Second-line rescue therapy of *Helicobacter pylori* infection

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***Abstract*:** *Helicobacter pylori* infection is the main known cause of gastritis, gastroduodenal ulcer disease and gastric cancer. After more than 20 years of experience in *H. pylori* treatment, however, the ideal regimen to treat this infection has still to be found. Nowadays, apart from having to know well first-line eradication regimens, we must also be prepared to face treatment failures. Therefore, in designing a treatment strategy we should not focus on the results of primary therapy alone, but also on the final (overall) eradication rate. The 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 (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. 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.

***Keywords*:** eradication, *Helicobacter pylori*, levofloxacin, rescue, rifabutin, salvage

Introduction

Helicobacter pylori infection is the main known cause of gastritis, gastroduodenal ulcer disease and gastric cancer. After more than 20 years of experience in *H. pylori* treatment, however, the ideal regimen to treat this infection has still to be found [Vakil, 2009]. Consensus conferences have recommended therapeutic regimens that achieve *H. pylori* cure rates higher than 80% on an intention-to-treat basis [Malfertheiner *et al.* 2007, 2002; Howden *et al.* 1998]. 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 [Gisbert *et al.* 2007d, 2000b], 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% [Paoluzi *et al.* 2006; Calvet *et al.* 2005; Gisbert *et al.* 2005b; Vakil *et al.* 2004; Hawkey *et al.* 2003; Veldhuyzen Van Zanten *et al.* 2003; Laine *et al.* 2000, 1998] and even lower than 50% [Altintas *et al.* 2004; Gumurdulu *et al.* 2004; Della Monica *et al.* 2002]. 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 [Egan *et al.* 2008; Megraud, 2004; Vakil *et al.* 1998].

Papers dealing with retreatment of *H. pylori* after failure are difficult to analyze due to several reasons [Axon, 2000]. Firstly, patients who fail with their first treatment probably include a higher percentage of individuals who are unreliable

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tablet takers, others who have resistant organisms and also 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 in 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-line therapies [Gisbert, 2008; Gisbert and Pajares, 2002, 2005].

Several 'rescue' therapies have been recommended, but they still fail to eradicate *H. pylori* in more than 20% of the cases [Gisbert and Pajares, 2002], and these patients constitute a therapeutic dilemma [Gisbert, 2008; Gisbert and Pajares, 2005]. Patients who are not cured with two consecutive treatments including clarithromycin and metronidazole will have at least single, and usually double, resistance [Romano *et al.* 2008; Megraud, 2004]. 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 culture in these patients to select a third-line treatment according to microbial sensitivity to antibiotics [Malfertheiner *et al.* 2007, 2002]. 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 [Gisbert, 2008; Gisbert and Pajares, 2005; Zullo *et al.* 2003b; Gisbert and Pajares, 2002]. Therefore, the evaluation of drugs without cross-resistance to nitroimidazole or macrolides as components of retreatment combination therapies would be worthwhile [Graham, 2009].

Probiotics have been proposed as a useful adjunct. Some studies prescribing probiotics with *H. pylori* eradication therapy had no effect on the side-effect profile but did increase the rates of eradication [Kim *et al.* 2008]. However, other studies on concurrent probiotic administration suggested the inverse with better side-effect profiles but no increase in eradication or rates of compliance with therapy [Cremonini *et al.* 2002].

All these issues are important at the present time, but they will be even more relevant in a 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 [Calvet *et al.* 2001; De Boer and Tytgat, 2000; Gisbert, 2008; Gisbert *et al.* 2005a; Gisbert and Pajares, 2002].

The aim of the present manuscript will be to review the experience dealing with 'nonresponders' 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 in 'rescue' regimen when these triple combinations fail. Bibliographical searches were performed in the PubMed (Internet) database including studies available until July 2009, 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 (i.e. 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 [Dore *et al.* 2000; Houben *et al.* 1999; Peitz *et al.* 1999; Van Der Wouden *et al.* 1999; Tompkins *et al.* 1997]. 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 [Parente *et al.* 2003]. 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* [Battaglia *et al.* 1998]. This recommendation is based on the observation that acquired bacterial resistance to metronidazole or clarithromycin results primarily from the previous treatment failure [Kobayashi *et al.* 2006; Peitz *et al.* 1999; Deltenre *et al.* 1998],

