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RESEARCH FRONTIER

"Rescue" regimens after *Helicobacter pylori* treatment failure

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Abstract

Helicobacter pylori (*H pylori*) infection is the main cause of gastritis, gastroduodenal ulcer disease, and gastric cancer. After more than 20 years of experience in *H pylori* treatment, in my opinion, the ideal regimen to treat this infection is still to be found. Currently, apart from having to know first-line eradication regimens well, 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 choice of a "rescue" treatment depends on which treatment is used initially. If a clarithromycin-based regimen was used initially, a subsequent metronidazole-based treatment (quadruple therapy) may be used afterwards, and then a levofloxacin-based combination would be a third "rescue" option. 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, a 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. Even after two consecutive failures, several studies have demonstrated that *H pylori* eradication can finally be achieved in almost all patients if several rescue therapies are consecutively given. Therefore, the attitude in *H pylori* eradication therapy failure, even after two or more unsuccessful attempts, should be to fight and not to surrender.

Key words: *Helicobacter pylori*; Rescue; Salvage; Rifabutin; Levofloxacin

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INTRODUCTION

Helicobacter pylori (*H pylori*) infection is the main cause of gastritis, gastroduodenal ulcer disease, and gastric cancer. After more than 20 years of experience in *H pylori* treatment, in my opinion, the ideal regimen to treat this infection is still to be found. Consensus conferences have recommended therapeutic regimens that achieve *H pylori* cure rates higher than 80% on an intention-to-treat 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 the clinical routine setting, the treatment failure rate might be even higher. Moreover, during the last few years, the efficacy of PPI-based regimens seems to be decreasing, and several studies have reported intention-to-treat eradication rates lower than 75%[6-14] and 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].

Reports dealing with retreatment of *H pylori* after failure are difficult to analyze for several reasons[19]. Firstly, patients who fail with their first-line treatment

probably include a higher percentage of individuals who are unreliable tablet takers, others have resistant organisms and there is the "constitutional" group, where failure will be inevitable. On the other hand, some patients submitted for rescue therapy have already had more than one previous treatment for *H pylori*, and this circumstance is not always clarified in the protocols. Furthermore, the original primary treatments vary among the different studies, not only with respect to the antibiotic type, but also with respect to the dose and duration of the regimen. Finally, only a few studies have directly compared, in the same protocol, two or more second therapies[20,21].

Several rescue therapies have been recommended, but they still fail to eradicate *H pylori* in more than 20% of cases[20], and these patients constitute a therapeutic dilemma[21]. Patients who are not cured with two consecutive treatments, including clarithromycin and metronidazole, will have at least single, and usually double, resistance[18]. Furthermore, bismuth salts are not available worldwide anymore and, therefore, management of first-line eradication failures is becoming challenging. Currently, a standard third-line therapy is lacking, and European guidelines recommend a culture for these patients to select a third-line treatment according to 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 failed several treatments seems not to be feasible[20-22]. 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, as 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[20,21,23,24].

The aim of the present manuscript will be to review the experience dealing with "non-responders" to *H pylori* eradication therapy. As, at present, the current most prescribed first-line regimens include a combination of PPI plus two antibiotics, the present review will focus only on rescue regimens when these triple combinations fail. Bibliographical searches were performed in the PubMed (Internet) database including studies available until March 2008, looking for the following words (all fields): pylori AND (retreatment OR re-treatment OR rescue OR failure OR salvage OR second-line OR third-line OR fourth-line). References of reviews on *H pylori* eradication treatment, and from the articles selected for the study, were also examined in search of articles meeting inclusion criteria (that is, dealing with *H pylori* rescue therapies).

IS IT NECESSARY TO PERFORM CULTURE AFTER FAILURE OF THE FIRST ERADICATION TREATMENT?

Pretreatment antibiotic resistance is the most important factor in nonresponse to initial treatment[25-29]. Thus, the choice of a second-line treatment depends on which treatment was used initially, as it would appear that retreatment with the same regimen cannot be recommended[30]. If a clarithromycin-based regimen was used, a metronidazole-based treatment (or at least a clarithromycin-free regimen) should be used afterwards, and *vice versa*[31]. This recommendation is based on the observation that acquired bacterial resistance to metronidazole or clarithromycin results primarily from the previous treatment failure[26,32,33], and therefore rescue therapies should avoid these antibiotics and use different combinations.

An antimicrobial susceptibility test for *H pylori* before second-line treatment is sometimes performed, although whether the test is truly necessary remains unknown. Some authors have evaluated the efficacy of susceptibility-guided *vs* empiric retreatment for *H pylori* after a treatment failure. In the study by Yahav *et al*[34], patients in whom at least one treatment regimen for *H pylori* eradication had failed underwent gastric biopsy and culture, and were retreated according to the *in vitro* susceptibility results. Findings were compared with those of control patients (where culture was unavailable). Susceptibility-guided retreatment was associated with better eradication rates (86%) than empiric treatment (63%). However, several methodological drawbacks exist in this study. Firstly, more than 50% of the patients received first-line eradication treatment with both clarithromycin and metronidazole (instead of including clarithromycin and amoxicillin), which is not the generally recommended combination; consequently, no logical empirical treatment remained afterwards (levofloxacin-based regimens were not available at that time). In this respect, when only the eradication rates in control (culture unavailable) patients treated with a first regimen of PPI-amoxicillin-clarithromycin followed by a second *empiric* quadruple regimen were considered (the generally recommended first and second-line strategies), the success figures were not significantly different from those reported in patients receiving susceptibility-guided retreatment. Secondly, because this study was nonrandomized, there might have been heterogeneity among the two groups with respect to the treatment regimens prescribed by the treating physicians. Finally, this study was limited by the lack of susceptibility data for the controls, which restricted the ability to analyze the reasons why empiric therapy did not work as well as the susceptibility-guided protocol.

In a French multicenter study[35], patients in whom one previous *H pylori* eradication therapy (mainly with PPI-amoxicillin-clarithromycin) had failed were randomized to receive one of three empirical triple therapy regimens or a strategy based on antibiotic susceptibility. The empirical regimens

were PPI-amoxicillin-clarithromycin (for 7 d or 14 d) or PPI-amoxicillin-metronidazole (for 14 d). In the susceptibility-based strategy, patients with clarithromycin-susceptible strains received PPI-amoxicillin-clarithromycin, whilst the others received PPI-amoxicillin-metronidazole. The eradication rates for empirical therapies were low, while the cure rate was higher (74%) for the susceptibility-based treatment. If the *H pylori* strain was clarithromycin-susceptible (which occurred in approximately 1/3 of the cases), a high success rate was obtained with the PPI-clarithromycin-amoxicillin rescue regimen. The study, however, was done in France, where bismuth is banned, so that the use of quadruple therapy with a PPI, bismuth, tetracycline, and metronidazole as recommended by the updated Maastricht Consensus Report[3], was not tested. In fact, as will be reviewed later, several studies have obtained relatively good results with this quadruple regimen empirically prescribed, with a mean eradication rate of 77%, which is similar to the 74% achieved for the susceptibility-based treatment in the present study. Thus, in this study, instead of not readministering any of the antibiotics against which *H pylori* had probably become resistant, the authors insist on prescribing again clarithromycin (or metronidazole) for the second-line treatment. Furthermore, statistically significant differences were not demonstrated when comparing the efficacy of the empirical PPI-amoxicillin-metronidazole and the susceptibility-based strategy, suggesting that the metronidazole-based combination may be an effective empirical alternative after failure of a clarithromycin-based combination.

In the updated Maastricht Consensus Report[3], it was recommended that culture and antimicrobial sensitivity testing should be routinely performed only after two treatment failures with different antibiotics. According to this statement, some studies have suggested that an antimicrobial susceptibility test for *H pylori* before administering second-line treatment is not necessary. In this respect, in the study by Avidan *et al*[36], after failure of first-line eradication treatment, half of the patients were randomly assigned to treatment with a different PPI-based triple regimen regardless of the culture obtained, and the other half was assigned to treatment with PPI and two antibacterial agents chosen according to a susceptibility test; the authors found that the culture results did not influence the treatment protocol employed. Similarly, in the study by Miwa *et al*[37], patients with *H pylori* infection for whom first-line treatment with a PPI-amoxicillin-clarithromycin regimen had failed were randomly assigned to two groups: those having or not having the susceptibility test before retreatment. For those patients in the susceptibility-test group, the authors used what they considered the best regimen based on susceptibility testing; while for those patients in the group with no susceptibility testing, PPI-amoxicillin-metronidazole was prescribed. The cure rates in the groups with and without susceptibility testing were not different.

SECOND-LINE *H PYLORI* RESCUE THERAPY AFTER FAILURE OF ONE ERADICATION TREATMENT

Rescue regimen after PPI-clarithromycin-amoxicillin failure

PPI, amoxicillin and metronidazole: After failure of a combination of PPI, amoxicillin and clarithromycin, a theoretically correct alternative would be the use, as second option, of other PPI-based triple therapy including amoxicillin (which does not induce resistance) and metronidazole (an antibiotic not used in the first trial), and several authors have reported encouraging results with this strategy[37-44]. However, in our experience, when this therapy has been administered twice-daily for one week, eradication rates lower than 50% have been obtained[45]; the subsequent use of higher (three times per day) antibiotic doses was followed only by a mild increase in eradication rate (58%), which was still unacceptable[45]. However, if ranitidine bismuth citrate (RBC) is used instead of PPI, also plus amoxicillin and nitroimidazole, encouraging results have been reported (81% cure rate), although in this protocol antibiotics were administered for 14 d instead of 7 d[46]. In this same study, the readministration of clarithromycin, even when co-prescribed with RBC, was associated with poor eradication rates. In the same way, Nagahara *et al*[47] studied a group of patients who, after failure of first-line PPI-clarithromycin-amoxicillin therapy, had received second-line therapy with the same regimen (for 14 d) or had received PPI-amoxicillin-metronidazole (for 10 d). The eradication rates for second-line therapy with the same regimen (thus readministering clarithromycin) was only 53%, while it was 81% with PPI-amoxicillin-metronidazole. These observations underlie the idea that antibiotics, and specifically clarithromycin, should not be readministered in successive treatments.

Quadruple therapy: Another alternative, the use of a quadruple regimen (i.e. PPI, bismuth, tetracycline and metronidazole), has been generally used as an optimal second-line therapy after PPI-clarithromycin-amoxicillin failure, and has been the recommended rescue regimen in several guidelines[3,48-50]. Several studies have obtained relatively good results with this quadruple regimen, and the results are summarized in Table 1[45,51-71]. Thus, the weighted mean eradication rate with this rescue therapy, calculated from the studies included in the table, is 77%. In this combination regimen, PPI should be prescribed in the usual dose for twice a day, colloidal bismuth subcitrate 120 mg four times per day, tetracycline 500 mg four times per day, and metronidazole is probably best prescribed at high doses (i.e. 500 mg three times per day). The study with the lowest efficacy[57] administered metronidazole at low doses (250 mg four times per day). Limited experience suggests that quadruple therapy may also be effective when the first (failed) regimen included RBC instead of PPI. Thus, Beales *et al*[72] reported that four of the five patients

Table 1 Eradication rates with quadruple therapy (proton pump inhibitor, bismuth, tetracycline and a nitroimidazole) as "rescue" therapy for proton pump inhibitor-clarithromycin-amoxicillin failure

Author	Number of patients	Duration (d)	Eradication rate (%)
Baena Diez *et al*[51]	31	14	90
Bilardi *et al*[52]	46	7	37
Elizalde *et al*[53]	31	7	87
Choung *et al*[54]	56	7	77
Choung *et al*[54]	99	14	88
Chung *et al*[55]	87	7	84
Gasbarrini *et al*[56]	9	7	88
Gisbert *et al*[57]	30	7	57
Gisbert *et al*[45]	9	7	78
Gomollón *et al*[58]	21	7	95
Lee *et al*[59]	20	7	68
Lee *et al*[60]	63	7	75
Marko *et al*[61]	27	7	63
Michopoulos *et al*[62]	38	14	76
Navarro-Jarabo *et al*[63]	54	7	70
Nista *et al*[64]	70	7	63
Nista *et al*[64]	70	14	68
Orsi *et al*[65]	50	12	88
Perri *et al*[66]	45	10	67
Perri *et al*[67]	60	7	83
Sicilia *et al*[68]	21	10	83
Uygun *et al*[69]	100	14	82
Wong *et al*[70]	53	7	91
Wu *et al*[71]	47	7	77

Eradication rates by intention-to-treat analysis when available. *H pylori* eradication rate (weighted mean) with quadruple therapy is 77%.

initially failing RBC-clarithromycin-amoxicillin therapy were successfully treated with quadruple therapy. Seven-day treatment duration seems to be sufficient when quadruple therapy is used after a failed first regimen, as quite similar eradication rates with 7, 10 and 14 d have been reported (mean figures, calculated from Table 1, of 74%, 72% and 81%, respectively). Furthermore, in a recent retrospective study, patients who failed the standard triple therapy (PPI, amoxicillin, clarithromycin) received 1 or 2 wk quadruple therapy, and the eradication rate was similar between the two regimens[54]. These results are in agreement with those reported previously with quadruple therapy as a first-line regimen, where 1-wk therapy appeared sufficient, and prolonging treatment did not increase efficacy[73]. Finally, although PPIs are generally prescribed as the antisecretors in quadruple therapy, some authors have shown, in a randomized study, that omeprazole 20 mg *b.i.d.* and ranitidine 300 mg *b.i.d.* were equally effective as antisecretory agents combined in a second-line quadruple eradication regimen after failure with previous regimens without metronidazole[62]. Nevertheless, these regimens were administered over 14 d and, therefore, it remains to be demonstrated whether the equivalence between both antisecretors-PPIs and H_2-blockers- is also observable with 7 d regimens.

