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*World J Gastroenterol* 2022 December 7; 28(45): 6314-6432



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Ying-Yi Yuan; Production Department Director: Xiang Li; Editorial Office Director: Jia-Ru Fan.

**NAME OF JOURNAL**

*World Journal of Gastroenterology*

**ISSN**

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

**LAUNCH DATE**

October 1, 1995

**FREQUENCY**

Weekly

**EDITORS-IN-CHIEF**

Andrzej S Tarnawski

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

**PUBLICATION DATE**

December 7, 2022

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<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## Rifabutin as salvage therapy for *Helicobacter pylori* eradication: Cornerstones and novelties

Antonia Valeria Borraccino, Francesca Celiberto, Maria Pricci, Bruna Girardi, Andrea Iannone, Maria Rendina, Enzo Ierardi, Alfredo Di Leo, Giuseppe Losurdo

**Specialty type:** Gastroenterology and hepatology

**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind

**Peer-review report's scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Chen LW, Taiwan; Jing D, China

**Received:** September 17, 2022

**Peer-review started:** September 17, 2022

**First decision:** October 19, 2022

**Revised:** October 25, 2022

**Accepted:** November 17, 2022

**Article in press:** November 17, 2022

**Published online:** December 7, 2022



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### Abstract

When several *Helicobacter pylori* eradication treatments fail, guidelines recommend a cultured guided approach; however, culture is not widely available. Therefore, a rifabutin based regimen could be the best solution. Rifabutin indeed shows a low rate of antibiotic resistance. Rifabutin is generally used in combination with amoxicillin in a triple therapy, with eradication rates about 80% in third-line regimens. The ideal duration of this therapy should range between 10 and 12 d. Combinations with antibiotics other than amoxicillin have demonstrated even better results, such as vonoprazan, which is a type of novel acid suppressor drug. Finally, a new formulation of triple therapy in a single capsule is under investigation, which is a field that deserves further investigation. Some notes of caution about rifabutin should be mentioned. This drug is used to treat tuberculosis or atypical mycobacteria; therefore, before starting a rifabutin-based eradication regimen, *Mycobacterium tuberculosis* infection should be thoroughly tested, since its use could promote the development of antibiotic resistance, thus affecting its effectiveness against Koch's bacillus. Additionally, some serious side effects must be evaluated before starting any rifabutin-based therapy. Adverse effects include fever, nausea, vomiting and bone marrow suppression. For this reason, full blood count surveillance is required.

**Key Words:** *Helicobacter pylori*; Eradication; Rifabutin; Antibiotic resistance; Rescue therapy; Treatment

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**Core Tip:** Rifabutin is an antibiotic that is commonly used to treat tuberculosis or atypical mycobacteria. However, it shows antimicrobial effect against *Helicobacter pylori* as well. It is indicated when multiple eradication treatments have failed. In this review, we summarized current evidence about traditional triple therapy containing amoxicillin and rifabutin as salvage therapy, based on the most recent meta-analyses. Furthermore, other novelties regarding rifabutin based regimens have been mentioned.

**Citation:** Borraccino AV, Celiberto F, Pricci M, Girardi B, Iannone A, Rendina M, Ierardi E, Di Leo A, Losurdo G. Rifabutin as salvage therapy for *Helicobacter pylori* eradication: Cornerstones and novelties. *World J Gastroenterol* 2022; 28(45): 6356-6362

**URL:** <https://www.wjgnet.com/1007-9327/full/v28/i45/6356.htm>

**DOI:** <https://dx.doi.org/10.3748/wjg.v28.i45.6356>

## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a widespread cause of infectious disease, mainly causing chronic gastritis, peptic ulcer disease, but also causing gastric cancer or mucosa-associated lymphoid tissue lymphoma [1]. In Italy, it is estimated that more than one-third of the adult population is infected by this [2]. The Kyoto consensus report on gastritis appointed *H. pylori* gastritis as a nosologically distinct entity in the new International Classification of Disease 11<sup>th</sup> Revision; this entails that all *H. pylori*-infected patients must be treated, regardless of clinical manifestations [3].

