

The Role of Levofloxacin in First-line and “Rescue” *Helicobacter pylori* Treatment Regimens



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Helicobacter pylori (*H. pylori*) infection is the main cause of gastritis, gastroduodenal ulcers, and gastric cancer. However, after more than 20 years experience with *H. pylori* treatment, the ideal treatment regimen remains to be found. The most commonly used first-line therapies – including proton pump inhibitors (PPIs) plus clarithromycin and either amoxicillin or metronidazole – may fail in up to 20% of patients. Therefore, clarithromycin-based triple therapies fail

to achieve a high enough cure rate, and more effective alternatives should be sought. Levofloxacin is a fluoroquinolone antibacterial agent that exhibits, *in vitro*, remarkable activity against *H. pylori*. A synergistic effect of quinolone antimicrobial agents and PPIs on strains of *H. pylori* has been reported. Furthermore, and very importantly, it has been shown *in vitro* that levofloxacin retains its activity when *H. pylori* strains are resistant to clarithromycin and metronidazole. The levofloxacin-amoxicillin-PPI combination represents an alternative to clarithromycin-based therapy, and may be suggested as first-line treatment of *H. pylori* infection, particularly in areas with high primary resistance to clarithromycin and low resistance to levofloxacin. It has recently been suggested that levofloxacin-based “rescue” therapy also constitutes an encouraging second-line strategy, offering an alternative to quadruple therapy in patients with previous PPI-clarithromycin-amoxicillin failure, with the advantages of improved efficacy, simplicity and safety. Levofloxacin-based “rescue” therapy constitutes an encouraging empirical third-line strategy after multiple previous *H. pylori* eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole and tetracycline. Finally, the levofloxacin-based regimen can also be administered with good results even after three previous eradication failures with several antibiotics, including rifabutin.

Introduction

Helicobacter pylori (*H. pylori*) infection is the main cause of gastritis, gastroduodenal ulcers, and gastric cancer. However, after more than 20 years experience with *H. pylori* treatment, the ideal regimen to treat this infection remains to be found. Consensus conferences have recommended therapeutic regimens that achieve *H. pylori* cure rates higher than 80% on an intent-to-treat (ITT) basis (1–3). However, several large clinical trials and meta-analyses have shown that the most commonly used first-line therapies – including proton pump inhibitors (PPIs) plus two antibiotics – may fail in up to 20% of patients (4, 5) and, in a routine clinical setting, the treatment failure rate might be even higher. Moreover, during the last few years, the efficacy of PPI-based regimens seems to be de-

creasing, and several studies have reported ITT eradication rates lower than 75% (6–14) and some even lower than 50% (15, 16). Antibiotic resistance to clarithromycin has been identified as one of the major factors affecting our ability to cure *H. pylori* infection, and the rate of resistance to this antibiotic seems to be increasing in many geographical areas (17, 18). These data convincingly show that, at present, clarithromycin-based triple therapies may achieve unsatisfactory cure rates, and more effective alternatives are required.

Several “rescue” therapies have been recommended, but they still fail to eradicate *H. pylori* in more than 20% of the cases (19), and these patients present a therapeutic dilemma (20). Patients who are not cured with two consecutive treatments including clarithromycin and metronidazole will

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exhibit at least single and, usually, double resistance (18). Furthermore, since bismuth salts are no longer available worldwide, management of first-line eradication failures is becoming a real challenge. Currently, there is also a lack of standard third-line therapy, and European guidelines recommend cultures in these patients to select a third-line treatment according to the microbial sensitivity to antibiotics (2, 3). However, cultures are often carried out only in research centers, and the use of this procedure as “routine practice” in patients who have failed several treatments does not seem feasible (19–21). Therefore, the evaluation of drugs without cross-resistance to nitroimidazole or macrolides as components of retreatment combination therapies would be worthwhile.

All these issues are important at the present time, but they will be even more relevant in the near future, since therapy for *H. pylori* infection is becoming more and more frequently prescribed. Therefore, the evaluation of second or third “rescue” regimens for these problematic cases seems to be worthwhile. In designing a treatment strategy we should not focus on the results of primary therapy alone; an adequate strategy for treating this infection should use several therapies which, if consecutively prescribed, come as close to the 100% cure rate as possible (19, 20, 22, 23).