The question may be suggested whether treatment with PPI-clarithromycin-amoxicillin followed by rescue with quadruple therapy if initial failure occurs is preferable to the inverse strategy. To analyze this interesting aspect, Gomollón *et al*[74] randomized consecutive patients to one of two strategies: (1) treatment during 7 d with quadruple therapy, and if failure occurs then second-line treatment with omeprazole-clarithromycin-amoxicillin during 7 d; and (2) initial treatment with omeprazole-clarithromycin-amoxicillin and if failure occurs then treatment with quadruple therapy. Direct and indirect costs were estimated, and a cost-effectiveness analysis using a decision-tree model was undertaken after real clinical data. Eradication was obtained (intention-to-treat) in 73% with the first strategy, *versus* 92% with the second strategy. Furthermore, cost per case eradicated was lower in the second group (320 *versus* 296 euros). However, in a similar but more recent study, Marko *et al*[61] assessed the usefulness and the cost-effectiveness of these two treatment strategies, performing a decision analysis. The effectiveness of "triple first" and "quadruple first" strategies was similar, although the latter seemed slightly more cost-effective.

RBC, tetracycline and metronidazole: More recently, it has been reported that replacing the PPI and the bismuth compound of the quadruple therapy by RBC also achieves good results as a rescue regimen[57,75-80]. RBC is a compound that has, on the one hand, the antisecretory activity of ranitidine, and, on the other hand, the mucosal protective and anti-*H pylori* effects of certain other bismuth salts[81-83]. To date, several studies have evaluated 7-14 d RBC-based second-line regimens after PPI-based triple therapy failures, achieving encouraging results, with eradication rates of 67%[77], 68%[79], 76%[84], 82%[75], 83%[57], 86%[80], and 96%[76]. Furthermore, one randomized study has demonstrated that triple RBC-based therapy, when prescribed to patients with previous PPI-clarithromycin-amoxicillin failure, achieved an even higher efficacy than quadruple therapy, with additional advantages of a lower number of drugs and a simpler dose scheme[57]. Nevertheless, the eradication rate with a quadruple regimen in this last study was remarkably low, which was explained by the low dose of metronidazole prescribed. The favorable results obtained with RBC in the aforementioned studies were explained, at least in part, by the fact that RBC-based therapies may overcome the impact of metronidazole resistant and clarithromycin resistant strains on *H pylori* eradication treatment[18,81-83]. In summary, due to the aforementioned encouraging results, quadruple therapy (as well as RBC-based regimens) may be considered as the preferred regimen after initial treatment failure with PPI-clarithromycin-amoxicillin[3,20,78,85]. However, bismuth salts, including RBC, are no longer available worldwide, and some National Guidelines have been changed accordingly[86].

PPI, amoxicillin and levofloxacin: As previously mentioned, after failure of a combination of a PPI-based triple regimen, the use of the quadruple therapy has been generally recommended as the optimal second-line therapy based on the relatively good results reported

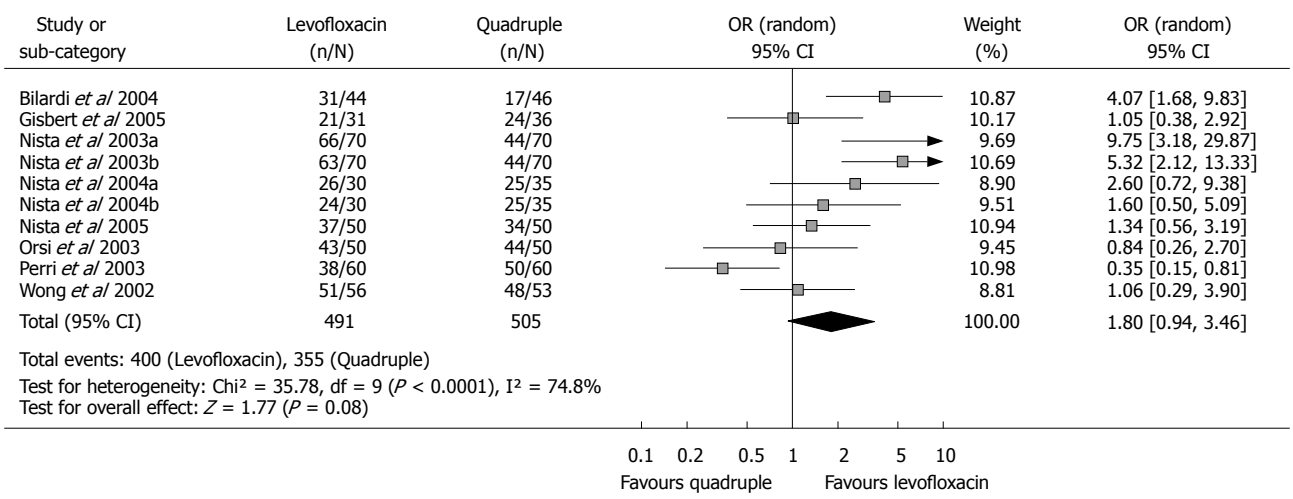

Figure 1 Meta-analysis comparing *H pylori* eradication efficacy with levofloxacin-based triple regimens *versus* quadruple therapy, as second-line "rescue" regimen after failure of a proton pump inhibitor-amoxicillin-clarithromycin.

by several authors[3,20,78,85]. However, this quadruple regimen requires the administration of 4 drugs with a complex scheme (bismuth and tetracycline usually prescribed every 6 h, and metronidazole every 8 h) and is associated with a relatively high incidence of adverse effects[20]. 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 have double resistance[20].

Levofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens[87]. 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 interestingly, as second-line regimens[21,88-90]. In this respect, levofloxacin-based second-line therapies represent an encouraging strategy for eradication failures, as some studies have demonstrated that levofloxacin has, *in vitro*, remarkable activity against *H pylori*[91], and that primary resistances to such an antibiotic are (still) relatively infrequent (when compared with metronidazole or clarithromycin)[92-96]. A recent *in vitro* study also showed a synergistic effect of quinolone antimicrobial agents and PPIs on strains of *H pylori*[97]. Furthermore, it has been shown *in vitro* that levofloxacin retains its activity when *H pylori* strains are resistant to clarithromycin and metronidazole[95,98,99]. These favorable results have been confirmed *in vivo*, indicating that most of the patients with both metronidazole and clarithromycin resistance are cured with the levofloxacin-based regimen[52,94,100].

A combination of a PPI, amoxicillin and levofloxacin, as a first-line regimen, has been associated with favorable results, with mean eradication rates of about 90%[95,101-106]. Subsequently, 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%[52,64,65,67,70,98, 100,106-111]. 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[89]. This systematic review found higher *H pylori* cure rates with a 10-d rather than a 7-d regimen, both in general (81% *vs* 73%) and also with the levofloxacin-amoxicillin-PPI combination in particular (80% *vs* 68%), suggesting that the longer (10-d) therapeutic scheme should be chosen.

Furthermore, two recent meta-analyses have suggested that after *H pylori* eradication failure, a levofloxacin-based rescue regimen is more effective than the generally recommended quadruple therapy[88,89]. In one of these meta-analyses[89], higher *H pylori* cure rates with the levofloxacin-based triple regimens than with the quadruple combinations were found (81% *vs* 70%), but with borderline statistical significance (Figure 1). Nevertheless, results were heterogeneous, mainly due to the discordant results of the study by Perri *et al*[67], who reported a cure rate of only 63% with the levofloxacin-regimen, which is the lowest reported in the literature, and is a figure that contrasts with the mean eradication rate of 80% calculated in a systematic review[89]. Nevertheless, when that single outlier study[67] was excluded from the meta-analysis, the difference between cure rates with both regimens reached statistical significance and 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 heterogeneity among studies almost disappeared[89].

As previously mentioned, the quadruple regimen requires the administration of a complex scheme[20]. On the contrary, levofloxacin-based regimens (with amoxicillin and PPIs administered twice daily, and levofloxacin every 12 or 24 h) represents 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[20]. In contrast, levofloxacin is generally well tolerated, and most adverse events associated with its use are mild to moderate in severity and transient[87]. The most frequent adverse effects affect the gastrointestinal tract[87]. Occasional cases of tendinitis and tendon rupture have been reported in the literature with levofloxacin therapy[52,87]. However, data derived from more than 15 million prescriptions in the US indicated the rate is fewer than 4 per million prescriptions[112]. In the aforementioned systematic review[89], 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 the cases. Furthermore, the incidence of adverse effects was not different when levofloxacin-amoxicillin-PPI was administered for 7 d or 10 d, supporting the aforementioned recommendation of prescribing the more effective 10-d regimen. Moreover, two meta-analyses have demonstrated a lower incidence of adverse effects with levofloxacin-based treatments than with the quadruple combinations[88,89].

Unfortunately, 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[94,103,107,113-123]. More importantly, it has been demonstrated that the presence of levofloxacin resistance significantly reduce the eradication rate following a therapy with this antibiotic[94,103,121,124]. Therefore, it has been suggested to reserve levofloxacin for rescue treatment to avoid the increase of the resistance phenomenon.

Rescue regimen after PPI-amoxicillin-nitroimidazole failure

After PPI-amoxicillin-nitroimidazole failure, retreatment with PPI-amoxicillin-clarithromycin has proved to be very effective, and it seems to be a logical strategy, as while amoxicillin is maintained (which does not induce resistance), clarithromycin is substituted for metronidazole. Furthermore, the absence of cross-resistance among nitroimidazoles and clarithromycin favors this position. With this therapy, some authors[45] have achieved *H pylori* eradication in 85% of cases, while others have reported success rates of 86%[125] or even 100%[126]. In favor of this strategy is the study by Magaret *et al*[127], who studied a group of 48 patients after failure of previous *H pylori* therapy with a metronidazole-containing regimen, and randomized them to either lansoprazole, amoxicillin and clarithromycin twice daily for 14 d, which is the logical approach with triple therapy not repeating metronidazole, or to lansoprazole, bismuth, metronidazole and tetracycline for 14 d, which is the quadruple therapy repeating metronidazole. Intention-to-treat efficacies were 75% for a triple regimen and 71% for a quadruple. Although this difference did not reach statistical significance, the small sample size of this study does not preclude the possibility of a small but clinically significant difference in efficacy between the regimens. Finally, preliminary studies have suggested that RBC may be used instead of PPI in this triple second-line strategy (i.e., RBC-clarithromycin-amoxicillin), with similar or even better results[72].

Rescue regimen after PPI-clarithromycin-nitroimidazole failure

As previously mentioned, acquired bacterial resistance to metronidazole or clarithromycin results primarily from the previous treatment failure[26,32], and therefore the first choice probably should not be a regimen that combines these two antibiotics in the same regimen[23,24,128]. Although this regimen is very effective[4], patients who are not cured will probably have double resistance[26,129], and no logical empirical treatment remains afterwards (although, more recently, the levofloxacin-based regimens may represent an option). Thus, some authors have demonstrated that initial regimens containing both clarithromycin and nitroimidazole are associated with significantly worse results overall, with lower eradication rates after logically chosen second-line therapy and sensitivity-directed third-line therapy; these poor results were due to the emergence of multiple resistant strains as evidenced by the results of culture testing after the second failed course[72]. In summary, due to problems with resistance it could be suggested that both key antibiotics-clarithromycin and metronidazole- should not be used together until a valid empirical back up regimen is available[23].

Nevertheless, if culture is not performed after failure of PPI-clarithromycin-metronidazole, and hence antibiotic susceptibility is unknown, several rescue options may be suggested. Firstly, omeprazole plus amoxicillin, with a high dose of both the antibiotic and the antisecretor, could, in theory, be recommended[128,130]; however, we must remember that this "old-fashioned" dual combination has achieved disappointing results in many countries. Therefore, a second antibiotic should be added, and at this point a difficult decision appears, as both antibiotics used in the first trial (clarithromycin and metronidazole) are capable of inducing secondary resistance to *H pylori*, playing a negative role in future efficacy[25-29,131]. Nevertheless, the following possibilities exist:

Readministering metronidazole: Due to the fact that metronidazole resistance is frequent and clinically relevant[25-28], if this antibiotic is readministered, it should be used within a bismuth-based quadruple regimen (thus PPI might reduce the negative effect of metronidazole resistance[28,58,132,133]). With this regimen, eradication rates up to 80% have been achieved[45]. RBC, which may overcome the impact of resistance to metronidazole[81], may also play a role in this regimen. Thus, some authors have reported an 88% cure rate with a 2-wk regimen or RBC-tetracycline-tinidazole in patients who had previously failed a clarithromycin-tinidazole based triple therapy[76].

Readministering clarithromycin: Several studies have underlined the relevance of clarithromycin

resistance[25-27,29], and advise against readministering this antibiotic. Therefore, a further option which has been proposed, is to add (for example to PPI-amoxicillin-clarithromycin) a fourth medication (such as bismuth) with a bactericidal effect against *H pylori*, with which a 70% eradication rate has been achieved[45].