The diagnosis of *H. pylori* infection is understood by performing different tests; however, the most appropriate one to achieve an accurate diagnosis is still being debated. On the other hand, an increase of *H. pylori* resistance to previously efficacious antimicrobics has been observed, thus making eradication of the bacterium more and more complex [4]. The eradication of this bacterium requires the combination of multiple antibiotics, which in return reduces patients adherence to the treatment and increases rates of adverse events secondary to therapy. Molecular methods, such as real-time polymerase chain reaction may allow an understanding of if the isolated strain carries genes that confer resistance to antibiotics (mostly against levofloxacin or clarithromycin) [5]. The Maastricht VI/Florence consensus report suggests the microbiological culture is a gold standard for antibiotic susceptibility; however, culture cannot be considered a routine diagnostic test as it is complex, expensive, and requires dedicated personnel [6].

The first-line eradication therapy should be chosen according to the local prevalence of antimicrobial resistance; however, in several areas of Italy it is unknown, but in some areas of Central and Southern Italy there is proof regarding the high prevalence of clarithromycin resistance, close to the 30% [7]. International guidelines recommend a 10-14-d regimen based on quadruple therapy as a first-line choice in countries with high (> 15%) resistance to clarithromycin: (1) Bismuth-based quadruple therapy: Proton pump inhibitor (PPI) + bismuth + tetracycline + metronidazole, also known as Pylera®, with an eradication rate of 90% [8,9]; and (2) Non-bismuth concomitant quadruple therapy: PPI + clarithromycin + amoxicillin + metronidazole/tinidazole, which raises the eradication rate to 75%. If the first-line bismuth quadruple therapy regimen fails, levofloxacin containing regimen is recommended as the second line. However, after multiple treatment failures, empirical rescue regimens have been suggested and rifabutin has proven to be effective in this scenario [10,11].

## RIFABUTIN MECHANISM OF ACTION, PHARMACODYNAMICS, AND PHARMACOKINETICS

Rifabutin is a rifampicin derivative compound; it has a high lipid-solubility, an elevated oral absorption (with high tissue-to-plasma ratio), and chemical stability at a wide pH range (*i.e.*, in the gastric environment): In an *in vivo* study in rats, the concentration of rifabutin in gastric secretion was 10-17 times superior to that in plasma, suggesting considerable gastric secretion [12]. Rifabutin is extensively metabolized, which means dosage adjustments are necessary in patients with severe renal or hepatic dysfunction. This drug shows a broad spectrum of antimicrobial activity; it is mostly used against mycobacteria (*Mycobacterium leprae*, *M. tuberculosis*, and atypicals [13]), some gram-positive and gram-negative bacteria, *Toxoplasma gondii*, and *Chlamydia trachomatis*.

The *in vitro* sensitivity of *H. pylori* to this antibiotic is high (with minimum inhibitory concentration (MICs) lower than that found for amoxicillin, clarithromycin, and metronidazole [14,15]), and it does not share resistance to clarithromycin, metronidazole or levofloxacin [16,17], making rifabutin-based rescue regimen a potential treatment after multiple failures [18-20]. Rifabutin acts by inhibiting the  $\beta$ -subunit of bacterial DNA-dependent RNA polymerase encoded by the beta subunit of RNA polymerase (rpoB)

gene, thus having bactericidal action.

## H. PYLORI RESISTANCE TO RIFABUTIN

*H. pylori* antibiotic resistance is the main worldwide problem affecting current eradication regimens; *H. pylori* shows great *in vitro* susceptibility *in vitro* to rifabutin[21,22], and resistance to this antimicrobial is lower than that found for amoxicillin, clarithromycin, and metronidazole[23]. The reference methodology to identify resistance is microbiological testing, which is often hard to perform because the culture of this germ may be difficult, and requires expert hands.

This antibiotic is used for tuberculosis (TB) treatment, especially in subjects with human immunodeficiency virus co-infection. For this reason, before starting a rifabutin-based eradication regimen, *M. tuberculosis* infection should be tested, as its use could promote the development of antibiotic resistance, thus affecting its effectiveness against Koch's bacillus[24]. Some laboratory mutants of *H. pylori*, obtained *in vitro*, with amino acid alterations in codons from 524 to 545 or in codon 585 of *rpoB*, showed resistance to rifabutin[25]. In a Japanese study, a negligible resistance rate (0.24%) to rifabutin was observed in cultures of strains isolated from more than 400 patients. Only one rifabutin-resistant strain was found in a subject with previous rifampin therapy for lung tuberculosis[26]. It was observed that previous rifampicin exposure may be related to high MICs to rifabutin, with point mutations in the *rpoB* gene, hinting at possible cross-resistance between rifabutin and rifampicin[27].