The aim of the present paper is to review the role of levofloxacin in treating *H. pylori* infection, both in first-line and “rescue” regimens.

Antibacterial activity of levofloxacin against *H. pylori*

Levofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens (24, 25). Several randomized comparative trials have demonstrated the efficacy of levofloxacin in the treatment of infections of the respiratory tract, genitourinary tract, skin and skin structures (24, 25). Recently, some studies have evaluated the efficacy of new fluoroquinolones, such as levofloxacin, that could prove to be a valid alternative to standard antibiotics not only as first-line therapies but, more interesting, as second-line regimens (20, 26–28). Levofloxacin-based therapies represent an encouraging strategy for *H. pylori* infection, as some studies have demonstrated that levofloxacin exhibits, *in vitro*, remarkable activity against this microorganism (29), and primary resistance to this antibiotic is (still) relatively infrequent (when compared with metronidazole or clarithromycin) (30–34). A recent *in vitro* study also showed a synergistic effect of quinolone antimicrobial agents and PPIs on strains of *H. pylori* (35). Furthermore, it has been shown *in vitro* that

levofloxacin retains its activity when *H. pylori* strains are resistant to clarithromycin and metronidazole (33, 36, 37). These favourable results have been confirmed *in vivo*, indicating that most of the patients with both metronidazole and clarithromycin resistance can be cured with the levofloxacin-based regimen (32, 38, 39).

Levofloxacin-based first-line *H. pylori* eradication treatment

As previously mentioned, although the high efficacy of clarithromycin-based regimens in eradicating *H. pylori* infection is well known, recent data suggest that the efficacy of standard PPI-based triple therapies (with clarithromycin and either amoxicillin or a nitroimidazole) is decreasing worldwide. Since resistance to clarithromycin is increasing (18), and resistance to this drug is correlated with a reduction in therapeutic efficacy (18), regimens that avoid clarithromycin but retain high success rates are, at present, clearly needed.

Some authors have reported favourable experience with levofloxacin-based regimens, but most of the studies evaluated this antibiotic as a second-line therapy after one or more *H. pylori* eradication failures (19, 20). Thus, the number of studies evaluating a combination of levofloxacin and amoxicillin (together with an antisecretor) as a first-line regimen has been very small, and the number of patients included in each of the studies very limited. Some authors have reported that a first-line triple clarithromycin-free regimen including ranitidine bismuth citrate (RBC), levofloxacin and amoxicillin achieved an 84% *H. pylori* eradication rate (40). However, bismuth salts, including RBC, are no longer available worldwide.

Up to now, six studies have evaluated a combination of levofloxacin and amoxicillin, together with a PPI, as a first-line regimen (Table 1) (33, 41–45). Eradication rates in all of these studies have been very high, ranging from 83% to 92%. As an example, we recently had the opportunity to evaluate this regimen in our region, including prospectively 75 *H. pylori*-positive patients complaining of dyspeptic symptoms (43). An eradication regimen with levofloxacin (500 mg twice daily), amoxicillin (1 g twice daily) and omeprazole (20 mg twice daily) was prescribed for 10 days. Two patients (2.7%) did not return for follow-up. All patients apart from these two were compliant; they suffered adverse effects (diarrhoea in both cases). No severe side effects were reported. Mild adverse effects were reported by 10 patients (13%), the most frequent being diarrhoea, which was reported by 9.3%. Per-protocol eradication was achieved in 85% of the patients, and the ITT eradication was 83%.