Readministering no antibiotic: A final alternative, obviously, consists of no readministering of either metronidazole or clarithromycin. Although only published in abstract form, one study has prescribed RBC, tetracycline and amoxicillin for 2 wk and has reported eradication in 89% of the cases which had previously failed PPI, clarithromycin and tinidazole[134]. These encouraging results may be due, at least in part, to the use of RBC instead of bismuth in this regimen, as "classic" triple therapy with bismuth, tetracycline and amoxicillin have been previously considered relatively ineffective. Finally, although not specifically evaluated in PPI-clarithromycin-metronidazole failures, rifabutin or levofloxacin-based regimens (e.g. PPI, amoxicillin and either levofloxacin or rifabutin) could play a role in this difficult situation.

IS IT NECESSARY TO PERFORM CULTURE AFTER FAILURE OF THE SECOND ERADICATION TREATMENT?

As previously mentioned, it has been generally recommended that performing culture after a first eradication failure is not necessary, and therefore assessing *H pylori* sensitivity to antibiotics only after failure of the second treatment may be suggested in clinical practice[3,23,48,135]. However, the utility of the culture (with consequent antibiotic susceptibility testing) and the moment when it must be performed after eradication failure are both controversial[21]. It is evident that, as pretreatment, antibiotic resistance is the most important factor in nonresponse to initial treatment[25-29], and knowledge of the organism's antibiotic susceptibility may represent an aid in selecting the therapy regimen. However, performing culture systematically after the second eradication failure also has some limitations, which are summarized as follows:

(1) Culture implies, obviously, the performance of endoscopic exploration, which has several disadvantages: it is not free of risk, and, since endoscopy centers have been meeting increasing demand, culture usually involves prolonged waiting times.

(2) *H pylori* culture is expensive, due to the cost of the procedure itself, but mainly the costs of the associated endoscopy, which is necessary to obtain biopsy samples.

(3) Culture is time-consuming, as *H pylori* is a rather "fastidious" bacterium at culture, especially when a low bacterial load is present, as generally occurs after eradication failure[22].

(4) Culture is not always available on a routine basis.

(5) The sensitivity of bacterial culture is not 100%, and therefore the antimicrobial susceptibility cannot be obtained in all cases[136]. Indeed, even in the optimal conditions usually encountered in therapeutic trials- when both gastroenterologist and microbiologist are thoroughly motivated- a culture sensitivity of "only" approximately 90% has been achieved in patients not previously treated[22]. Furthermore, in several studies enrolling patients who had failed one or more eradication treatments, the bacterium was isolated in less than 80% of cases[22]. Therefore, an even lower probability of isolating the bacterium is to be expected in routine clinical practice. This indicates that, even in the hands of experts, antimicrobial sensitivity would not be obtained in several eradication failure patients, who had undergone an upper endoscopy solely for bacterial culture[22].

(6) Antibiotic susceptibility testing in clinical practice yields useful information only regarding a few antibiotics. Antibiotics effective and generally used against *H pylori* are mainly the following four: amoxicillin, clarithromycin, metronidazole, and tetracycline. Resistance to amoxicillin has been estimated to be less than 1% in most studies[18,22]. Hence, its role in clinical practice may even be marginalized. Similarly, resistance to tetracycline is also very low, or even absent, in most countries[18,22]. Therefore, it may even be assumed that antibiotic susceptibility testing in clinical practice yields useful information only regarding the latter two antibiotics, namely clarithromycin and metronidazole[22].

(7) *In vitro* antibiotic susceptibility does not necessarily lead to eradication *in vivo*. Even knowing the susceptibility of *H pylori*, eradication rates do not achieve 100%, as the results observed *in vivo* by following *in vitro* susceptibility to anti-*H pylori* antibiotics are often disappointing[137]. Some discrepancies between antibiotic susceptibility and *H pylori* eradication may occur, due for example, to the possibility of co-infection with different *H pylori* strains[138]. Thus, a variable proportion of non-eradicated patients is made of subjects who harbor strains sensitive to the administered drugs, and in these patients the reasons for treatment failure are unclear[139]. For example, Gomollón *et al*[140] reported how third-line treatment often (in 50% of the cases) failed to eradicate *H pylori* infection, in spite of giving a 14-d, full-dose, quadruple culture-guided combination, showing that *in vitro* susceptibility did not predict eradication success. In the same way, Vicente *et al*[141] determined the effectiveness of a third, culture-guided, treatment of *H pylori* infection after two unsuccessful attempts. Patients received a two-week quadruple culture-guided therapy, and overall eradication was achieved in only 60% of the patients. In fact, paradoxically, the lowest eradication rate was obtained in patients with *H pylori* strains sensitive to all antibiotics. In summary, it seems that despite the use of culture-guided combinations of drugs, a third treatment is frequently unsuccessful, indicating that other factors, different from *in vitro* antibiotic susceptibility, influence eradication rates. On the other hand, the reverse situation is also possible, as *H pylori* eradication may, nonetheless, be achieved in the presence of metronidazole- or clarithromycin-

resistant strains, even with a drug combination including these antibiotics. Therefore, *in vitro* resistance to either clarithromycin or metronidazole could be overcome *in vivo* in a significant proportion of patients by prescribing the same antibiotics[22].

(8) When a repeat (rescue) therapy must be selected, we have several data that will aid us in suspecting resistance to a particular antibiotic, without the necessity of a culture, based on the observation that acquired bacterial resistance to metronidazole or clarithromycin results primarily from previous treatment failure[26,32]. Thus, when a therapy with clarithromycin fails, resistance to this antibiotic appears in most cases, and the same is true when a nitroimidazole is the antibiotic first used[18,29,131,142]. Even if resistance to these antibiotics does not appear, it remains uncertain whether their readministration is adequate, as they were not efficacious (for unknown reasons) for the first time. Some studies suggest that retreatment of *H pylori* infection with the same combination is still a choice when the status of bacterial resistance to antibiotics is unknown, however, full doses and a longer treatment duration must be used and a poor eradication rate has usually been reported[143]. Therefore, the position in the case of therapy failure would be clear: do not readminister any of the antibiotics against which *H pylori* has probably become resistant[1,49].

(9) Finally, relatively high eradication rates have been obtained with *empirical* third-line treatment after two consecutive failures in several studies[76,144-156].

However, limited experience suggests that endoscopy with culture and susceptibility testing may be appropriate after failure of two eradication therapies; in this situation, a non-randomized retrospective study suggests that third-line therapy directed by the results of sensitivity testing improve eradication compared to further empirical antibiotics, demonstrating that the success rate of sensitivity-directed therapy is superior to PPI-amoxicillin-rifabutin triple therapy, and therefore suggesting that endoscopy and sensitivity testing at this point may be worthwhile rather than more widespread use of rifabutin-based regimens[72]. Cammarota *et al*[122] assessed the efficacy of a third-line, culture-guided treatment approach for the eradication of *H pylori*. After the first two eradication attempts, all patients were resistant to metronidazole, and 95% were resistant to clarithromycin. Consequently, most patients (89 out of 94) received a quadruple regimen including PPI, bismuth, tetracycline and amoxicillin, and *H pylori* eradication was obtained in 90% of the cases. Although the authors concluded that a culture-guided, third-line therapeutic approach is effective for the eradication of *H pylori*, it would seem more appropriate to conclude, in fact, that the tetracycline- and amoxicillin-based quadruple regimen may be a good *empirical* third-line rescue treatment option (as to choose such a regimen, which implies not readministering metronidazole or clarithromycin, it would not be necessary to know antibiotic susceptibilities).

In summary, when critically reviewing the role of culture in the management of *H pylori* infection in clinical practice it may be concluded, in coincidence with other authors, that *H pylori* culture is an invasive, time-consuming method, offering quite low sensitivity, requiring significant cost, and which, in practice, tests very few antibiotics, with a questionable contribution to the management of non-responder patients[22,157]. Obviously, the importance of *H pylori* culture remains unaltered both in epidemiological and pharmacological research fields. However, whether patients should undergo an upper endoscopy for bacterial culture after second-line therapy failure remains a debatable matter, and the role of culture in clinical practice requires a critical reappraisal[22,157]. As it has been brilliantly expressed by Zullo *et al*, regrettably, gastroenterologists need to accept that gastric biopsy culture is not as simple as filling a sample bottle![22]

Nevertheless, it is recommended that those prescribing *H pylori* eradication therapies continually assess their success rate and adjust the relevant local practices and policies in line with the results and local bacterial resistance patterns. Thus, it would be recommendable that culture should be routinely performed after eradication failure in some specialized centers with special interest in *H pylori* research and treatment, with the intention to study the incidence of resistances after failures and also to evaluate the influence of such resistances on the efficacy of rescue regimens[158]. Data coming from this experience on *H pylori* resistance will be used as a reference for the corresponding population. This preventive approach has been recommended to avoid an increase in refractory *H pylori* infection in the future[158].

EMPIRICAL THIRD-LINE *H PYLORI* RESCUE THERAPY AFTER FAILURE OF TWO ERADICATION TREATMENTS

If it is decided, finally, not to perform culture before the administration of a 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 eradication regimens may be less efficacious for retreatment, as compared to their efficacy when used as primary treatment, it may be suggested that the course of the rescue therapy should be extended to 10-14 d, at least when rescue therapy fails and third-line regimens are therefore prescribed[159]. As several studies have underlined the relevance of metronidazole[25-28] and clarithromycin[25-27,29] resistance, these two antibiotics should not be readministered, and several regimens have been evaluated in this scenario.

Amoxicillin ± tetracycline-based regimens

In a recent study, patients with at least one treatment failure who were infected with *H pylori* resistant to both metronidazole and clarithromycin, were treated with high doses of omeprazole (4 × 40 mg) and amoxicillin (4 × 750 mg) for 14 d, and the infection was cured

Table 2 Rifabutin-based "rescue" therapies (rifabutin-amoxicillin-proton pump inhibitor) in patients with previously failed eradication treatments and/or resistance to clarithromycin and nitroimidazoles

Author	Number of patients	Drugs and doses	Duration of treatment (d)	Eradication rate (%)
Beales *et al*[72]	10	Rifabutin 300 mg *o.d.* Amoxicillin 1 g *b.i.d.* Omeprazole 20 mg *b.i.d.*	14	60
Bock *et al*[152]	25	Rifabutin 150 mg *b.i.d.* Amoxicillin 1 g *b.i.d.* Lansoprazole 30 mg *b.i.d.*	7	72
Borody *et al*[169]	67	Rifabutin 150 mg *b.i.d.* Amoxicillin 1-1.5 g *t.i.d.* Pantoprazole 60 mg *t.i.d*	12	90
Canducci *et al*[153]	10	Rifabutin 300 mg *o.d.* Amoxicillin 1 g *b.i.d.* Omeprazole 20 mg *b.i.d.*	10	70
Gisbert *et al*[149]	14	Rifabutin 150 mg *b.i.d.* Amoxicillin 1 g *b.i.d.* Omeprazole 20 mg *b.i.d.*	14	79
Gisbert *et al*[155]	20	Rifabutin 150 mg *b.i.d.* Amoxicillin 1 g *b.i.d.* Omeprazole 20 mg *b.i.d.*	10	45
Gonzalez Carro[170]	92	Rifabutin 150 mg *b.i.d.* Amoxicillin 1 g *b.i.d.* Pantoprazole 40 mg *b.i.d*	10	61
Miehlke *et al*[130]	73	Rifabutin 150 mg *b.i.d.* Amoxicillin 1 g *b.i.d.* Esomeprazole 20 mg *b.i.d.*	7	74
Navarro-Jarabo *et al*[63]	45	Rifabutin 150 mg *b.i.d.* Amoxicillin 1 g *b.i.d.* Omeprazole 20 mg *b.i.d.*	7	44
Perri *et al*[151]	41	Rifabutin 300 mg *o.d.* Amoxicillin 1 g *b.i.d.* Pantoprazole 40 mg *b.i.d.*	7	71
Toracchio *et al*[171]	65	Rifabutin 150 mg *b.i.d.* Amoxicillin 1 g *b.i.d.* Pantoprazole 40 mg *b.i.d.*	10	78
Van der Poorten *et al*[172]	44	Rifabutin 150 mg *b.i.d.* Amoxicillin 1 g *b.i.d.* PPI *b.i.d.*	10	68

PPI: Proton pump inhibitor (omeprazole, pantoprazole, rabeprazole or esomeprazole) at the usual dose. Eradication rates by intention-to-treat analysis when available. *H pylori* eradication rate (weighted mean) with rifabutin-based "rescue" therapy is 69%.

in 76% of the cases[160]. This study suggests that, although the "old-fashioned" dual combination of omeprazole plus amoxicillin is generally considered quite ineffective as a first-line regimen, it may be associated with relatively good results if prescribed at high doses, even for *H pylori* resistant to both metronidazole and clarithromycin, in patients who experienced previous treatment failures. Another possibility to avoid retreatment with clarithromycin or metronidazole is to prescribe a quadruple combination of PPI, bismuth, tetracycline and amoxicillin (instead of metronidazole), which has been used by some authors with favorable results[161]. Nevertheless, this regimen has been tested only as second-line (and not third-line) therapy, and only after failure of PPI-clarithromycin-amoxicillin (and not after metronidazole-based therapy), emphasizing that the experience should be extended to patients with two previous eradication failures containing both clarithromycin and metronidazole. Finally, as previously mentioned, one study prescribed RBC, tetracycline and amoxicillin for 2 wk and achieved eradication in 89% of the cases which had previously failed PPI, clarithromycin and tinidazole[134].