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 *versus* empiric retreatment for *H. pylori* after a treatment failure. In the study by Yahav *et al.* [2006a], 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 for 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 empirical 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 [Lamouliatte *et al.* 2003], patients in whom one previous *H. pylori* eradication therapy (mainly with PPI-amoxicillin-clarithromycin) has 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 or 14 days) or PPI-amoxicillin-metronidazole (for 14 days). 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 one-third 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 [Malfertheiner *et al.* 2007], was not tested. In fact, as will be reviewed later, several studies have obtained relatively good results with this quadruple regimen empirically prescribed, with mean eradication rate of 77% (i.e. a similar figure than 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* has 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 [Malfertheiner *et al.* 2007], 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.* [2001], 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 were 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.* [2003], 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 (that does not induce resistance) and metronidazole (an antibiotic not used in the first trial), and several authors have reported encouraging results with this strategy [Ueki *et al.* 2009; Murakami *et al.* 2008, 2006; Shirai *et al.* 2007; Matsuhisa *et al.* 2006; Nagahara *et al.* 2004; Shimoyama *et al.* 2004; Isomoto *et al.* 2003; Miwa *et al.* 2003]. However, in our experience, when this therapy has been administered twice-daily for 1 week, eradication rates lower than 50% have been obtained [Gisbert *et al.* 1999a]; the subsequently use of higher (three times per day) antibiotic doses, was followed only by a mild increase in eradication rate (58%), which was still unacceptable [Gisbert *et al.* 1999a]. 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 instead of 7 days [Perri *et al.* 2001b]. In this same study, the readministration of clarithromycin, even when coprescribed with RBC, was associated with poor eradication rates. In the same way, Nagahara *et al.* [2001] 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 days) or had received PPI-amoxicillin-metronidazole (for 10 days). The eradication rates for second-line therapy with the same regimen (thus readministering clarithromycin) was of only 53%, while it was of 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 the optimal second-line therapy after PPI-clarithromycin-amoxicillin failure, and has been the recommended 'rescue' regimen in several guidelines [Malfertheiner *et al.* 2007; Gisbert *et al.* 2000a; Lam and Talley, 1998]. Several studies have obtained relatively good results with this quadruple regimen, the results being summarized in Table 1 [Usta *et al.* 2008; Uygun *et al.* 2008; Chung *et al.* 2007; Navarro-Jarabo *et al.* 2007; Choung *et al.* 2006, Wu *et al.* 2006; Lee *et al.* 2005, 1999; Marko *et al.* 2005; Bilardi *et al.* 2004; Nista *et al.* 2003; Orsi *et al.* 2003; Perri *et al.* 2003, 2001a; Wong *et al.* 2003; Baena Diez *et al.* 2000; Michopoulos *et al.* 2000; Sicilia *et al.* 2000; Gasbarrini *et al.* 2000b; Gomollon *et al.* 1999; Gisbert *et al.* 1999a, 1999b; Elizalde *et al.* 1998]. Thus, the weighted mean eradication rate with this 'rescue' therapy, calculated from the studies included in the table, is of 77%. In this combination regimen, PPI should be prescribed in the usual dose and 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). Precisely, the study with the lowest efficacy [Gisbert *et al.* 1999b] 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 PPI. Thus, Beales [2001] reported that four of the five patients initially failing RBC-clarithromycin-amoxicillin therapy were successfully treated with quadruple therapy. A 7-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 days have been reported (mean figures, calculated from Table 1, of 74%, 72% and 81%, respectively). Furthermore, in a recent retrospective study, patients who failed to the standard triple therapy (PPI, amoxicillin, clarithromycin) received 1 or 2 weeks quadruple therapy, and the eradication rate was similar between the two regimens [Choung *et al.* 2006].

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 *et al.* [2000]	31	14	90
Bilardi *et al.* [2004]	46	7	37
Elizalde *et al.* [1998]	31	7	87
Choung *et al.* [2006]	56	7	77
Choung *et al.* [2006]	99	14	88
Chung *et al.* [2007]	87	7	84
Gasbarrini *et al.* [2000b]	9	7	88
Gisbert *et al.* [1999b]	30	7	57
Gisbert *et al.* [1999a]	9	7	78
Gomollon *et al.* [1999]	21	7	95
Lee *et al.* [1999]	20	7	68
Lee *et al.* [2005]	63	7	75
Marko *et al.* [2005]	27	7	63
Michopoulos *et al.* [2000]	38	14	76
Navarro-Jarabo *et al.* [2007]	54	7	70
Nista *et al.* [2003]	70	7	63
Nista *et al.* [2003]	70	14	68
Orsi *et al.* [2003]	50	12	88
Perri *et al.* [2001a]	45	10	67
Perri *et al.* [2003]	60	7	83
Sicilia *et al.* [2000]	21	10	83
Usta *et al.* [2008]	89	14	67
Uygun *et al.* [2008]	100	14	82
Wong *et al.* [2003]	53	7	91
Wu *et al.* [2006]	47	7	77