Table 1. Studies evaluating a combination of levofloxacin, amoxicillin and a PPI as first-line treatment for *Helicobacter pylori* infection

Author	Year of publication	Number of patients	Duration of treatment	Levofloxacin (dose)	Amoxicillin (dose)	PPI (type and dose)	ITT eradication rate (%)
Antos et al. (33)	2006	30	7	500 mg b.i.d	1 g b.i.d	Esomeprazole 40 mg b.i.d	87
Cammarota et al. (41)	2000	50	7	500 mg q.d.	1 g b.i.d	Rabeprazole 20 mg q.d.	92
Di Caro et al. (42)	2002	40	7	500 mg q.d.	1 g b.i.d	Rabeprazole 20 mg q.d.	90
Gisbert et al. (43)	2008	75	10	500 mg b.i.d	1 g b.i.d	Esomeprazole 20 mg b.i.d	83
Marzio et al. (44)	2006	39	10	500 mg b.i.d	1 g b.i.d	Esomeprazole 20 mg b.i.d	92
Rispo et al. (45)	2007	65	7	250 mg b.i.d	1 g b.i.d	Esomeprazole 20 mg b.i.d	91

Abbreviations: PPI = proton pump inhibitor, ITT = intent-to-treat, b.i.d. = twice daily, q.d. = once daily.

The levofloxacin-based regimen (with PPI, amoxicillin and levofloxacin administered twice daily) and standard PPI-based therapy are both very simple. In most of the studies, compliance with the levofloxacin-based regimen has been excellent, with most patients taking all their medications correctly. Furthermore, levofloxacin (and amoxicillin) is generally well tolerated, and the most common adverse events associated with its use are mild or moderate and transient (24, 27).

One of the main concerns of using quinolones as a first-line therapy is the fear that the resistance rate will increase with the widespread use of these drugs. For this reason the Maastricht III Consensus Report (3) recommended clarithromycin-based triple regimens as first choice treatment in populations with less than 15–20% clarithromycin resistance. A systematic review evaluated the experience in Spain of the prevalence of *H. pylori* resistance to several antibiotics a few years ago, and found that *H. pylori* resistance to clarithromycin varied markedly among different studies (minimum of 1%, maximum of 13%), with an average of 6.7% (46). On the other hand, it has been shown that resistance to quinolones is easily acquired and, in countries with a high consumption of these drugs, the resistance rate is increasing and is already relatively high (32, 44, 47–58). More importantly, it has been demonstrated that the presence of levofloxacin resistance significantly reduces the eradication rate following treatment with this antibiotic (32, 44, 56, 59). Therefore, it has been suggested that these drugs should be used as initial therapy only in areas where primary resistance is low or only after susceptibility testing (58, 60). In this respect, it has been suggested that triple therapy with levofloxacin and amoxicillin may be proposed as an initial therapy for *H. pylori* eradication without previous susceptibility testing in areas where primary resistance to levofloxacin is $\leq 10\%$ (44).

In summary, a levofloxacin-amoxicillin-PPI combination represents an alternative to clarithromycin-based therapy, as it meets the criteria set

for regimens used as primary *H. pylori* treatment: effectiveness ($> 80\%$ cure rate), simplicity (twice-daily dosing and excellent compliance), and safety (low incidence of adverse effects). Therefore, this levofloxacin-based regimen may be suggested as a first-line treatment of *H. pylori* infection, particularly in areas with high primary resistance to clarithromycin and low resistance to levofloxacin.

Second-line *H. pylori* “rescue” therapy after failure of one eradication treatment

After failure of a combination of a PPI-based triple regimen, the use of so called quadruple therapy (that is, PPI, bismuth, tetracycline and metronidazole) has been generally recommended as the optimal second-line therapy based on the relatively good results reported by several authors and guidelines (3, 19, 61–65). However, this quadruple regimen requires the administration of 4 drugs according to a complex dosing schedule (bismuth and tetracycline usually prescribed every 6 hours, and metronidazole every 8 hours) and is associated with a relatively high incidence of adverse effects (19). Furthermore, this quadruple regimen still fails to eradicate *H. pylori* in approximately 20 to 30% of the patients, and these cases constitute a therapeutic dilemma, as patients who are not cured with two consecutive treatments including clarithromycin and metronidazole will usually exhibit double resistance (19).