Levofloxacin-based rescue regimens

It has been suggested that levofloxacin-based therapies may also represent an alternative when two (or more) consecutive eradication treatments have failed to eradicate the infection[52,94,118,147,154,155,162-164]. As an example, a recent study by Zullo *et al*[147] aimed to evaluate the efficacy of a levofloxacin-amoxicillin-PPI combination in patients who previously had failed two or more therapeutic attempts, and they found the eradication rate was 83% (intention-to-treat analysis). More recently, Gisbert *et al*[155] evaluated, in a multicenter study including 100 patients, the efficacy of a third-line levofloxacin-based regimen in patients with two consecutive *H pylori* eradication failures. An intention-to-treat 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, as will be reviewed in the following section, also constitutes a possible strategy after previous eradication failures, although it has been recently shown that a 10 d triple levofloxacin-based regimen is more effective than the same combination with rifabutin as a rescue regimen[155]. 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).

Rifabutin-based rescue regimens

As previously mentioned, the evaluation of drugs without cross-resistance to nitroimidazole or macrolides as components of retreatment combination therapies seem to be worthwhile. *H pylori* has been proved to be highly susceptible *in vitro* to rifabutin, a rifamycin derivate of the established tuberculostatic drug[165-167]. Moreover, rifabutin is chemically stable at a wide pH range and its antibacterial activity is likely not to be hampered by the acidic environment of the stomach[168]. Furthermore, selection of resistant *H pylori* strains has been low in experimental conditions. Thus, until now, no rifabutin resistant strain has been isolated from patients who were either treated or untreated for *H pylori* infection[166].

As summarized Table 2, rifabutin-based rescue therapy constitutes an encouraging strategy after multiple previous eradication failures[63,72,130,149,151-153,155,169-172]. As an example, Perri *et al*[151,173] used a 1-wk regimen of PPI, amoxicillin and rifabutin in patients who were still *H pylori* infected after two or more courses of PPI-based triple therapies, and achieved an eradication rate of 71% by intention-to-treat analysis. Gisbert *et al*[149], in a prospective multicenter study, included patients in whom a first eradication trial with PPI, clarithromycin and amoxicil-

lin and a second trial with PPI, bismuth, tetracycline and metronidazole had failed. A third 14 d eradication regimen with rifabutin, amoxicillin and a PPI was effective in 79% of the patients (intention-to-treat analysis). However, these encouraging results were not confirmed in a more recent study by these same authors[155]. In the largest study on rifabutin[170], 92 consecutive patients diagnosed with *H pylori* infection resistant to two previous treatment regimens were treated with a PPI, rifabutin and amoxicillin for 10 d and the intention-to-treat eradication rate was 61%. In summary, the weighted mean eradication rate with rifabutin-based rescue therapy, calculated from the studies included in the Table 2, is 69%.

These findings suggest that new rifabutin-based combinations are effective for *H pylori* strains resistant to antibiotics, and specifically to clarithromycin or metronidazole[174]. Furthermore, rifabutin-based therapies have been compared with the widely used "classic" quadruple therapy. Perri *et al*[66] performed a randomized study where three groups of patients were treated for 10 d with pantoprazole, amoxicillin, and rifabutin 150 mg *o.d.*, or 300 mg *o.d.*, and quadruple therapy. On intention-to-treat analysis, eradication rates were 67% in the rifabutin 150 mg and quadruple groups, and higher (87%) in the rifabutin 300 mg group. Finally, in this comparative study, side-effects were less frequent in rifabutin-treated patients than in those on quadruple therapy[66].

Several concerns still remain, however, regarding rifabutin treatment. Firstly, this drug is very expensive. Secondly, severe leucopenia and thrombocytopenia have been reported in one patient treated with rifabutin, with myelotoxicity demonstrated by bone marrow aspirate[153]. Although blood cell count returned to normal at day 15 after discontinuation of therapy, physicians should be aware of the risk of major side-effects arising during a rifabutin-based regimen[149,155]. Finally, there is some concern about wide-spread use of rifabutin, a member of a class of established antimycobacterial drugs, in patients with *H pylori* infection. Because multiresistant strains of *Mycobacterium tuberculosis* increase in numbers, indications for these drugs should be chosen very carefully to avoid further acceleration of development of resistance[152]. At present, therefore, rifabutin should be considered only as the last option (e.g. restricted to infected patients even after several eradication regimens including, among them, levofloxacin).

Furazolidone-based rescue regimens

Furazolidone is an antimicrobial drug that belongs to synthetic nitrofurans and is active against a broad spectrum of gram-negative and gram-positive bacteria and protozoa. This antibiotic has demonstrated a high antimicrobial activity against *H pylori* if given as a single drug[175], and the majority of first-line furazolidone-based combination therapies revealed eradication rates above 80%[92]. Primary resistance to furazolidone is virtually absent[158,176,177], and its potential to develop resistance is as low as for bismuth compounds or amoxicillin[178]. Moreover, this drug has no cross-resistance potential to metronidazole[176]. Triple therapy in which furazolidone is used instead of metronidazole achieves high eradication rates, even in populations with a high prevalence of nitroimidazole resistance[179-182]. In this respect, a recent study has evaluated furazolidone-based triple therapy (combined with bismuth and tetracycline) in the eradication of *H pylori* resistant to metronidazole, with favorable results (86% eradication rate)[183]. A few years ago, some authors tested a quadruple combination of furazolidone, bismuth, tetracycline and PPI as a second-line eradication therapy, and reported encouraging results[184]. More recently, Treiber *et al*[145] investigated whether this quadruple regimen containing furazolidone could be effective as a third-line therapy in patients with *H pylori* treatment failure after first-line (clarithromycin-metronidazole ± amoxicillin) and second-line (PPI-bismuth-tetracycline-metronidazole) regimens, and *H pylori* infection was cured in up to 90% of the cases. Furthermore, a 7 d triple-regimen comprising furazolidone, amoxicillin and a PPI achieved an eradication rate of 60% in 10 patients who failed first-line, second-line and even rifabutin-based triple therapy[185].

A recent systematic review and meta-analysis of the effect of furazolidone- and nitrofurantoin-based regimens in the eradication of *H pylori* infection has been performed[186]. The pooled eradication rate of primary PPI-based regimens containing furazolidone was 76%. Second-line schedules containing furazolidone obtained eradication rates of 76%. Finally, third-line rescue therapies were effective in 65% of the cases. In summary, a quadruple regimen including furazolidone, bismuth, tetracycline and PPI seems to represent a promising alternative after two consecutive failures with regimens including both metronidazole and clarithromycin.

CUMULATIVE ERADICATION RATES WITH THREE (OR MORE) CONSECUTIVE ERADICATION TREATMENTS

In patients with conditions where the indication for *H pylori* eradication is definitively accepted, as is the case of peptic ulcer disease (or gastric MALT lymphoma), rescue treatment after first-line failure is clearly advisable. Furthermore, if the second therapy fails, a third or even a fourth regimen should be prescribed, as infected patients continue to have high risk of ulcer recurrence and ulcer complications and are in an obviously disadvantageous situation in view of the enormous benefits that follow *H pylori* eradication in peptic ulcer disease: increased ulcer healing, less ulcer recurrence, and less ulcer bleeding. However, multiple repeated antibiotic treatment of patients where benefits of *H pylori* eradication has not been so clearly established, such as those with functional dyspepsia[174,187], may not be completely justified.

Some authors have evaluated, in the same study,

different regimens after failure of two eradication treatments, which provide interesting information about cumulative, and not only absolute, eradication rates[21]. For example, in the study by Gasbarrini *et al*[188], a total of 2606 patients were administered a PPI, tinidazole and clarithromycin for 1 wk. Patients with continuing infection were then given a second 1-wk course of amoxicillin, clarithromycin and RBC. Finally, patients still infected after the second course underwent upper gastrointestinal endoscopy with *H pylori* culture, and then received a 1-wk quadruple scheme established on antibiotic sensitivity. Eradication rates after the first, second and third treatment, were, respectively, 79%, 77%, and 52%. This algorithm led to overall per-protocol eradication rates of 99%. Chan *et al*[146] prescribed quadruple therapy to a group of patients who had failed to respond to RBC-based regimens (as first regimen) and PPI-clarithromycin-amoxicillin combination (as second regimen), and achieved successful eradication in 83% of the cases receiving a quadruple regimen, finally achieving a 99% cumulative eradication rate. Beales *et al*[72] evaluated 469 patients receiving eradication therapy in routine clinical practice. Second-line therapy was chosen empirically, using whichever of clarithromycin or metronidazole was not used initially. All patients requiring third-line therapy underwent endoscopy, choice of therapy being guided by sensitivities. Overall success after one, two and three courses of therapy were 73%, 94% and 98%, respectively. Zullo *et al*[76] reported 83% cure rate in patients who had previously failed two courses of clarithromycin-amoxicillin and clarithromycin-tinidazole based triple therapies. Gomollón *et al*[140] studied the effectiveness of third-line treatment of *H pylori* infection with two-week quadruple, culture-guided regimens. The combination of omeprazole, tetracycline, bismuth and clarithromycin showed an eradication rate of only 36%, but if amoxicillin was used the rate was 67%. In the study by Vicente *et al*[141], after two unsuccessful attempts at eradication, all patients underwent endoscopy and culture, and patients received a quadruple culture-guided therapy. Cumulative *H pylori* eradication rate with this strategy was as high as 99.6%. Treiber *et al*[145] investigated whether a quadruple regimen containing furazolidone could be effective as a third-line therapy in patients with two previous *H pylori* treatment failures. Cure of *H pylori* was achieved in 90% of the patients nonresponsive to a second eradication trial, which gave a final eradication rate of 99%. In the study by Qasim *et al*[185], 3280 patients received standard first-line eradication therapy, which was successful in 77% of the cases. Second-line therapy (bismuth-based quadruple) or triple therapy (altering constituent antibiotics) was successful in 56% of treated patients. Subsequent eradication attempts using rifabutin-based regimen was successful in 38% of patients, giving a cumulative eradication rate of 94%. Gisbert *et al*[150] included consecutive patients in whom two eradication regimens had failed to eradicate *H pylori*, prescribed empirical third-line rescue regimens, and achieved *H pylori* eradication in 71% of the cases (intention-to-treat analysis). Based on these results, with estimated efficacy of 85%, 75% and 71%, respectively with first, second and third regimens, *H pylori* eradication could finally be achieved in 99% of the patients. Finally, Gisbert *et al*[156] evaluated the efficacy of different rescue therapies empirically prescribed during 10 years to 500 patients in whom at least one eradication regimen had failed to cure *H pylori* infection. Antibiotic susceptibility was unknown (therefore rescue regimens were chosen empirically). Overall, *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%.

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. Thus, as represented in Figure 2, it can be concluded that *H pylori* eradication can finally be achieved in almost 100% of the patients if three rescue therapies are consecutively given[72,76,140,141,144-146,150,156,185,188].

Furthermore, these encouraging (cumulative) results have been obtained when more than three consecutive treatments have been prescribed[21]. As an example, Seppälä *et al*[144] reported a cumulative eradication rate of 93% (intention-to-treat analysis) and even 100% (per-protocol analysis) after four empirical retreatments. We have recently confirmed that a 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[163]. Thus, we prospectively evaluated 10 patients with three consecutive *H pylori* eradication failures (1st treatment with PPI-clarithromycin-amoxicillin, 2nd treatment with RBC-tetracycline-metronidazole, and 3rd treatment with PPI-amoxicillin-rifabutin). A fourth eradication regimen with 10 d levofloxacin, amoxicillin and PPI was prescribed, and intention-to-treat eradication rates were 70%. When we reviewed our experience with different rescue therapies empirically prescribed during 10 years to 500 patients, the cumulative *H pylori* eradication rate with 4 successive treatments was 99.5%[156].

Finally, reports of "ineradicable" *H pylori* infection after more than four eradicating treatments failed have been recently published. Dore *et al*[148] prescribed a quadruple combination of PPI, bismuth, tetracycline, and metronidazole to patients who had failed two or more treatment courses of *H pylori* eradication therapy (33 patients had failed prior treatment twice, 19 had failed three times, and 16 had failed four or more times); despite this *a priori* difficult task, *H pylori* eradication was finally achieved in 93% of the patients. Tucci *et al*[189] reported their experience of 13 patients with at least 5 eradication failures and *H pylori* strains resistant to both clarithromycin and nitroimidazoles. The treatment was organized into three sequential schedules employing partially different drug combinations (to face the various resistant strains), suspension formulations were preferred to tablets (to improve the dispersal of the drugs into the stomach), antibiotics were administered after meals and

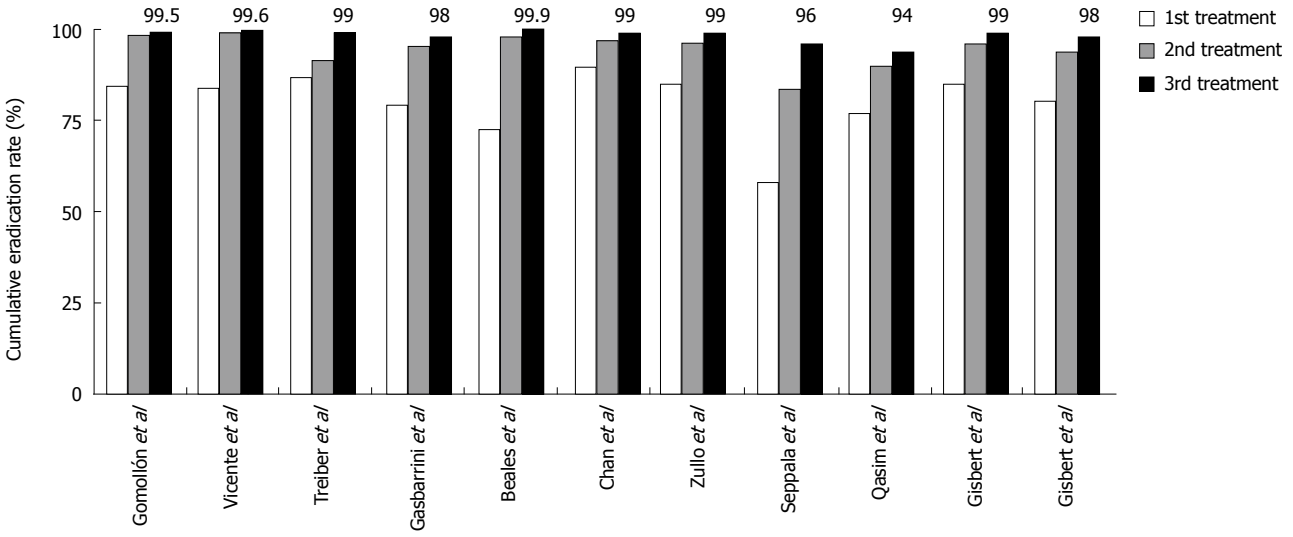

Figure 2 Cumulative *H pylori* eradication rates with three consecutive eradication treatments.