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

These results are in agreement with those reported previously with quadruple therapy as first-line regimen, where 1-week therapy appeared sufficient, and prolonging treatment did not increase efficacy [De Boer *et al.* 1994]. Finally, although PPIs are generally prescribed as the antisecretors in quadruple therapy, some authors have shown, in a randomized study, that omeprazole 20 mg twice daily. and ranitidine 300 mg twice daily. were equally effective as antisecretory agents combined in a second-line quadruple eradication regimen after failure with previous regimens without metronidazole (although the power of the study to find statistically significant differences was limited) [Michopoulos *et al.* 2000]. Nevertheless, these regimens were administered during 14 days and, therefore, remains to be demonstrated if the equivalence between both antisecretors – PPIs and H_2-blockers – is also observable with 7-day regimens.

The question may be suggested whether treatment with PPI-clarithromycin-amoxicillin followed by 'rescue' with quadruple therapy if failure is preferable to the inverse strategy. To analyze this interesting aspect, Gomollon *et al.* [2000b] randomized consecutive patients to one of two strategies: (1) treatment during 7 days with quadruple therapy, and if failure second-line treatment with omeprazole-clarithromycin-amoxicillin during 7 days; and (2) initial treatment with omeprazole-clarithromycin-amoxicillin and if failure 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 one. 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.* [2005] 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 'rescue' regimen [Gisbert *et al.* 2007a, 2005c, 1999; Koksal *et al.* 2005; Hojo *et al.* 2001, Zullo *et al.* 2001a; Rinaldi *et al.* 1999]. RBC is a compound that has, on one hand, the antisecretory activity of ranitidine, and, on the other, the mucosal protective and anti-*H. pylori* effects of certain other bismuth salts [Gisbert et al. 2005d, 1999c, Van Oijen *et al.* 2000]. To date, several studies have evaluated 7–14 day RBC-based second-line regimens after PPI-based triple therapy failures, achieving encouraging results, with eradication rates of 67% [Gisbert *et al.* 2005c], 68% [Gisbert *et al.* 2007a], 76% [Thong-Ngam and Mahachai, 2006], 82% [Rinaldi *et al.* 1999], 83% [Gisbert *et al.* 1999b], 86% [Koksal *et al.* 2005] and 96% [Zullo *et al.* 2001a]. Furthermore, one randomized study has demonstrated that triple RBC-based therapy, when prescribed to patients with previous PPI-clarithromycin-amoxicillin failure, achieves even a higher efficacy than quadruple therapy, with additional advantages of a lower number of drugs and a simpler dose scheme [Gisbert *et al.* 1999b]. Nevertheless, the eradication rate with quadruple regimen in this last study was remarkably low, which was possibly explained by the low dose of metronidazole prescribed. The favorable results obtained with RBC in aforementioned studies are probably 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 [Gisbert et al. 2005d, 1999c; Megraud, 2004; Van Oijen *et al.* 2001]. 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 [Malfertheiner *et al.* 2007; Hojo *et al.* 2001; Kearney, 2001; Gisbert and Pajares, 2002]. However, bismuth salts, including RBC, are no longer available worldwide, and some National Guidelines have been accordingly changed [Caselli *et al.* 2007].

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 by several authors [Malfertheiner *et al.* 2007; Gisbert and Pajares, 2002; Hojo *et al.* 2001; Kearney, 2001]. However, this quadruple regimen requires the administration of four drugs with a complex scheme (bismuth and tetracycline usually prescribed every 6 hours, and metronidazole every 8 hours) and is associated with a relatively high incidence of adverse effects [Gisbert and Pajares, 2002]. Furthermore, this quadruple regimen still fails to eradicate *H. pylori* in approximately 20–30% 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 [Gisbert and Pajares, 2002].