As previously mentioned, a combination of a PPI, amoxicillin and levofloxacin, as a first-line regimen, has been associated with favourable results. Later, other authors studied this same regimen in patients with one previous eradication failure, also reporting exciting results, with *H. pylori* cure rates ranging from 60% to 94% (36, 38, 39, 52, 66–76). A recent systematic review showed a mean eradication rate with levofloxacin-based “rescue” regimens (combined with amoxicillin and a PPI in most studies) of 80%, which represents a relatively high figure when considering that this regimen was evaluated as a “rescue” therapy (27). This systematic review found higher *H. pylori* cure rates

with the 10-day regimen rather than the 7-day one in general (81% vs. 73%) and also with the levofloxacin-amoxicillin-PPI combination in particular (80% vs. 68%), suggesting that the longer (10-day) therapeutic scheme should be chosen.

Furthermore, two recent meta-analyses have suggested that after *H. pylori* eradication failure, the levofloxacin-based “rescue” regimen is more effective than the generally recommended quadruple therapy (26, 27). In one of these meta-analyses (27), higher *H. pylori* cure rates with the levofloxacin-based triple regimens than with the quadruple combinations were found (81% vs. 70%), but the statistical significance was borderline (Figure 1). Nevertheless, results were heterogeneous, mainly due to the discordant results of the study by Perri et al. (66), who reported a cure rate of only 63% with the levofloxacin-regimen, the lowest reported in the literature, a figure that contrasts with the mean eradication rate of 80% calculated in a systematic review (27). Nevertheless, when that single outlier study (66) was excluded from the meta-analysis, the difference between cure rates with both regimens reached statistical significance and the heterogeneity markedly decreased. Furthermore, when only high-quality studies were considered, the advantage of the levofloxacin regimen over the quadruple regimen increased (88% vs. 64%), also achieving statistical significance, and the heterogeneity among studies almost disappeared (27).

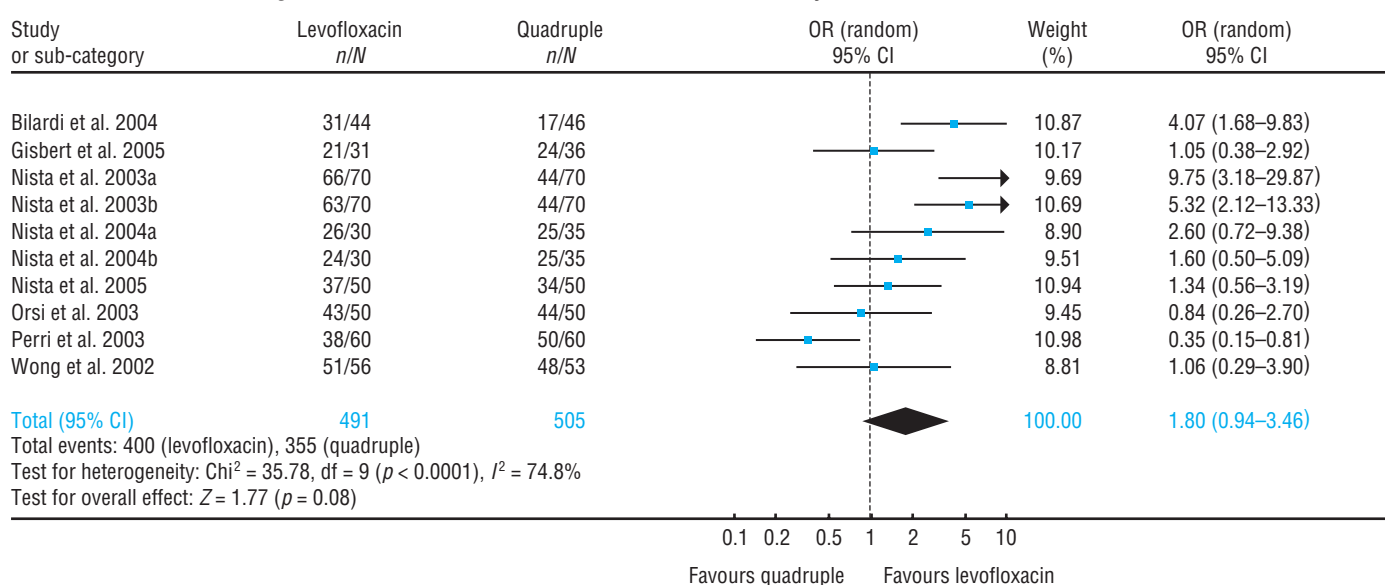
As previously mentioned, the quadruple regimen requires administration according to a complex dosing scheme (19). However, levofloxacin-based regimens (with amoxicillin and PPIs