It has been postulated that multiple strains of *H. pylori*, either resistant and/or susceptible to different antibiotics, can be present in the same patient, thus suggesting the combined use of rifabutin with other antibiotics. In fact, several studies have shown that the risk of antimicrobial resistance onset is lower when it is used in combination with other antibiotics such as amoxicillin[28].

## EFFICACY OF RIFABUTIN REGIMENS IN H. PYLORI ERADICATION

Recent studies have revealed that the prevalence of *H. pylori* resistance to rifabutin and amoxicillin is minimal, so therapy with the association of rifabutin and amoxicillin could achieve satisfactory eradication rates. This regimen is recommended for rescue therapy in some consensus reports[29-31].

A systematic review by Malfertheiner *et al*[32] showed that rifabutin containing rescue therapy is a powerful therapy after several (usually three) previous eradication failures. The prevalence rate of rifabutin resistance of only about 1% was found, and furthermore, when studies included patients naïve to *H. pylori* eradication treatment, the data were even lower (0.6%). In general, mean-weighted *H. pylori* eradication rate (at intention-to-treat analysis) was 73%; eradication rates of second-, third-, and fourth-/fifth-line regimens were 79%, 66%, and 70%, respectively. All studies examined in the review used rifabutin at the dose of 300 mg/d, which seemed to be more successful than 150 mg/d. The optimal treatment duration for rifabutin was 10 to 12 d.

A systematic review and meta-analysis by Liu *et al*[33] analyzed 537 articles from medical journals (PubMed, the Cochrane Central Register of Controlled Trials, Embase, and SCI) of randomized clinical trials evaluating *H. pylori* therapy, recruiting a treatment group with a PPI, rifabutin, and amoxicillin. Twenty-one articles were selected, and the overall eradication rate was 70.4% at intent-to-treat (ITT) and 72.0% by per-protocol (PP) analyses. The eradication effectiveness obtained with rifabutin and amoxicillin was lower than the other triple therapies (68.4% *vs* 81.9% success rate). The effectiveness of the combination was not greater than the association of amoxicillin and levofloxacin. The effectiveness of the association of amoxicillin and rifabutin was comparable to the quadruple therapy, which included a PPI and amoxicillin. The cure rate of rifabutin plus amoxicillin was lower than bismuth-containing quadruple therapy. This review established that a regimen with PPI, rifabutin, and amoxicillin for *H. pylori* infection could not be the optimal choice for rescue therapy after several eradication failures.

Gingold-Belfer *et al*[34] conducted another meta-analysis of 33 randomized controlled trials, which used triple therapy with rifabutin and amoxicillin and found a pooled success of 71.8%. Lee *et al*[35] analyzed 84 patients' overall resistance rates to amoxicillin, clarithromycin, metronidazole, and moxifloxacin and found that they were 13.1%, 83.3%, 47.6%, and 71.4%, respectively. A susceptibility-guided therapy was proposed, based on culture, and it was shown that it was both effective and devoid of complications, even for patients reporting high antimicrobial resistance; in particular, in the arm receiving rifabutin due to multiple resistances, the eradication rate was 100%.

In 2022, Nyssen *et al*[36] data analyses based on the European multicenter prospective observational registry about *H. pylori* management was performed, analyzing 18 different rifabutin-containing treatments including two or three other antibiotics and recruiting 500 patients. Rifabutin was mostly used in second-line (32%), third-line (25%), and fourth-line (27%) regimens, with a success rate of 78%, 80% and 66%, respectively, according to modified intention-to-treat analysis.



In 2022, Inokuchi *et al*[37] enrolled patients who did not respond to second-line therapy to assess the efficacy and safety of 7-d rifabutin, amoxicillin, and vonoprazan triple therapy [20 mg vonoprazan twice daily (b.i.d.), 500 mg amoxicillin four times daily (q.i.d.), and 150 mg rifabutin twice daily (q.d.)] lasting 7 d as third- or later-line treatment for *H. pylori* infection. Intention-to-treat and PP analyses showed a high eradication rate [91.2%, 95% confidence interval (CI): 84%-99% and 92.7%, 95%CI: 86%-100%, respectively]. The results indicate that this regimen is efficient and safe as a third-line treatment or in successive efforts of *H. pylori* eradication.