Levofloxacin is a fluoroquinolone antibacterial agent with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and atypical respiratory pathogens [Croom and Goa, 2003]. Recently, some studies have evaluated the efficacy of new fluoroquinolones, such as levofloxacin, that could prove to be a valid alternative to standard antibiotics not only as first-line therapies but, more interesting, as second-line regimens [Vaira *et al.* 2007; Gisbert and Morena, 2006c; Gisbert and Pajares, 2005; Saad *et al.* 2006]. 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* [Sanchez *et al.* 2000], and that primary resistances to such antibiotic are (still) relatively infrequent (when compared with metronidazole or clarithromycin) [Chang *et al.* 2009, Chisholm and Owen, 2009; Antos *et al.* 2006; Kumala and Rani, 2006; Gatta *et al.* 2005; Zou *et al.* 2003; Xia *et al.* 2002]. A recent *in vitro* study also showed a synergistic effect of quinolone antimicrobial agents and PPIs on strains of *H. pylori* [Tanaka *et al.* 2002]. Furthermore, it has been shown *in vitro* that levofloxacin retains its activity when *H. pylori* strains are resistant to clarithromycin and metronidazole [Antos *et al.* 2006; Yahav *et al.* 2006b; Watanabe *et al.* 2003]. 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 [Gatta *et al.* 2005; Matsumoto *et al.* 2005; Bilardi *et al.* 2004].

A combination of a PPI, amoxicillin and levofloxacin, as first-line regimen, has been associated with favorable results, with mean eradication rates of about 90% [Rispo *et al.* 2007; Gisbert *et al.* 2007b; Antos *et al.* 2006; Lee *et al.* 2006; Marzio *et al.* 2006; Di Caro *et al.* 2002; Cammarota *et al.* 2000]. Later, other authors studied this same regimen in patients with one previous eradication failure, also reporting exciting results, with *H. pylori* cures rates ranging from 60% to 94% [Di Caro *et al.* 2009; Eisig *et al.* 2009; Kuo *et al.* 2009; Schrauwen *et al.* 2009; Gisbert *et al.* 2007c; Page *et al.* 2007; Giannini *et al.* 2006; Lee *et al.* 2006; Wong *et al.* 2006; Matsumoto *et al.* 2005; Bilardi *et al.* 2004; Nista *et al.* 2003; Orsi *et al.* 2003; Perri *et al.* 2003; Watanabe *et al.* 2003; Wong *et al.* 2003]. 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 [Gisbert *et al.* 2006c]. This systematic review found higher *H. pylori* cure rates with 10-day than with 7-day regimens, both in general (81% *versus* 73%) and also with the levofloxacin-amoxicillin-PPI combination in particular (80% *versus* 68%), suggesting that the longer (10-day) therapeutic scheme should be chosen.

Furthermore, two recent meta-analyses have suggested that after *H. pylori* eradication failure, levofloxacin-based 'rescue' regimen is more effective than the generally recommended quadruple therapy [Saad *et al.* 2006; Gisbert *et al.* 2006c]. In one of these meta-analyses [Gisbert *et al.* 2006c], higher *H. pylori* cure rates with the levofloxacin-based triple regimens than with the quadruple combinations were found (81% *versus* 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.* [2003], who reported a cure rate of only 63% with the levofloxacin regimen, the lowest reported in the literature, a figure that contrasts with the mean eradication rate of 80% calculated in a systematic review [Gisbert *et al.* 2006c]. Nevertheless, when that single outlier study [Perri *et al.* 2003] 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% *versus* 64%), also achieving statistical significance, and heterogeneity among studies almost disappeared [Gisbert *et al.* 2006c].

As previously mentioned, the quadruple regimen requires the administration of a complex scheme [Gisbert *et al.* 2002]. On the contrary, levofloxacin-based regimens (with amoxicillin and PPIs administered twice daily, and levofloxacin every 12 or 24 hours) 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 [Gisbert *et al.* 2002].