administered twice daily, and levofloxacin every 12 or 24 hours) represent an encouraging alternative to quadruple therapy, with the advantage of simplicity. Furthermore, the quadruple regimen is associated with a relatively high incidence of adverse effects (19). In contrast, levofloxacin is generally well tolerated, and, as previously mentioned, most adverse events associated with its use are mild to moderate in severity and transient (24). The most frequent adverse effects involve the gastrointestinal tract (24). Occasional cases of tendinitis and tendon rupture have been reported in the literature with levofloxacin therapy (24, 38). However, data based on more than 15 million prescriptions in the United States indicate that the rate is fewer than 4 per million prescriptions (77). In the aforementioned systematic review (27), adverse effects were reported, overall, by 18% of the patients treated with levofloxacin-based therapies, and these adverse effects were severe (defined so by the authors or explaining treatment discontinuation) in only 3% of cases. Furthermore, the incidence of adverse effects was no different when levofloxacin-amoxicillin-PPI was administered for 7 or 10 days, supporting the aforementioned recommendation for prescribing the more effective 10-day regimen. Moreover, two meta-analyses have demonstrated a lower incidence of adverse effects with levofloxacin-based treatment than with the quadruple combination (26, 27).

Third-line *H. pylori* “rescue” therapy after failure of two eradication treatments

If the decision has been made not to perform cul-

Figure 1. Meta-analysis comparing *Helicobacter pylori* eradication efficacy with levofloxacin-based triple regimens versus quadruple therapy, as second-line “rescue” regimen after failure of a PPI, amoxicillin and clarithromycin combination



Abbreviations: PPI = proton pump inhibitor, OR = odds ratio, CI = confidence interval.

ture before the administration of the third-line “rescue” treatment after failure of the first two trials (generally including clarithromycin and metronidazole), different possibilities for empirical treatment may be suggested. As several studies have underlined the relevance of metronidazole (78–81) and clarithromycin (78–80, 82) resistance, these two antibiotics should not be readministered, and several regimens have been evaluated in this scenario, based on: 1) amoxicillin ± tetracycline; 2) rifabutin; 3) furazolidone; and, finally, 4) levofloxacin.

It has been suggested that levofloxacin-based therapies may represent an alternative when two (or more) consecutive eradication treatments have failed (32, 38, 53, 83–88). As an example, a recent study by Zullo et al. (84) evaluated the efficacy of a levofloxacin–amoxicillin–PPI combination in patients who previously had failed two or more therapeutic attempts, and the eradication rate was 83% (ITT analysis). More recently, Gisbert et al. (87) carried out a multicenter study involving 100 patients to evaluate the efficacy of a third-line levofloxacin-based regimen in patients with two consecutive *H. pylori* eradication failures. The ITT eradication rate was 66%, which represents a relatively high figure when considering that this regimen was evaluated as a third-line therapy. Other alternative “rescue” therapies, different from levofloxacin-based regimens, have been suggested. Rifabutin-based “rescue” therapy also constitutes a possible strategy after previous eradication failures, although it has been recently shown that a 10-day triple levofloxacin-based regimen is more effective than the same combination with rifabutin as a “rescue” regimen (87). In summary, levofloxacin-based “rescue” therapy constitutes an encouraging empirical third-line strategy after multiple previous *H. pylori* eradication failures with key antibiotics (such as amoxicillin, clarithromycin, metronidazole and tetracycline).