New drugs, combining rifabutin all-in-one with other drugs, are in course of study: A phase three, double-blind study (ERADICATE Hp) driven by Kalfus *et al*[38], randomized (2:1) treatment-naïve dyspeptic patients with *H. pylori* infection to RHB-105 (Talicia®), a new all-in-one association of omeprazole 40 mg, amoxicillin 1000 mg, and rifabutin 50 mg, randomized *vs* placebo, both given every 8 h for 2 wk. The study showed an *H. pylori* eradication rate ITT of 89.4%.

An association of rifabutin with other antibiotics has been tried: An intervention study in Southern Italy considered rifabutin and tetracycline association after three or more eradication therapy attempt failures[39]. Only rifabutin and tetracycline were tested in a relevant number of patients, reporting an eradication rate of 80.4% (per protocol) and 77.4% (intention-to-treatment).

Italian guidelines suggest the 12-d rifabutin-amoxicillin triple therapy (*i.e.*, PPI at standard dose b.i.d., amoxicillin 1 g b.i.d., and rifabutin 150 mg b.i.d.) as a rescue regimen[40], which has been demonstrated to be useful after several previous therapeutic failures[19]. In other studies, such as the one performed by Malfertheiner *et al*[32], an ideal length of treatment from 10 to 12 d was suggested, whereas the latest publication of Inokuchi *et al*[37] suggested a 7-d regimen.

## SIDE EFFECTS

Despite the effectiveness of rifabutin-based regimens, serious side effects must be evaluated before starting any rifabutin-based therapy. Adverse effects include fever, nausea, vomiting, with a “not common” and reversible effect, *i.e.*, bone marrow suppression. For this reason, full blood count surveillance is required. Uveitis has recently been described in patients under an association of rifabutin and other antimycobacterial drugs[41,42].

In the study by Inokuchi *et al*[37], adverse events occurred in 31.6% of the patients; also in the article by Nyssen *et al*[36] one or more side effects were recorded in the 26% of the patients (nausea was the most common), and only one severe bone marrow adverse event (0.2%) was described. Furthermore, it is possible that rifabutin may induce changes in the intestinal microbiota even if there are no studies in the literature on this topic, to the best of our knowledge. Presumably, this can be explained by the limited use of this antibiotic in *H. pylori* infection therapy.

## CONCLUSION

*H. pylori* eradication is currently a worldwide challenge for clinicians. In 2017, the World Health Organization classified resistance to clarithromycin as a “high-priority” issue for *H. pylori*[43]. Microbiological cultures are advised[7], but they are difficult to perform for the slow bacterial growth and particular nutritional requirements, making it very expensive as they require specialized staff with a specialized laboratory. Furthermore, in latest studies, Pylera® therapy eradication rates are comparable to culture-tailored therapies[44].

Facing treatment failures, rifabutin has an interesting role against *H. pylori*, since such drug shows excellent *in vitro* effectiveness, and the diffusion of its resistance is very low (< 1%). Side effects should be weighed, even though severe adverse events are exceptional. In all the studies analyzed, rifabutin has a great effectiveness, safety and tolerability when used as a “rescue regimen”, *i.e.*, third or fourth-line therapy; in conclusion, the use of rifabutin as a new first-line treatment alternative for *H. pylori* gastritis should be thoroughly pondered, by evaluating the risk of microbial resistance, the high cost of treatment and the wide availability and effectiveness of alternative drugs. This could be precociously evaluated in the eradication algorithm in high resistance areas.

## FOOTNOTES

**Author contributions:** Losurdo G and Di Leo A planned the investigation; Borraccino AV and Celiberto F carried out the research; Borraccino AV, Losurdo G, and Ierardi E wrote the paper; Di Leo A supervised the study; and all authors read and validated the final version.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

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**S-Editor:** Wang JJ

**L-Editor:** Filipodia

**P-Editor:** Wang JJ

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