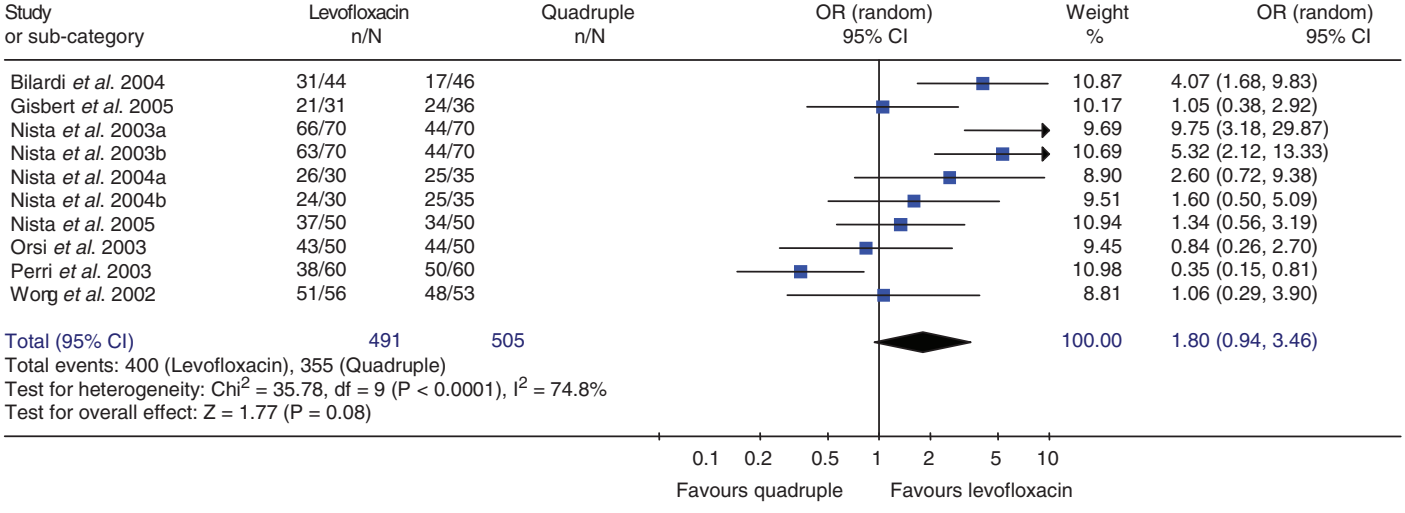

Figure 1. Meta-analysis comparing *H. pylori* eradication efficacy with levofloxacin-based triple regimens *versus* quadruple therapy, as second-line 'rescue' regimen after failure of a proton-pump inhibitor (PPI)-amoxicillin-clarithromycin.

In contrast, levofloxacin is generally well tolerated, and most adverse events associated with its use are mild to moderate in severity and transient [Croom and Goa, 2003]. The most frequent adverse effects affect the gastrointestinal tract [Croom and Goa, 2003]. Occasional cases of tendinitis and tendon rupture have been reported in the literature with levofloxacin therapy [Bilardi *et al.* 2004; Croom and Goa, 2003]. However, data derived from more than 15 million prescriptions in the US indicated the rate is fewer than 4 per million prescriptions [Kahn, 2001]. *Clostridium difficile* infection may be associated with the use of this broad spectrum activity antibiotic [Croom and Goa, 2003]. In the aforementioned systematic review [Gisbert *et al.* 2006c], 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 or 10 days, supporting the aforementioned recommendation of prescribing the more effective 10-day regimen. Moreover, two meta-analyses have demonstrated a lower incidence of adverse effects with levofloxacin-based treatments than with the quadruple combinations [Gisbert *et al.* 2006c; Saad *et al.* 2006].

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 [Carothers *et al.* 2007; Cattoir *et al.* 2007; Glocker *et al.* 2007; Perna *et al.* 2007; Zullo *et al.* 2007; Bogaerts *et al.* 2006; Kim *et al.* 2006; Marzio *et al.* 2006; Miyachi *et al.* 2006; Wong *et al.* 2006; Coelho *et al.* 2005; Gatta *et al.* 2005; Cammarota *et al.* 2004; Cabrita *et al.* 2000]. More importantly, it has been demonstrated that the presence of levofloxacin resistance significantly reduce the eradication rate following a therapy with this antibiotic [Perna *et al.* 2007; Marzio *et al.* 2006; Gatta *et al.* 2005; Krakowka *et al.* 1996]. 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 [Gisbert *et al.* 1999a] have achieved *H. pylori* eradication in 85% of cases, while others have reported success rates of 86% [Reilly *et al.* 1995] or even 100% [Lerang *et al.* 1997]. In favor of this strategy is the study by Magaret *et al.* [2001], 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 days (i.e. the logical approach with triple therapy not repeating metronidazole), or to lansoprazole, bismuth, metronidazole and tetracycline for 14 days (i.e. the quadruple therapy repeating metronidazole). Intention-to-treat efficacies were 75% for triple regimen and 71% for 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 [Beales, 2001]