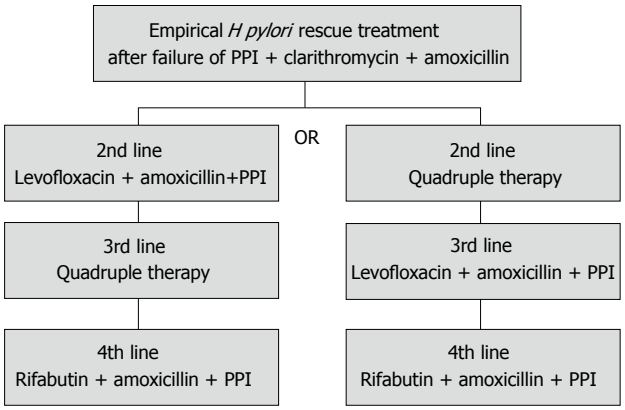

Figure 3 Choice of a empirical retreatment regimen, without culture and antimicrobial sensitivity testing, after failure of proton pump inhibitor (PPI), amoxicillin and clarithromycin combination. Quadruple therapy: Combination of PPI, bismuth, tetracycline and nitroimidazole (metronidazole or tinidazole).

a variation on a standard diet exceeding the normal fat composition was given (to increase the time of contact of the antimicrobials with gastric mucosa), and patients were invited to lie down after the meals, changing their position every 5 min (to facilitate the penetration of drugs amid the anfractuosities of fundic mucosa). With this particular therapy, eradication was successful in 70% of the patients. In another example of "ineradicable" *H pylori* infection, levofloxacin-amoxicillin combination was successfully employed in a patient with a clarithromycin- and metronidazole-resistant strain, who previously failed eight consecutive therapeutic attempts[162].

CONCLUSION

Even with the current most effective treatment regimens, ⩾ 20% of patients will fail to eradicate *H pylori* infection. This issue seems important at the present time, as therapy for *H pylori* infection is becoming more and more frequently prescribed. Currently, apart from having to know first-line eradication regimens well, 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 choice of a rescue treatment depends on which treatment is used initially. If a first-line clarithromycin-based regimen was 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. 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, 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 several rescue therapies are consecutively given. As a final conclusion, therefore, the attitude in *H pylori* eradication therapy failure, even after two or more unsuccessful attempts, should be to fight and not to surrender[190].

REFERENCES

1 **Howden CW**, Hunt RH. Guidelines for the management of Helicobacter pylori infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 1998; **93**: 2330-2338

2 **Malfertheiner P**, Megraud F, O'Morain C, Hungin AP, Jones R, Axon A, Graham DY, Tytgat G. Current concepts in the management of Helicobacter pylori infection--the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* 2002; **16**: 167-180

3 **Malfertheiner P**, Megraud F, O'Morain C, Bazzoli F, El-

Omar E, Graham D, Hunt R, Rokkas T, Vakil N, Kuipers EJ. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. *Gut* 2007; **56**: 772-781

4 **Gisbert JP**, Gonzalez L, Calvet X, Garcia N, Lopez T, Roque M, Gabriel R, Pajares JM. Proton pump inhibitor, clarithromycin and either amoxycillin or nitroimidazole: a meta-analysis of eradication of Helicobacter pylori. *Aliment Pharmacol Ther* 2000; **14**: 1319-1328

5 **Gisbert JP**, Pajares R, Pajares JM. Evolution of Helicobacter pylori therapy from a meta-analytical perspective. *Helicobacter* 2007; **12** Suppl 2: 50-58

6 **Hawkey CJ**, Atherton JC, Treichel HC, Thjodleifsson B, Ravic M. Safety and efficacy of 7-day rabeprazole- and omeprazole-based triple therapy regimens for the eradication of Helicobacter pylori in patients with documented peptic ulcer disease. *Aliment Pharmacol Ther* 2003; **17**: 1065-1074

7 **Paoluzi P**, Iacopini F, Crispino P, Nardi F, Bella A, Rivera M, Rossi P, Gurnari M, Caracciolo F, Zippi M, Pica R. 2-week triple therapy for Helicobacter pylori infection is better than 1-week in clinical practice: a large prospective single-center randomized study. *Helicobacter* 2006; **11**: 562-568

8 **Veldhuyzen Van Zanten S**, Machado S, Lee J. One-week triple therapy with esomeprazole, clarithromycin and metronidazole provides effective eradication of Helicobacter pylori infection. *Aliment Pharmacol Ther* 2003; **17**: 1381-1387

9 **Vakil N, Lanza F**, Schwartz H, Barth J. Seven-day therapy for Helicobacter pylori in the United States. *Aliment Pharmacol Ther* 2004; **20**: 99-107

10 **Laine L**, Fennerty MB, Osato M, Sugg J, Suchower L, Probst P, Levine JG. Esomeprazole-based Helicobacter pylori eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *Am J Gastroenterol* 2000; **95**: 3393-3398

11 **Laine L**, Suchower L, Frantz J, Connors A, Neil G. Twice-daily, 10-day triple therapy with omeprazole, amoxicillin, and clarithromycin for Helicobacter pylori eradication in duodenal ulcer disease: results of three multicenter, double-blind, United States trials. *Am J Gastroenterol* 1998; **93**: 2106-2112

12 **Calvet X**, Ducons J, Bujanda L, Bory F, Montserrat A, Gisbert JP. Seven versus ten days of rabeprazole triple therapy for Helicobacter pylori eradication: a multicenter randomized trial. *Am J Gastroenterol* 2005; **100**: 1696-1701

13 **Gisbert JP**, Dominguez-Munoz A, Dominguez-Martin A, Gisbert JL, Marcos S. Esomeprazole-based therapy in Helicobacter pylori eradication: any effect by increasing the dose of esomeprazole or prolonging the treatment? *Am J Gastroenterol* 2005; **100**: 1935-1940

14 **Della Monica P**, Lavagna A, Masoero G, Lombardo L, Crocella L, Pera A. Effectiveness of Helicobacter pylori eradication treatments in a primary care setting in Italy. *Aliment Pharmacol Ther* 2002; **16**: 1269-1275

15 **Altintas E**, Sezgin O, Ulu O, Aydin O, Camdeviren H. Maastricht II treatment scheme and efficacy of different proton pump inhibitors in eradicating Helicobacter pylori. *World J Gastroenterol* 2004; **10**: 1656-1658

16 **Gumurdulu Y**, Serin E, Ozer B, Kayaselcuk F, Ozsahin K, Cosar AM, Gursoy M, Gur G, Yilmaz U, Boyacioglu S. Low eradication rate of Helicobacter pylori with triple 7-14 days and quadriple therapy in Turkey. *World J Gastroenterol* 2004; **10**: 668-671

17 **Vakil N**, Hahn B, McSorley D. Clarithromycin-resistant Helicobacter pylori in patients with duodenal ulcer in the United States. *Am J Gastroenterol* 1998; **93**: 1432-1435

18 **Megraud F**. H pylori antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 2004; **53**: 1374-1384

19 **Axon A**. Quadruple therapy should be second-line treatment for Helicobacter pylori infection. In: Hunt RH, Tytgat GNJ, eds. Helicobacter pylori: Basic Mechanisms to Clinical Cure. London: Kluwer, 2000: 631-635

20 **Gisbert JP**, Pajares JM. Review article: Helicobacter pylori "rescue" regimen when proton pump inhibitor-based triple therapies fail. *Aliment Pharmacol Ther* 2002; **16**: 1047-1057

21 **Gisbert JP**, Pajares JM. Helicobacter pylori "rescue" therapy after failure of two eradication treatments. *Helicobacter* 2005; **10**: 363-372

22 **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**: 357-361

23 **de Boer WA**, Tytgat GN. Regular review: treatment of Helicobacter pylori infection. *BMJ* 2000; **320**: 31-34

24 **Calvet X**, Gene E, Sanfeliu I. [Therapeutic strategies in Helicobacter pylori infection] *Med Clin* (Barc) 2001; **116**: 239

25 **Houben MH**, van de Beek D, Hensen EF, Craen AJ, Rauws EA, Tytgat GN. A systematic review of Helicobacter pylori eradication therapy--the impact of antimicrobial resistance on eradication rates. *Aliment Pharmacol Ther* 1999; **13**: 1047-1055

26 **Peitz U**, Hackelsberger A, Malfertheiner P. A practical approach to patients with refractory Helicobacter pylori infection, or who are re-infected after standard therapy. *Drugs* 1999; **57**: 905-920

27 **Dore MP**, Leandro G, Realdi G, Sepulveda AR, Graham DY. Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of Helicobacter pylori therapy: a meta-analytical approach. *Dig Dis Sci* 2000; **45**: 68-76

28 **van der Wouden EJ**, Thijs JC, van Zwet AA, Sluiter WJ, Kleibeuker JH. The influence of in vitro nitroimidazole resistance on the efficacy of nitroimidazole-containing anti-Helicobacter pylori regimens: a meta-analysis. *Am J Gastroenterol* 1999; **94**: 1751-1759

29 **Tompkins DS**, Perkin J, Smith C. Failed treatment of Helicobacter pylori infection associated with resistance to clarithromycin. *Helicobacter* 1997; **2**: 185-187

30 **Parente F**, Cucino C, Bianchi Porro G. Treatment options for patients with Helicobacter pylori infection resistant to one or more eradication attempts. *Dig Liver Dis* 2003; **35**: 523-528

31 **Battaglia G**, Di Mario F, Vigneri S, Vianello F, Benvenuti ME, Donisi PM, Stracca-Pansa V, Pasquino M. Strategy for the retreatment of failed Helicobacter pylori eradication therapy: a case series. *Ital J Gastroenterol Hepatol* 1998; **30**: 370-374

32 **Deltenre M**, Ntounda R, Jonas C, De Koster E. Eradication of Helicobacter pylori: why does it fail? *Ital J Gastroenterol Hepatol* 1998; **30** Suppl 3: S326-S328

33 **Kobayashi I**, Saika T, Muraoka H, Murakami K, Fujioka T. Helicobacter pylori isolated from patients who later failed H. pylori eradication triple therapy readily develop resistance to clarithromycin. *J Med Microbiol* 2006; **55**: 737-740

34 **Yahav J**, Samra Z, Niv Y, Evans CT, Passaro DJ, Dinari G, Shmuely H. Susceptibility-guided vs. empiric retreatment of Helicobacter pylori infection after treatment failure. *Dig Dis Sci* 2006; **51**: 2316-2321

35 **Lamouliatte H**, Megraud F, Delchier JC, Bretagne JF, Courillon-Mallet A, De Korwin JD, Fauchere JL, Labigne A, Flejou JF, Barthelemy P. Second-line treatment for failure to eradicate Helicobacter pylori: a randomized trial comparing four treatment strategies. *Aliment Pharmacol Ther* 2003; **18**: 791-797

36 **Avidan B**, Melzer E, Keller N, Bar-Meir S. The effect of culture results for Helicobacter pylori on the choice of treatment following failure of initial eradication. *Isr Med Assoc J* 2001; **3**: 163-165

37 **Miwa H**, Nagahara A, Kurosawa A, Ohkusa T, Ohkura R, Hojo M, Enomoto N, Sato N. Is antimicrobial susceptibility testing necessary before second-line treatment for Helicobacter pylori infection? *Aliment Pharmacol Ther* 2003; **17**: 1545-1551

38 **Shimoyama T**, Fukuda S, Mikami T, Fukushi M, Munakata A. Efficacy of metronidazole for the treatment of clarithromycin-resistant Helicobacter pylori infection in a