Cumulative eradication rates with three (or more) consecutive eradication treatments

Some authors have administered, in the same study, different regimens after failure of two eradication treatments, which provides interesting information about cumulative, and not only absolute, eradication rates (20, 89–98). As an example, we evaluated the efficacy of different “rescue” therapies empirically prescribed over a period of 10 years to 500 patients in whom at least one eradication regimen had failed to cure *H. pylori* infection (98). The antibiotic susceptibility was unknown (therefore “rescue” regimens were chosen empirically). Overall, the *H. pylori* cure rates with the second and third-line “rescue” regimens were 70% and 74%, giving

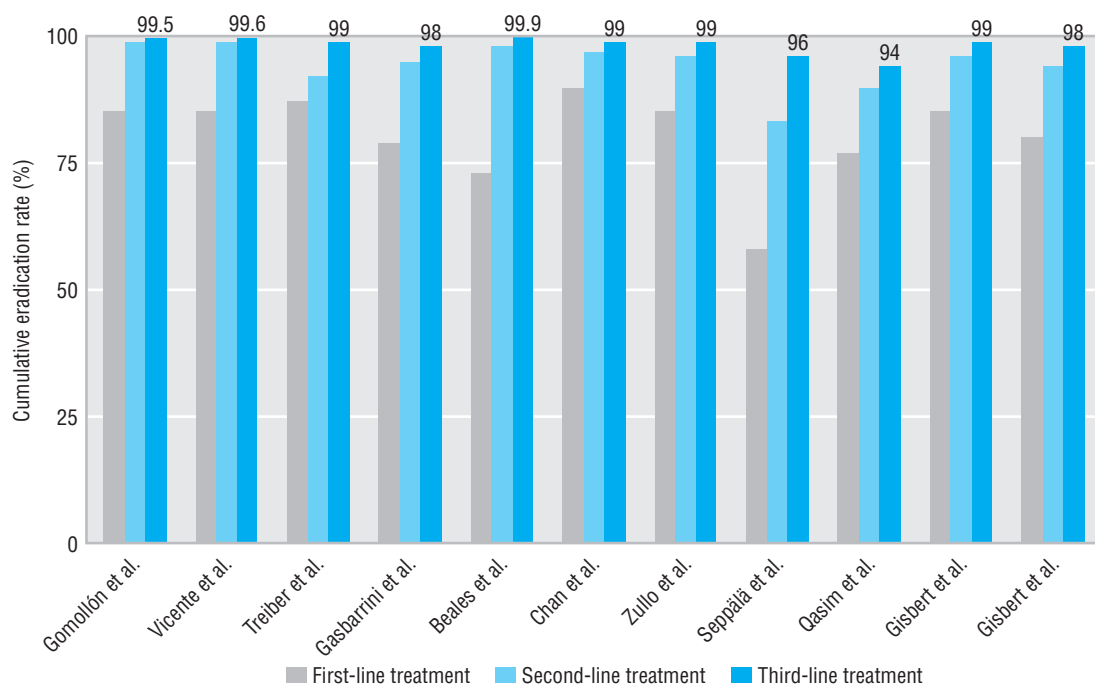
a cumulative eradication rate as high as 98%. Furthermore, these encouraging (cumulative) results have been obtained when more than three consecutive treatments have been prescribed (20). As an example, we have recently confirmed that the levofloxacin-based regimen can also be administered with good results after three previous eradication failures with antibiotics such as amoxicillin, clarithromycin, metronidazole, tetracycline, and even rifabutin (86). Thus, we prospectively evaluated 10 patients with three consecutive *H. pylori* eradication failures (first treatment with PPI–clarithromycin–amoxicillin, second treatment with RBC–tetracycline–metronidazole, and third treatment with PPI–amoxicillin–rifabutin). A fourth eradication regimen of 10-day levofloxacin, amoxicillin and PPI was prescribed and the ITT eradication rate was 70%. When we reviewed our experience with different “rescue” therapies empirically prescribed over a period of 10 years to 500 patients, the cumulative *H. pylori* eradication rate with 4 successive treatments was 99.5% (98). Finally, reports of “ineradicable” *H. pylori* infection after more than four eradication treatment failures have been recently published. Thus, Zullo et al. (83) reported that the levofloxacin–amoxicillin combination was successfully employed in a patient with a clarithromycin- and metronidazole-resistant strain, who previously failed eight consecutive therapeutic attempts.