'Rescue' regimen after PPI-clarithromycin-nitroimidazole failure

As previously mentioned, acquired bacterial resistance to metronidazole or clarithromycin results primarily from the previous treatment failure [Peitz *et al.* 1999; Deltenre *et al.* 1998], and therefore the first choice probably should not be a regimen that combines these two antibiotics in the same regimen [Calvet *et al.* 2001; Axon, 2000; De Boer *et al.* 2000b]. Although this regimen is very effective [Gisbert *et al.* 2000b], patients who are not cured will probably have double resistance [Peitz *et al.* 2002, 1999], 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 multiply resistant strains as evidenced by the results of culture testing after the second failed course [Beales, 2001]. 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 [De Boer *et al.* 2000b].

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 [Miehlke *et al.* 2006; Axon, 2000]; 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 [Saad and Chey, 2008; Dore *et al.* 2000; Pilotto *et al.* 2000; Houben *et al.* 1999; Peitz *et al.* 1999; Van Der Wouden *et al.* 1999; Tompkins *et al.* 1997]. Nevertheless, the following possibilities exist.

Readministering metronidazole. Due to the fact that metronidazole resistance is frequent and clinically relevant [Dore *et al.* 2000; Houben *et al.* 1999; Peitz *et al.* 1999; Van Der Wouden *et al.* 1999], if this antibiotic is readministered, it should be used within bismuth-based quadruple regimen (thus PPI might reduce the negative effect of metronidazole resistance [Graham *et al.* 2000; Gomollon *et al.* 1999, Van Der Wouden *et al.* 1999; De Boer *et al.* 1995]). With this regimen, eradication rates up to 80% have been achieved [Gisbert *et al.* 1999a]. RBC, which may overcome the impact of resistance to metronidazole [Gisbert *et al.* 1999c], may also play a role in this regimen. Thus, some authors have reported an 88% cure rate with 2-week regimen or RBC-tetracycline-tinidazole in patients who had previously failed a clarithromycin-tinidazole based triple therapy [Zullo *et al.* 2001a].

Readministering clarithromycin. Several studies have underlined the relevance of clarithromycin resistance [Dore *et al.* 2000; Houben *et al.* 1999; Peitz *et al.* 1999; Tompkins *et al.* 1997], which advise against readministering this antibiotic. Therefore, a further option which has been proposed is to add (e.g. to PPI-amoxicillin-clarithromycin) a fourth medication (as bismuth) with bactericidal effect against *H. pylori*, with which a 70% eradication rate has been achieved [Gisbert *et al.* 1999a].

Readministering no antibiotic. A final alternative, obviously, consists of no readministering either metronidazole or clarithromycin. Although only published in abstract form, one study has prescribed RBC, tetracycline and amoxicillin for 2 weeks and has reported the eradication in 89% of the cases who had previously failed PPI, clarithromycin and tinidazole [Cudia *et al.* 1997]. 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 has 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.

Patients allergic to penicillin. When penicillin allergy is documented, replacing amoxicillin with metronidazole has been recommended in PPI-based triple combinations. *H. pylori* eradication is a challenge in patients allergic to penicillin, especially in those who have failed a first-eradication trial with these two key antibiotics, clarithromycin and nitroimidazoles. To date, only few studies have evaluated the efficacy of *H. pylori* eradication treatment specifically in those patients allergic to penicillin, which constitutes a relatively common subgroup [Gisbert *et al.* 2009, 2005e; Rodriguez-Torres *et al.* 2005]. In our previous study, *H. pylori* infected patients allergic to penicillin failing first-line treatment with PPI-clarithromycin-metronidazole therapy received a second-line treatment with RBC, tetracycline and metronidazole, but this rescue regimen cured the infection in only 47% of the patients [Gisbert *et al.* 2005e]. In this same study, it was shown that rifabutin-clarithromycin-PPI regimen was ineffective and poorly tolerated. However, a final rescue regimen including levofloxacin cured the infection in all treated patients [Gisbert *et al.* 2005e]. In a more recent study, it has been confirmed that a

levofloxacin-containing regimen (together with omeprazole and clarithromycin) represents an encouraging second-line alternative in the presence of penicillin allergy [Gisbert *et al.* 2009].