Japanese population. *J Gastroenterol* 2004; **39**: 927-930
39 **Nagahara A**, Miwa H, Kawabe M, Kurosawa A, Asaoka D, Hojo M, Iijima K, Terai T, Ohkusa T, Miyazaki A, Sato N. Second-line treatment for Helicobacter pylori infection in Japan: proton pump inhibitor-based amoxicillin and metronidazole regimen. *J Gastroenterol* 2004; **39**: 1051-1055
40 **Murakami K**, Okimoto T, Kodama M, Sato R, Watanabe K, Fujioka T. Evaluation of three different proton pump inhibitors with amoxicillin and metronidazole in retreatment for Helicobacter pylori infection. *J Clin Gastroenterol* 2008; **42**: 139-142
41 **Shirai N**, Sugimoto M, Kodaira C, Nishino M, Ikuma M, Kajimura M, Ohashi K, Ishizaki T, Hishida A, Furuta T. Dual therapy with high doses of rabeprazole and amoxicillin versus triple therapy with rabeprazole, amoxicillin, and metronidazole as a rescue regimen for Helicobacter pylori infection after the standard triple therapy. *Eur J Clin Pharmacol* 2007; **63**: 743-749
42 **Isomoto H**, Inoue K, Furusu H, Enjoji A, Fujimoto C, Yamakawa M, Hirakata Y, Omagari K, Mizuta Y, Murase K, Shimada S, Murata I, Kohno S. High-dose rabeprazole-amoxicillin versus rabeprazole-amoxicillin-metronidazole as second-line treatment after failure of the Japanese standard regimen for Helicobacter pylori infection. *Aliment Pharmacol Ther* 2003; **18**: 101-107
43 **Murakami K**, Okimoto T, Kodama M, Sato R, Miyajima H, Ono M, Inoue K, Watanabe K, Otsu S, Fujioka T. Comparison of amoxicillin-metronidazole plus famotidine or lansoprazole for amoxicillin-clarithromycin-proton pump inhibitor treatment failures for Helicobacter pylori infection. *Helicobacter* 2006; **11**: 436-440
44 **Matsuhisa T**, Kawai T, Masaoka T, Suzuki H, Ito M, Kawamura Y, Tokunaga K, Suzuki M, Mine T, Takahashi S, Sakaki N. Efficacy of metronidazole as second-line drug for the treatment of Helicobacter pylori Infection in the Japanese population: a multicenter study in the Tokyo Metropolitan Area. *Helicobacter* 2006; **11**: 152-158
45 **Gisbert JP**, Boixeda D, Bermejo F, Nieves Rincon M, Jesus Higes M, Angeles Arpa M, Garcia Arata I, Martin de Argila C, Garcia Plaza A. Re-treatment after Helicobacter pylori eradication failure. *Eur J Gastroenterol Hepatol* 1999; **11**: 1049-1054
46 **Perri F**, Villani MR, Quitadamo M, Annese V, Niro GA, Andriulli A. Ranitidine bismuth citrate-based triple therapies after failure of the standard 'Maastricht triple therapy': a promising alternative to the quadruple therapy? *Aliment Pharmacol Ther* 2001; **15**: 1017-1022
47 **Nagahara A**, Miwa H, Ohkura R, Yamada T, Sato K, Hojo M, Sato N. Strategy for retreatment of therapeutic failure of eradication of Helicobacter pylori infection. *J Gastroenterol Hepatol* 2001; **16**: 613-618
48 **European Helicobacter Pylori Study Group.** Current European concepts in the management of Helicobacter pylori infection. The Maastricht Consensus Report. *Gut* 1997; **41**: 8-13
49 **Lam SK**, Talley NJ. Report of the 1997 Asia Pacific Consensus Conference on the management of Helicobacter pylori infection. *J Gastroenterol Hepatol* 1998; **13**: 1-12
50 **Gisbert JP**, Calvet X, Gomollon F, Sainz R. [Treatment for the eradication of Helicobacter pylori. Recommendations of the Spanish Consensus Conference] *Med Clin* (Barc) 2000; **114**: 185-195
51 **Baena Diez JM**, Lopez Mompo C, Rams Rams F, Garcia Lareo M, Rosario Hernandez Ibanez M, Teruel Gila J. [Efficacy of a multistep strategy for Helicobacter pylori eradication: quadruple therapy with omeprazole, metronidazole, tetracycline and bismuth after failure of a combination of omeprazole, clarithromycin and amoxycillin] *Med Clin* (Barc) 2000; **115**: 617-619
52 **Bilardi C**, Dulbecco P, Zentilin P, Reglioni S, Iiritano E, Parodi A, Accornero L, Savarino E, Mansi C, Mamone M, Vigneri S, Savarino V. A 10-day levofloxacin-based therapy in patients with resistant Helicobacter pylori infection: a controlled trial. *Clin Gastroenterol Hepatol* 2004; **2**: 997-1002
53 **Elizalde IR**, Borda F, Jara C, Martínez A, Rodríguez C, Jiménez J. Eficacia de dos tratamientos consecutivos en la erradicación de Helicobacter pylori. *Anales Sis San Navarra* 1998; **21** Supl 2: 83-88
54 **Choung RS**, Lee SW, Jung SW, Han WS, Kim MJ, Jeen YT, Park JJ, Lee HS, Chun HJ, Um SH, Choi JH, Kim CD, Ryu HS, Hyun JH. [Comparison of the effectiveness of quadruple salvage regimen for Helicobacter pylori infection according to the duration of treatment] *Korean J Gastroenterol* 2006; **47**: 131-135
55 **Chung SJ**, Lee DH, Kim N, Jung SH, Kim JW, Hwang JH, Park YS, Lee KH, Jung HC, Song IS. Eradication rates of helicobacter pylori infection with second-line treatment: non-ulcer dyspepsia compared to peptic ulcer disease. *Hepatogastroenterology* 2007; **54**: 1293-1296
56 **Gasbarrini A**, Ojetti V, Pitocco D, Armuzzi A, Silveri NG, Pola P, Ghirlanda G, Gasbarrini G. Efficacy of different Helicobacter pylori eradication regimens in patients affected by insulin-dependent diabetes mellitus. *Scand J Gastroenterol* 2000; **35**: 260-263
57 **Gisbert JP**, Gisbert JL, Marcos S, Gravalos RG, Carpio D, Pajares JM. Seven-day 'rescue' therapy after Helicobacter pylori treatment failure: omeprazole, bismuth, tetracycline and metronidazole vs. ranitidine bismuth citrate, tetracycline and metronidazole. *Aliment Pharmacol Ther* 1999; **13**: 1311-1316
58 **Gomollón F**, Ducons JA, Ferrero M, Garcia Cabezudo J, Guirao R, Simon MA, Montoro M. Quadruple therapy is effective for eradicating Helicobacter pylori after failure of triple proton-pump inhibitor-based therapy: a detailed, prospective analysis of 21 consecutive cases. *Helicobacter* 1999; **4**: 222-225
59 **Lee JM**, Breslin NP, Hyde DK, Buckley MJ, O'Morain CA. Treatment options for Helicobacter pylori infection when proton pump inhibitor-based triple therapy fails in clinical practice. *Aliment Pharmacol Ther* 1999; **13**: 489-496
60 **Lee JH**, Cheon JH, Park MJ, Kim N, Lee DH, Kim JM, Kim JS, Jung HC, Song IS. [The trend of eradication rates of second-line quadruple therapy containing metronidazole for Helicobacter pylori infection: an analysis of recent eight years] *Korean J Gastroenterol* 2005; **46**: 94-98
61 **Marko D**, Calvet X, Ducons J, Guardiola J, Tito L, Bory F. Comparison of two management strategies for Helicobacter pylori treatment: clinical study and cost-effectiveness analysis. *Helicobacter* 2005; **10**: 22-32
62 **Michopoulos S**, Tsibouris P, Bouzakis H, Balta A, Vougadiotis J, Broutet N, Kralios N. Randomized study comparing omeprazole with ranitidine as anti-secretory agents combined in quadruple second-line Helicobacter pylori eradication regimens. *Aliment Pharmacol Ther* 2000; **14**: 737-744
63 **Navarro-Jarabo JM**, Fernandez N, Sousa FL, Cabrera E, Castro M, Ramirez LM, Rivera R, Ubina E, Vera F, Mendez I, Rivas-Ruiz F, Moreno JL, Perea-Milla E. Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate helicobacter pylori infection. *BMC Gastroenterol* 2007; **7**: 31
64 **Nista EC**, Candelli M, Cremonini F, Cazzato IA, Di Caro S, Gabrielli M, Santarelli L, Zocco MA, Ojetti V, Carloni E, Cammarota G, Gasbarrini G, Gasbarrini A. Levofloxacin-based triple therapy vs. quadruple therapy in second-line Helicobacter pylori treatment: a randomized trial. *Aliment Pharmacol Ther* 2003; **18**: 627-633
65 **Orsi P**, Pinazzi O, Aragona G, Di Mario F. Rabeprazole/Levofloxacin based triple therapy as a Salvatage Treatment after Failure of H pylori eradication with standard regimens. *Helicobacter* 2003; **8**: 339-493
66 **Perri F**, Festa V, Clemente R, Villani MR, Quitadamo M, Caruso N, Bergoli ML, Andriulli A. Randomized study of two "rescue" therapies for Helicobacter pylori-infected

patients after failure of standard triple therapies. *Am J Gastroenterol* 2001; **96**: 58-62
67 **Perri F**, Festa V, Merla A, Barberani F, Pilotto A, Andriulli A. Randomized study of different 'second-line' therapies for Helicobacter pylori infection after failure of the standard 'Maastricht triple therapy'. *Aliment Pharmacol Ther* 2003; **18**: 815-820
68 **Sicilia B**, Sierra E, Lago A, Villar M, Garcia S, Gomollon F. [High eradication rates in Helicobacter pylori infection in patients with duodenal ulcer who failed previous eradication therapy] *Med Clin* (Barc) 2000; **115**: 641-643
69 **Uygun A**, Ozel AM, Yildiz O, Aslan M, Yesilova Z, Erdil A, Bagci S, Gunhan O. Comparison of three different second-line quadruple therapies including bismuth subcitrate in Turkish patients with non-ulcer dyspepsia who failed to eradicate Helicobacter pylori with a 14-day standard first-line therapy. *J Gastroenterol Hepatol* 2008; **23**: 42-45
70 **Wong WM**, Gu Q, Lam SK, Fung FM, Lai KC, Hu WH, Yee YK, Chan CK, Xia HH, Yuen MF, Wong BC. Randomized controlled study of rabeprazole, levofloxacin and rifabutin triple therapy vs. quadruple therapy as second-line treatment for Helicobacter pylori infection. *Aliment Pharmacol Ther* 2003; **17**: 553-560
71 **Wu DC**, Hsu PI, Chen A, Lai KH, Tsay FW, Wu CJ, Lo GH, Wu JY, Wu IC, Wang WM, Tseng HH. Randomized comparison of two rescue therapies for Helicobacter pylori infection. *Eur J Clin Invest* 2006; **36**: 803-809
72 **Beales IL**. Efficacy of Helicobacter pylori eradication therapies: a single centre observational study. *BMC Gastroenterol* 2001; **1**: 7
73 **de Boer WA**, Driessen WM, Potters VP, Tytgat GN. Randomized study comparing 1 with 2 weeks of quadruple therapy for eradicating Helicobacter pylori. *Am J Gastroenterol* 1994; **89**: 1993-1997
74 **Gomollón F**, Valdeperez J, Garuz R, Fuentes J, Barrera F, Malo J, Tirado M, Simon MA. [Cost-effectiveness analysis of 2 strategies of Helicobacter pylori eradication: results of a prospective and randomized study in primary care] *Med Clin* (Barc) 2000; **115**: 1-6
75 **Rinaldi V**, Zullo A, De Francesco V, Hassan C, Winn S, Stoppino V, Faleo D, Attili AF. Helicobacter pylori eradication with proton pump inhibitor-based triple therapies and re-treatment with ranitidine bismuth citrate-based triple therapy. *Aliment Pharmacol Ther* 1999; **13**: 163-168
76 **Zullo A**, Hassan C, Campo SM, Lorenzetti R, Febbraro I, De Matthaeis M, Porto D, Morini S. A triple therapy regimen after failed Helicobacter pylori treatments. *Aliment Pharmacol Ther* 2001; **15**: 1193-1197
77 **Gisbert JP**, Fuentes J, Carpio D, Tito L, Guardiola J, Tomas A, Olivares D, Calvet X. 7-day rescue therapy with ranitidine bismuth citrate after Helicobacter pylori treatment failure. *Aliment Pharmacol Ther* 2005; **21**: 1249-1253
78 **Hojo M**, Miwa H, Nagahara A, Sato N. Pooled analysis on the efficacy of the second-line treatment regimens for Helicobacter pylori infection. *Scand J Gastroenterol* 2001; **36**: 690-700
79 **Gisbert JP**, Gisbert JL, Marcos S, Moreno-Otero R, Pajares JM. Levofloxacin- vs. ranitidine bismuth citrate-containing therapy after H. pylori treatment failure. *Helicobacter* 2007; **12**: 68-73
80 **Koksal AS**, Parlak E, Filik L, Yolcu OF, Odemis B, Ulker A, Sasmaz N, Ozden A, Sahin B. Ranitidine bismuth citrate-based triple therapies as a second-line therapy for Helicobacter pylori in Turkish patients. *J Gastroenterol Hepatol* 2005; **20**: 637-642
81 **Gisbert JP**, Pajares JM, Valle J. Ranitidine bismuth citrate therapy regimens for treatment of Helicobacter pylori infection: a review. *Helicobacter* 1999; **4**: 58-66
82 **Van Oijen AH**, Verbeek AL, Jansen JB, De Boer WA. Review article: treatment of Helicobacter pylori infection with ranitidine bismuth citrate- or proton pump inhibitor-based triple therapies. *Aliment Pharmacol Ther* 2000; **14**: 991-999
83 **Gisbert JP**, Gonzalez L, Calvet X. Systematic review and meta-analysis: proton pump inhibitor vs. ranitidine bismuth citrate plus two antibiotics in Helicobacter pylori eradication. *Helicobacter* 2005; **10**: 157-171
84 **Thong-Ngam D**, Mahachai V. 14-day quadruple therapy with ranitidine bismuth citrate after Helicobacter pylori treatment failure in Thailand. *J Med Assoc Thai* 2006; **89** Suppl 3: S119-S125
85 **Kearney DJ**. Retreatment of Helicobacter pylori infection after initial treatment failure. *Am J Gastroenterol* 2001; **96**: 1335-1339
86 **Caselli M**, Zullo A, Maconi G, Parente F, Alvisi V, Casetti T, Sorrentino D, Gasbarrini G. "Cervia II Working Group Report 2006": guidelines on diagnosis and treatment of Helicobacter pylori infection in Italy. *Dig Liver Dis* 2007; **39**: 782-789
87 **Croom KF**, Goa KL. Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. *Drugs* 2003; **63**: 2769-2802
88 **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
89 **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
90 **Vaira D**, Ricci C, Lanzini A, Perna F, Romano A, Corinaldesi R. How to proceed in Helicobacter pylori-positive chronic gastritis refractory to first- and second-line eradication therapy. *Dig Dis* 2007; **25**: 203-205
91 **Sanchez JE**, Saenz NG, Rincon MR, Martin IT, Sanchez EG, Martinez MJ. Susceptibility of Helicobacter pylori to mupirocin, oxazolidinones, quinupristin/dalfopristin and new quinolones. *J Antimicrob Chemother* 2000; **46**: 283-285
92 **Xia HH**, Yu Wong BC, Talley NJ, Lam SK. Alternative and rescue treatment regimens for Helicobacter pylori eradication. *Expert Opin Pharmacother* 2002; **3**: 1301-1311
93 **Zou J**, Yang ZX, Qin ZM. [Laboratory and clinical study of levofloxacin against Helicobacter pylori] *Zhonghua Yixue Zazhi* 2003; **83**: 1778-1781
94 **Gatta L**, Zullo A, Perna F, Ricci C, De Francesco V, Tampieri A, Bernabucci V, Cavina M, Hassan C, Ierardi E, Morini S, Vaira D. A 10-day levofloxacin-based triple therapy in patients who have failed two eradication courses. *Aliment Pharmacol Ther* 2005; **22**: 45-49
95 **Antos D**, Schneider-Brachert W, Bastlein E, Hanel C, Haferland C, Buchner M, Meier E, Trump F, Stolte M, Lehn N, Bayerdorffer E. 7-day triple therapy of Helicobacter pylori infection with levofloxacin, amoxicillin, and high-dose esomeprazole in patients with known antimicrobial sensitivity. *Helicobacter* 2006; **11**: 39-45
96 **Kumala W**, Rani A. Patterns of Helicobacter pylori isolate resistance to fluoroquinolones, amoxicillin, clarithromycin and metronidazoles. *Southeast Asian J Trop Med Public Health* 2006; **37**: 970-974
97 **Tanaka M**, Isogai E, Isogai H, Hayashi S, Hirose K, Kimura K, Sugiyama T, Sato K. Synergic effect of quinolone antibacterial agents and proton pump inhibitors on Helicobacter pylori. *J Antimicrob Chemother* 2002; **49**: 1039-1040
98 **Watanabe Y**, Aoyama N, Shirasaka D, Maekawa S, Kuroda K, Miki I, Kachi M, Fukuda M, Wambura C, Tamura T, Kasuga M. Levofloxacin based triple therapy as a second-line treatment after failure of helicobacter pylori eradication with standard triple therapy. *Dig Liver Dis* 2003; **35**: 711-715
99 **Yahav J**, Shmuely H, Niv Y, Bechor J, Samra Z. In vitro activity of levofloxacin against Helicobacter pylori isolates from patients after treatment failure. *Diagn Microbiol Infect Dis* 2006; **55**: 81-83
100 **Matsumoto Y**, Miki I, Aoyama N, Shirasaka D, Watanabe