Therefore, a wider perspective of the benefits of retreating *H. pylori* infection can be obtained if cumulative eradication rates with successive treatments are taken into account. As shown in Figure 2, it can be concluded that *H. pylori* eradication can finally be achieved in almost 100% of patients if three (or more) “rescue” therapies are given consecutively (89–99).

Conclusions

Even with the current most effective treatment regimens, ≥20% of patients will fail to exhibit eradication of *H. pylori* infection. This issue seems important at the present time since therapy for *H. pylori* infection is becoming more and more frequently prescribed. Nowadays, apart from having a good experience of first-line eradication regimens, we must also be prepared to face treatment failures. Therefore, in designing a treatment strategy we should not focus on the results of primary therapy alone, but also on the final (overall) eradication rate.

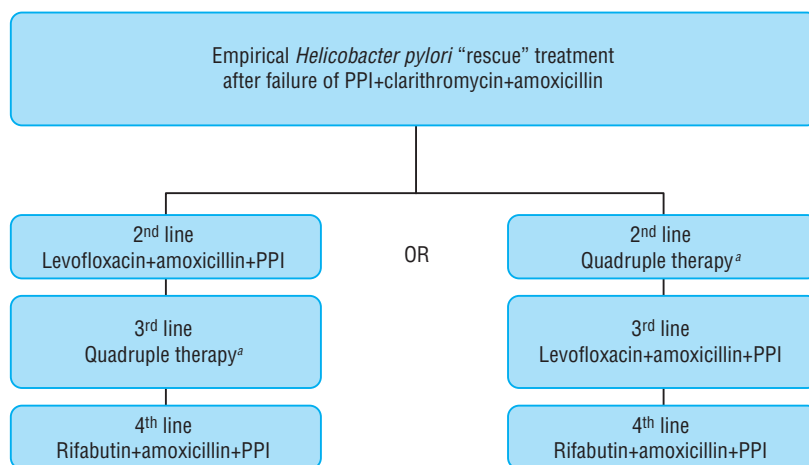
The levofloxacin–amoxicillin–PPI combination represents an alternative to clarithromycin-based therapy, as it meets the criteria set for regimens used as primary *H. pylori* treatment: effectiveness, simplicity, and safety. Therefore, this

Figure 2. Cumulative *Helicobacter pylori* eradication rates with three consecutive eradication treatments

levofloxacin-based regimen may be suggested as a first-line treatment of *H. pylori* infection, particularly in areas with high primary resistance to clarithromycin and low resistance to levofloxacin.

The choice of a “rescue” treatment depends on which treatment is used initially. If a first-line clarithromycin-based regimen is used, a second-line metronidazole-based treatment (such as the quadruple therapy) may be used afterwards, and then a levofloxacin-based combination would be a third-line “rescue” option. Thus, levofloxacin-based “rescue” therapy constitutes an encouraging empirical third-line strategy after multiple previous *H. pylori* eradication failures with several antibiotics. Alternatively, it has recently been suggested that levofloxacin-based “rescue” therapy constitutes an encouraging second-line strategy, representing an alternative to quadruple therapy in patients with previous PPI–clarithromycin–amoxicillin failure, with the advantage of efficacy, simplicity and safety. In this case, the quadruple regimen may be reserved as a third-line “rescue” option. Finally, rifabutin-based “rescue” therapy constitutes an encouraging empirical fourth-line strategy after multiple previous eradication failures with key antibiotics such as amoxicillin, clarithromycin, metronidazole, tetracycline, and levofloxacin (Figure 3).

Even after two consecutive failures, several studies have demonstrated that *H. pylori* eradication can finally be achieved in almost all patients if

Figure 3. Choice of an empirical retreatment regimen, without culture and antimicrobial sensitivity testing, after failure of a PPI, clarithromycin and amoxicillin combination

^a Combination of PPI, bismuth, tetracycline and nitroimidazole (metronidazole or tinidazole). Abbreviation: PPI = proton pump inhibitor.

several “rescue” therapies are given consecutively. As a final conclusion, therefore, the attitude to adopt following *H. pylori* eradication therapy failure, even after two or more unsuccessful attempts, should be to fight on and not to surrender (100).

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