin resistance prevalence as high as 19.1% in Italy, a prevalence rate even higher than that regarding clarithromycin resistance (16.9%) [17].

A 10-day rifabutin-amoxicillin based triple therapy is endorsed in the current Italian guideline as a rescue therapy [6]. By using such a therapy, we achieved *H. pylori* eradication in nearly 85% of patients, confirming data of previous Italian and Australian studies [20, 21], whilst lower success rates was observed in Spain and Ireland [22–24]. Of note, such a therapy regimen given for 7 days was effective in 74% of eradication failure patients harbouring both clarithromycin and metronidazole resistance [18]. This study also estimated a primary rifabutin resistance to a value as low as 0.7% in Germany [18]. However, the onset of myelotoxicity has been observed following rifabutin, suggesting that a caution should be used in such therapeutic

approach [25]. In addition, rifabutin is an antimycobacterial drug particularly useful for tuberculosis treatment in AIDS patients, and it deserves a careful use in order to avoid bacterial resistance.

To date, no therapy regimen has been established for those patients who failed the rescue therapy. Bacterial culture with antibiotic susceptibility testing would appear a logical approach in these patients. However, the actual role of bacterial culture in clinical practice has been questioned [26]. Indeed, *H. pylori* is a fastidious bacterium to be isolated in culture, and the presence of bacterial resistance to different antibiotics following two or more failed therapies is highly predictable without culture. In addition, the sensitivity in vitro towards a certain antibiotic does not accurately predict the efficacy in vivo. Although conflicting data on its use as first-line therapy have been reported [27, 28], a high-dose (omeprazole 40 mg and amoxicillin 1 g thrice daily) has been recently proposed as a rescue therapy. Indeed, a crossover study found that such a therapy regimen was effective in 80% of 10 patients who already failed a rifabutin-based rescue therapy [18]. In the present study, this high-dose dual therapy was effective in both treated patients. Further studies are required to assess if such a therapeutic regimen could be used as a rescue therapy instead of the more potentially toxic rifabutin-based regimen, which should be probably reserved to selected cases in order to avoid the extent of resistance in other relevant species such as mycobacteria.

**In conclusion**, the efficacy of levofloxacin-based second-line therapy seems to be decreasing, whilst the rescue therapy with rifabutin would appear as valid third-line therapy, and a high-dose, dual therapy may be used as a further rescue therapy. All eradication failure patients who accepted the successive therapy were finally cured.

## Conflicts of interest

No funding required. No conflict of interest.

## References

1. Selgrad M, Kandulski A, Malfertheiner P. Helicobacter pylori: diagnosis and treatment. *Curr Opin Gastroenterol* 2009; 25: 549–556.
2. Cover TL, Blaser MJ. Helicobacter pylori in health and disease. *Gastroenterology* 2009; 136: 1863–1873.
3. Suerbaum S, Michetti P. Helicobacter pylori infection. *N Engl J Med* 2002; 347: 1175–1186.
4. Chey WD, Wong BC; Practice Parameters Committee of the American College of Gastroenterology. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol* 2007; 102: 1808–1825.
5. Malfertheiner P, Megraud F, O’Morain C, et al. Current concepts in the management of Helicobacter pylori infection: The Maastricht III Consensus Report. *Gut* 2007; 56: 772–781.
6. Caselli M, Zullo A, Maconi G, et al. “Cervia II Working Group Report 2006”: guidelines on diagnosis and treatment of Helicobacter pylori infection in Italy. *Dig Liver Dis* 2007; 39: 782–789.
7. Fock KM, Katelaris P, Sugano K, et al. Second Asia–Pacific Consensus Guidelines for Helicobacter pylori infection. *J*