Y, Morita Y, Toyoda M, Mitani T, Miyachi H, Tamura T, Kasuga M. Levofloxacin- versus metronidazole-based rescue therapy for H. pylori infection in Japan. *Dig Liver Dis* 2005; **37**: 821-825

101 **Cammarota G**, Cianci R, Cannizzaro O, Cuoco L, Pirozzi G, Gasbarrini A, Armuzzi A, Zocco MA, Santarelli L, Arancio F, Gasbarrini G. Efficacy of two one-week rabeprazole/levofloxacin-based triple therapies for Helicobacter pylori infection. *Aliment Pharmacol Ther* 2000; **14**: 1339-1343

102 **Di Caro S**, Zocco MA, Cremonini F, Candelli M, Nista EC, Bartolozzi F, Armuzzi A, Cammarota G, Santarelli L, Gasbarrini A. Levofloxacin based regimens for the eradication of Helicobacter pylori. *Eur J Gastroenterol Hepatol* 2002; **14**: 1309-1312

103 **Marzio L**, Coraggio D, Capodicasa S, Grossi L, Cappello G. Role of the preliminary susceptibility testing for initial and after failed therapy of Helicobacter pylori infection with levofloxacin, amoxicillin, and esomeprazole. *Helicobacter* 2006; **11**: 237-242

104 **Rispo A**, Di Girolamo E, Cozzolino A, Bozzi R, Morante A, Pasquale L. Levofloxacin in first-line treatment of Helicobacter pylori infection. *Helicobacter* 2007; **12**: 364-365

105 **Gisbert JP**, Fernandez-Bermejo M, Molina-Infante J, Perez-Gallardo B, Prieto-Bermejo AB, Mateos-Rodriguez JM, Robledo-Andres P, Gonzalez-Garcia G. First-line triple therapy with levofloxacin for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2007; **26**: 495-500

106 **Lee JH**, Hong SP, Kwon CI, Phyun LH, Lee BS, Song HU, Ko KH, Hwang SG, Park PW, Rim KS, Kim S. [The efficacy of levofloxacin based triple therapy for Helicobacter pylori eradication] *Korean J Gastroenterol* 2006; **48**: 19-24

107 **Wong WM**, Gu Q, Chu KM, Yee YK, Fung FM, Tong TS, Chan AO, Lai KC, Chan CK, Wong BC. Lansoprazole, levofloxacin and amoxicillin triple therapy vs. quadruple therapy as second-line treatment of resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2006; **23**: 421-427

108 **Gisbert JP**, Bermejo F, Castro-Fernandez M, Perez-Aisa A, Fernandez-Bermejo M, Tomas A, Barrio J, Bory F, Almela P, Sanchez-Pobre P, Cosme A, Ortiz V, Nino P, Khorrami S, Benito LM, Carneros JA, Lamas E, Modolell I, Franco A, Ortuno J, Rodrigo L, Garcia-Duran F, O'Callaghan E, Ponce J, Valer MP, Calvet X. Second-line rescue therapy with levofloxacin after H. pylori treatment failure: a Spanish multicenter study of 300 patients. *Am J Gastroenterol* 2008; **103**: 71-76

109 **Giannini EG**, Bilardi C, Dulbecco P, Mamone M, Santi ML, Testa R, Mansi C, Savarino V. A study of 4- and 7-day triple therapy with rabeprazole, high-dose levofloxacin and tinidazole rescue treatment for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2006; **23**: 281-287

110 **Page RL 2nd**, Ferguson D, Cantu M. An alternative salvage regimen for Helicobacter pylori-resistant patients with heart failure. *Cardiology* 2008; **110**: 112-115

111 **Lee YC**, Wu HM, Chen TH, Liu TY, Chiu HM, Chang CC, Wang HP, Wu MS, Chiang H, Wu MC, Lin JT. A community-based study of Helicobacter pylori therapy using the strategy of test, treat, retest, and re-treat initial treatment failures. *Helicobacter* 2006; **11**: 418-424

112 **Kahn JB**. Latest industry information on the safety profile of levofloxacin in the US. *Chemotherapy* 2001; **47** Suppl 3: 32-37; discussion 44-48

113 **Cabrita J**, Oleastro M, Matos R, Manhente A, Cabral J, Barros R, Lopes AI, Ramalho P, Neves BC, Guerreiro AS. Features and trends in Helicobacter pylori antibiotic resistance in Lisbon area, Portugal (1990-1999). *J Antimicrob Chemother* 2000; **46**: 1029-1031

114 **Miyachi H**, Miki I, Aoyama N, Shirasaka D, Matsumoto Y, Toyoda M, Mitani T, Morita Y, Tamura T, Kinoshita S, Okano Y, Kumagai S, Kasuga M. Primary levofloxacin resistance and gyrA/B mutations among Helicobacter pylori in Japan. *Helicobacter* 2006; **11**: 243-249

115 **Bogaerts P**, Berhin C, Nizet H, Glupczynski Y. Prevalence and mechanisms of resistance to fluoroquinolones in Helicobacter pylori strains from patients living in Belgium. *Helicobacter* 2006; **11**: 441-445

116 **Carothers JJ**, Bruce MG, Hennessy TW, Bensler M, Morris JM, Reasonover AL, Hurlburt DA, Parkinson AJ, Coleman JM, McMahon BJ. The relationship between previous fluoroquinolone use and levofloxacin resistance in Helicobacter pylori infection. *Clin Infect Dis* 2007; **44**: e5-e8

117 **Cattoir V**, Nectoux J, Lascols C, Deforges L, Delchier JC, Megraud F, Soussy CJ, Cambau E. Update on fluoroquinolone resistance in Helicobacter pylori: new mutations leading to resistance and first description of a gyrA polymorphism associated with hypersusceptibility. *Int J Antimicrob Agents* 2007; **29**: 389-396

118 **Coelho LG**, Moretzsohn LD, Vieira WL, Gallo MA, Passos MC, Cindr JM, Cerqueira MC, Vitiello L, Ribeiro ML, Mendonca S, Pedrazzoli-Junior J, Castro LP. New once-daily, highly effective rescue triple therapy after multiple Helicobacter pylori treatment failures: a pilot study. *Aliment Pharmacol Ther* 2005; **21**: 783-787

119 **Kim JM**, Kim JS, Kim N, Kim SG, Jung HC, Song IS. Comparison of primary and secondary antimicrobial minimum inhibitory concentrations for Helicobacter pylori isolated from Korean patients. *Int J Antimicrob Agents* 2006; **28**: 6-13

120 **Glocker E**, Stueger HP, Kist M. Quinolone resistance in Helicobacter pylori isolates in Germany. *Antimicrob Agents Chemother* 2007; **51**: 346-349

121 **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

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

123 **Zullo A**, Perna F, Hassan C, Ricci C, Saracino I, Morini S, Vaira D. Primary antibiotic resistance in Helicobacter pylori strains isolated in northern and central Italy. *Aliment Pharmacol Ther* 2007; **25**: 1429-1434

124 **Krakowka S**, Ringler SS, Eaton KA, Green WB, Leunk R. Manifestations of the local gastric immune response in gnotobiotic piglets infected with Helicobacter pylori. *Vet Immunol Immunopathol* 1996; **52**: 159-173

125 **Reilly TG**, Ayres RC, Poxon V, Walt RP. Helicobacter pylori eradication in a clinical setting: success rates and the effect on the quality of life in peptic ulcer. *Aliment Pharmacol Ther* 1995; **9**: 483-490

126 **Lerang F**, Moum B, Haug JB, Berge T, Tolas P, Sandvei PK, Torp R, Tonnesen T. Highly effective second-line anti-Helicobacter pylori therapy in patients with previously failed metronidazole-based therapy. *Scand J Gastroenterol* 1997; **32**: 1209-1214

127 **Magaret N**, Burm M, Faigel D, Kelly C, Peterson W, Fennerty MB. A randomized trial of lansoprazole, amoxycillin, and clarithromycin versus lansoprazole, bismuth, metronidazole and tetracycline in the retreatment of patients failing initial Helicobacter pylori therapy. *Dig Dis* 2001; **19**: 174-178

128 **Axon AT**. Treatment of Helicobacter pylori: an overview. *Aliment Pharmacol Ther* 2000; **14** Suppl 3: 1-6

129 **Peitz U**, Sulliga M, Wolle K, Leodolter A, Von Arnim U, Kahl S, Stolte M, Borsch G, Labenz J, Malfertheiner P. High rate of post-therapeutic resistance after failure of macrolide-nitroimidazole triple therapy to cure Helicobacter pylori infection: impact of two second-line therapies in a randomized study. *Aliment Pharmacol Ther* 2002; **16**: 315-324

130 **Miehlke S**, Hansky K, Schneider-Brachert W, Kirsch C, Morgner A, Madisch A, Kuhlisch E, Bastlein E, Jacobs E,

Bayerdorffer E, Lehn N, Stolte M. 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

131 **Pilotto A**, Franceschi M, Rassu M, Leandro G, Bozzola L, Furlan F, Di Mario F. Incidence of secondary Helicobacter pylori resistance to antibiotics in treatment failures after 1-week proton pump inhibitor-based triple therapies: a prospective study. *Dig Liver Dis* 2000; **32**: 667-672

132 **de Boer W**, Driessen W, Jansz A, Tytgat G. Effect of acid suppression on efficacy of treatment for Helicobacter pylori infection. *Lancet* 1995; **345**: 817-820

133 **Graham DY**, Osato MS, Hoffman J, Opekun AR, Anderson SY, Kwon DH, El-Zimaity HM. Metronidazole containing quadruple therapy for infection with metronidazole resistant Helicobacter pylori: a prospective study. *Aliment Pharmacol Ther* 2000; **14**: 745-750

134 **Cudia B**, Romano M, Gioè FP, Barbera N, Lo Gerfo D, Montalto R. "Rescue" therapy including ranitidine bismuth citrate + minocicline + amoxicillin for eradication of Helicobacter pylori in previous H.P. treatment failure. *Gut* 1997; **41** suppl 1: A103

135 **The report of the Digestive Health InitiativeSM International Update Conference on Helicobacter pylori**. *Gastroenterology* 1997; 113: S4-S8

136 **Technical annex: tests used to assess Helicobacter pylori infection**. Working Party of the European Helicobacter pylori Study Group. *Gut* 1997; **41** Suppl 2: S10-S18

137 **Guslandi M**. Review article: alternative antibacterial agents for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2001; **15:** 1543-1547

138 **Kim JJ**, Kim JG, Kwon DH. Mixed-infection of antibiotic susceptible and resistant Helicobacter pylori isolates in a single patient and underestimation of antimicrobial susceptibility testing. *Helicobacter* 2003; **8**: 202-206

139 **Ali' A**, Menegatti M, Gatta L, Landi F, Ricci C, Acciardi C, Miglioli M, Vaira D, Holton J. A second-line anti-Helicobacter pylori therapy in patients with previously failed treatment. *Am J Gastroenterol* 1999; **94**: 2321-2323

140 **Gomollón F**, Sicilia B, Ducons JA, Sierra E, Revillo MJ, Ferrero M. Third line treatment for Helicobacter pylori: a prospective, culture-guided study in peptic ulcer patients. *Aliment Pharmacol Ther* 2000; **14**: 1335-1338

141 **Vicente R**, Sicilia B, Gallego S, Revillo MJ, Ducons J, Gomollon F. [Helicobacter pylori eradication in patients with peptic ulcer after two treatment failures: a prospective culture-guided study] *Gastroenterol Hepatol* 2002; **25**: 438-442

142 **Adamek RJ**, Suerbaum S, Pfaffenbach B, Opferkuch W. Primary and acquired Helicobacter pylori resistance to clarithromycin, metronidazole, and amoxicillin--influence on treatment outcome. *Am J Gastroenterol* 1998; **93**: 386-389

143 **Huang JQ**, Hunt RH. Treatment after failure: the problem of "non-responders". *Gut* 1999; **45** Suppl 1: I40-I44

144 **Seppala K**, Kosunen TU, Nuutinen H, Sipponen P, Rautelin H, Sarna S, Hyvarinen H, Farkkila M, Miettinen TA. Cure of Helicobacter pylori infection after failed primary treatment: one-center results from 120 patients. *Scand J Gastroenterol* 2000; **35**: 929-934

145 **Treiber G**, Ammon S, Malfertheiner P, Klotz U. Impact of furazolidone-based quadruple therapy for eradication of Helicobacter pylori after previous treatment failures. *Helicobacter* 2002; **7**: 225-231

146 **Chan FK**, Sung JJ, Suen R, Wu JC, Ling TK, Chung SC. Salvage therapies after failure of Helicobacter pylori eradication with ranitidine bismuth citrate-based therapies. *Aliment Pharmacol Ther* 2000; **14**: 91-95

147 **Zullo A**, Hassan C, De Francesco V, Lorenzetti R, Marignani M, Angeletti S, Ierardi E, Morini S. A third-line levofloxacin-based rescue therapy for Helicobacter pylori eradication. *Dig Liver Dis* 2003; **35**: 232-236

148 **Dore MP**, Marras L, Maragkoudakis E, Nieddu S, Manca A, Graham DY, Realdi G. Salvage therapy after two or more prior Helicobacter pylori treatment failures: the super salvage regimen. *Helicobacter* 2003; **8**: 307-309

149 **Gisbert JP**, Calvet X, Bujanda L, Marcos S, Gisbert JL, Pajares JM. 'Rescue' therapy with rifabutin after multiple Helicobacter pylori treatment failures. *Helicobacter* 2003; **8**: 90-94

150 **Gisbert JP**, Gisbert JL, Marcos S, Pajares JM. Empirical Helicobacter pylori "rescue" therapy after failure of two eradication treatments. *Dig Liver Dis* 2004; **36**: 7-12

151 **Perri F**, Festa V, Clemente R, Quitadamo M, Andriulli A. Rifabutin-based 'rescue therapy' for Helicobacter pylori infected patients after failure of standard regimens. *Aliment Pharmacol Ther* 2000; **14**: 311-316

152 **Bock H**, Koop H, Lehn N, Heep M. Rifabutin-based triple therapy after failure of Helicobacter pylori eradication treatment: preliminary experience. *J Clin Gastroenterol* 2000; **31**: 222-225

153 **Canducci F**, Ojetti V, Pola P, Gasbarrini G, Gasbarrini A. Rifabutin-based Helicobacter pylori eradication 'rescue therapy'. *Aliment Pharmacol Ther* 2001; **15**: 143

154 **Gisbert JP**, Castro-Fernandez M, Bermejo F, Perez-Aisa A, Ducons J, Fernandez-Bermejo M, Bory F, Cosme A, Benito LM, Lopez-Rivas L, Lamas E, Pabon M, Olivares D. Third-line rescue therapy with levofloxacin after two H. pylori treatment failures. *Am J Gastroenterol* 2006; **101**: 243-247

155 **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

156 **Gisbert JP**, Gisbert JL, Marcos S, Jimenez-Alonso I, Moreno-Otero R, Pajares JM. Empirical rescue therapy after Helicobacter pylori treatment failure: a 10-year single-centre study of 500 patients. *Aliment Pharmacol Ther* 2008; **27**: 346-354

157 **Cianci R**, Montalto M, Pandolfi F, Gasbarrini GB, Cammarota G. Third-line rescue therapy for Helicobacter pylori infection. *World J Gastroenterol* 2006; **12**: 2313-2319

158 **Megraud F**, Lamouliatte H. Review article: the treatment of refractory Helicobacter pylori infection. *Aliment Pharmacol Ther* 2003; **17**: 1333-1343

159 **de Boer WA**, Borody TJ. Treatment failures and secondary resistance to antibiotics. A growing concern in Helicobacter pylori therapy. *Dig Liver Dis* 2000; **32**: 673-675

160 **Miehlke S**, Kirsch C, Schneider-Brachert W, Haferland C, Neumeyer M, Bastlein E, Papke J, Jacobs E, Vieth M, Stolte M, Lehn N, Bayerdorffer E. A prospective, randomized study of quadruple therapy and high-dose dual therapy for treatment of Helicobacter pylori resistant to both metronidazole and clarithromycin. *Helicobacter* 2003; **8**: 310-319

161 **Chi CH**, Lin CY, Sheu BS, Yang HB, Huang AH, Wu JJ. Quadruple therapy containing amoxicillin and tetracycline is an effective regimen to rescue failed triple therapy by overcoming the antimicrobial resistance of Helicobacter pylori. *Aliment Pharmacol Ther* 2003; **18**: 347-353

162 **Zullo A**, Hassan C, Lorenzetti R, Morini S. Helicobacter pylori eradication: do we have another ace up our sleeve? *Dig Liver Dis* 2001; **33**: 805-806

163 **Gisbert JP**. Rescue therapy with levofloxacin after multiple H. pylori treatment failures. *Aliment Pharmacol Ther* 2005; **22**: 653-654; author reply 654-655

164 **Rokkas T**, Sechopoulos P, Robotis J, Pistiolas D. Triple levofloxacin-based rescue therapy is an accepted empirical third-line treatment. *Am J Gastroenterol* 2006; **101**: 1938; author reply 1938-1938; author reply 1939

165 **Akada JK**, Shirai M, Fujii K, Okita K, Nakazawa T. In vitro anti-Helicobacter pylori activities of new rifamycin derivatives, KRM-1648 and KRM-1657. *Antimicrob Agents Chemother* 1999; **43**: 1072-1076

166 **Heep M**, Beck D, Bayerdorffer E, Lehn N. Rifampin and rifabutin resistance mechanism in Helicobacter pylori. *Antimicrob Agents Chemother* 1999; **43**: 1497-1499

167 **Brogden RN**, Fitton A. Rifabutin. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; **47**: 983-1009

168 **Rossi G**. [An update on the antibiotic therapy of tuberculosis] *Recenti Prog Med* 1999; **90**: 241-243

169 **Borody TJ**, Pang G, Wettstein AR, Clancy R, Herdman K, Surace R, Llorente R, Ng C. Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant Helicobacter pylori infection. *Aliment Pharmacol Ther* 2006; **23**: 481-488

170 **Gonzalez Carro P**, Perez Roldan F, De Pedro Esteban A, Legaz Huidobro ML, Soto Fernandez S, Roncero Garcia Escribano O, Esteban Lopez-Jamar JM, Pedraza Martin C, Ruiz Carrillo F. Efficacy of rifabutin-based triple therapy in Helicobacter pylori infected patients after two standard treatments. *J Gastroenterol Hepatol* 2007; **22**: 60-63

171 **Toracchio S**, Capodicasa S, Soraja DB, Cellini L, Marzio L. Rifabutin based triple therapy for eradication of H. pylori primary and secondary resistant to tinidazole and clarithromycin. *Dig Liver Dis* 2005; **37**: 33-38

172 **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

173 **Perri F**, Festa V, Andriulli A. Treatment of antibiotic-resistant Helicobacter pylori. *N Engl J Med* 1998; **339**: 53

174 **Moayyedi P**, Soo S, Deeks J, Delaney B, Harris A, Innes M, Oakes R, Wilson S, Roalfe A, Bennett C, Forman D. Eradication of Helicobacter pylori for non-ulcer dyspepsia. *Cochrane Database Syst Rev* 2006; CD002096

175 **Xiao SD**, Liu WZ, Xia DH, Jiang SJ, Wang RN, Zhang ZH, Xu WW. The efficacy of furazolidone and metronidazole in the treatment of chronic gastritis associated with Helicobacter (Campylobacter) pylori--a randomized double-blind placebo-controlled clinical trial. *Hepatogastroenterology* 1990; **37**: 503-506

176 **Haas CE**, Nix DE, Schentag JJ. In vitro selection of resistant Helicobacter pylori. *Antimicrob Agents Chemother* 1990; **34**: 1637-1641

177 **Kwon DH**, Lee M, Kim JJ, Kim JG, El-Zaatari FA, Osato MS, Graham DY. Furazolidone- and nitrofurantoin-resistant Helicobacter pylori: prevalence and role of genes involved in metronidazole resistance. *Antimicrob Agents Chemother* 2001; **45**: 306-308

178 **Treiber G**, Wittig J, Ammon S, Walker S, van Doorn LJ, Klotz U. Clinical outcome and influencing factors of a new short-term quadruple therapy for Helicobacter pylori eradication: a randomized controlled trial (MACLOR study). *Arch Intern Med* 2002; **162**: 153-160

179 **Xiao SD**, Liu WZ, Hu PJ, Ouyang Q, Wang JL, Zhou LY, Cheng NN. A multicentre study on eradication of Helicobacter pylori using four 1-week triple therapies in China. *Aliment Pharmacol Ther* 2001; **15**: 81-86

180 **Nijevitch AA**, Shcherbakov PL, Sataev VU, Khasanov RSh, Al Khashash R, Tuygunov MM. Helicobacter pylori eradication in childhood after failure of initial treatment: advantage of quadruple therapy with nifuratel to furazolidone. *Aliment Pharmacol Ther* 2005; **22**: 881-887

181 **Eisig JN**, Silva FM, Rodriguez TN, Hashimoto CL, Barbuti RC. A furazolidone-based quadruple therapy for Helicobacter pylori retreatment in patients with peptic ulcer disease. *Clinics* 2005; **60**: 485-488

182 **Ebrahimi-Dariani N**, Mirmomen S, Mansour-Ghanaei F, Noormohammadpoor P, Sotodehmanesh R, Haghpanah B, Bahrami H. The efficacy of furazolidone-based quadruple therapy for eradication of Helicobacter pylori infection in Iranian patients resistant to metronidazole-based quadruple therapy. *Med Sci Monit* 2003; **9**: PI105-PI108

183 **Isakov V**, Domareva I, Koudryavtseva L, Maev I, Ganskaya Z. Furazolidone-based triple 'rescue therapy' vs. quadruple 'rescue therapy' for the eradication of Helicobacter pylori resistant to metronidazole. *Aliment Pharmacol Ther* 2002; **16**: 1277-1282

184 **Sotoudehmanesh R**, Malekzadeh R, Vahedi H, Dariani NE, Asgari AA, Massarrat S. Second-line Helicobacter pylori eradication with a furazolidone-based regimen in patients who have failed a metronidazole-based regimen. *Digestion* 2001; **64**: 222-225

185 **Qasim A**, Sebastian S, Thornton O, Dobson M, McLoughlin R, Buckley M, O'Connor H, O'Morain C. 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

186 **Buzas GM**, Jozan J. Nitrofuran-based regimens for the eradication of Helicobacter pylori infection. *J Gastroenterol Hepatol* 2007; **22**: 1571-1581

187 **Laine L**, Schoenfeld P, Fennerty MB. Therapy for Helicobacter pylori in patients with nonulcer dyspepsia. A meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; **134**: 361-369

188 **Gasbarrini A**, Ojetti V, Armuzzi A, Branca G, Canducci F, Torre ES, Candelli M, Pastorelli A, Anti M, Fedeli G, Fadda G, Pola P, Gasbarrini G. Efficacy of a multistep strategy for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2000; **14**: 79-83

189 **Tucci A**, Poli L, Caletti G. Treatment of the "ineradicable" Helicobacter pylori infection. *Am J Gastroenterol* 1999; **94**: 1713-1715

190 **Gisbert JP**. [The attitude in a failure to eradicate Helicobacter pylori: surrender or fight?] *Med Clin* (Barc) 1998; **111**: 778-782

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