- Gastroenterol Hepatol 2009; 24: 1587–1600.
8. Fuccio L, Minardi ME, Zagari RM, Grilli D, Magrini N, Bazzoli F. Meta-analysis: duration of first-line proton-pump inhibitor based triple therapy for *Helicobacter pylori* eradication. *Ann Intern Med* 2007; 147: 553–562.
  9. 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.
  10. 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.
  11. 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.
  12. Zullo A, Hassan C, De Francesco V, et al. A third-line levofloxacin-based rescue therapy for *Helicobacter pylori* eradication. *Dig Liver Dis* 2003; 35: 232–236.
  13. Gatta L, Zullo A, Perna F, Ricci C, et al. A 10-day levofloxacin-based triple therapy in patients who have failed two eradication courses. *Aliment Pharmacol Ther* 2005; 22: 45–49.
  14. Kuo CH, Hu HM, Kuo FC, et al. Efficacy of levofloxacin-based rescue therapy for *Helicobacter pylori* infection after standard triple therapy: a randomized controlled trial. *J Antimicrob Chemother* 2009; 63: 1017–1024.
  15. Perna F, Zullo A, Ricci C, Hassan C, Morini S, Vaira D. Levofloxacin-based triple therapy for *Helicobacter pylori* re-treatment: role of bacterial resistance. *Dig Liver Dis* 2007; 39: 1001–1005.
  16. Di Caro S, Franceschi F, Mariani A, et al. Second-line levofloxacin-based triple schemes for *Helicobacter pylori* eradication. *Dig Liver Dis* 2009; 41: 480–485.
  17. Zullo A, Perna F, Hassan C, et al. Primary antibiotic resistance in *Helicobacter pylori* strains isolated in northern and central Italy. *Aliment Pharmacol Ther* 2007; 25: 1429–1434.
  18. Miehke S, Hansky K, Schneider-Brachert W, et al. Randomized trial of rifabutin-based triple therapy and high-dose dual therapy for rescue treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Aliment Pharmacol Ther* 2006; 24: 395–403.
  19. Phillips RH, Whitehead MW, Doig LA, et al. Is eradication of *Helicobacter pylori* with colloidal bismuth subcitrate quadruple therapy safe? *Helicobacter* 2001; 6: 151–156.
  20. Perri F, Festa V, Clemente R, et al. Randomised study of two “rescue” therapies for *Helicobacter pylori*-infected patients after failure of standard triple therapies. *Am J Gastroenterol* 2001; 96: 58–62.
  21. Van der Poorten D, Katelaris PH. The effectiveness of rifabutin triple therapy for patients with difficult-to-eradicate *Helicobacter pylori* in clinical practice. *Aliment Pharmacol Ther* 2007; 26: 1537–1542.
  22. 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.
  23. González Carro P, Pérez Roldán F, De Pedro Esteban A, et al. Efficacy of rifabutin-based triple therapy in *Helicobacter pylori* infected patients after two standard treatments. *J Gastroenterol Hepatol* 2007; 22: 60–63.
  24. Qasim A, Sebastian S, Thornton O, et al. Rifabutin- and furazolidone-based *Helicobacter pylori* eradication therapies after failure of standard first- and second-line eradication attempts in dyspepsia patients. *Aliment Pharmacol Ther* 2005; 21: 91–96.
  25. Canducci F, Ojetti V, Pola P, Gasbarrini G, Gasbarrini A. Rifabutin-based *Helicobacter pylori* eradication ‘rescue therapy’. *Aliment Pharmacol Ther* 2001; 15: 143.
  26. Zullo A, Hassan C, Lorenzetti R, Winn S, Morini S. A clinical practice viewpoint: to culture or not to culture *Helicobacter pylori*? *Dig Liver Dis* 2003; 35: 357361.
  27. Malaty H, el-Zimaity HM, Genta RM, Cole RA, Graham DY. High-dose proton pump inhibitor plus amoxicillin for the treatment or retreatment of *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 1996; 10: 1001–1004.
  28. Delchier JC, Elamine I, Goldfain D, Chaussade S, Barthelemy P, Idström JP. Omeprazole-amoxicillin versus omeprazole-amoxicillin-clarithromycin in the eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 1996; 10: 263–268.