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 [Malfertheiner *et al.* 2007; De Boer *et al.* 2000b; European *Helicobacter pylori* Study Group 1997]. 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 [Gisbert, 2008a, 2005b]. It is evident that, as pretreatment antibiotic resistance is the most important factor in nonresponse to initial treatment [Dore *et al.* 2000; Houben *et al.* 1999; Peitz *et al.* 1999; Van Der Wouden *et al.* 1999; Tompkins *et al.* 1997], knowledge of the organism's antibiotic susceptibility may represents 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, 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 [Zullo *et al.* 2003b].
(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. 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 [Zullo *et al.* 2003b]. Furthermore, in several studies enrolling patients who had failed one or more eradication treatments, the bacterium was isolated in less than 80% of cases [Zullo *et al.* 2003b]. 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 [Zullo *et al.* 2003b].
(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 amoxicillin, clarithromycin, metronidazole, and tetracycline. Resistance to amoxicillin has been estimated to be less than 1% in most studies [Megraud, 2004; Zullo *et al.* 2003b]. Hence, its role in clinical practice may even be marginalized. Similarly, resistance to tetracycline is also very low, or even absent, in most countries [Megraud, 2004; Zullo *et al.* 2003b]. 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 [Zullo *et al.* 2003b].
(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 [Guslandi, 2001]. Some discrepancies between antibiotic susceptibility and *H. pylori* eradication may occur, due, for example, to the possibility of coinfection with different *H. pylori* strains [Kim *et al.* 2003]. Thus, a variable proportion of noneradicated patients is made of subjects who harbor strains sensitive to the administered drugs, and in these patients the reasons for treatment failure are unclear [Ali *et al.* 1999]. For example, Gomollon *et al.* [2000a] reported how third-line treatment often (in 50% of the cases) failed to eradicate *H. pylori* infection, in spite of giving 14-day, full-dose, quadruple culture-guided combination, showing that *in vitro* susceptibility did not predict eradication success. In the same way, Vicente *et al.* [2002] determined the effectiveness of a third, culture-guided, treatment of *H. pylori* infection after two unsuccessful attempts. Patients received a 2-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 [Zullo *et al.* 2003b].

(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 the previous treatment failure [Peitz *et al.* 1999; Deltenre *et al.* 1998]. 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 [Megraud, 2004; Pilotto *et al.* 2000; Adamek *et al.* 1998; Tompkins *et al.* 1997]. 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. Although 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 [Huang and Hunt, 1999]. 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 [Howden and Hunt, 1998; Lam and Talley, 1998].

(9) Finally, relatively high eradication rates have been obtained with empirical third-line treatment after two consecutive failures in several studies [Gisbert *et al.* 2008b, 2006a, 2006b, 2004, 2003; Dore *et al.* 2003; Zullo *et al.* 2003a; Treiber *et al.* 2002a; Canducci *et al.* 2001; Zullo *et al.* 2001a; Bock *et al.* 2000, Chan *et al.* 2000; Perri *et al.* 2000; Seppala *et al.* 2000].

However, limited experience suggests that endoscopy with culture and susceptibility testing may be appropriate after failure of two eradication therapies; in this situation, a nonrandomized 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 [Beales, 2001]. Cammarota *et al.* [2004] 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 quadruple regimen including PPI, bismuth, tetracycline and amoxicillin, and *H. pylori* eradication was obtained in 90% of the cases. Although the authors conclude 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 nonresponder patients [Zullo *et al.* 2003b, Cianci *et al.* 2006]. 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 [Cianci *et al.* 2006; Zullo *et al.* 2003b]. As it has been brilliantly expressed by Zullo *et al.* [2003b], regrettably, gastroenterologists need to accept

that gastric biopsy culture is not as simple as filling a sample bottle!

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 [Megraud and Lamouliatte, 2003]. Data coming from this experience on *H. pylori* resistance will be used as reference for the corresponding population. This preventive approach has been recommended to avoid an increase in refractory *H. pylori* infection in the future [Megraud and Lamouliatte, 2003].

Empirical third-line *H. pylori* 'rescue' therapy after failure of two eradication treatments

If we have decided, finally, not to perform culture before the administration of the third-line 'rescue' treatment after failure of the first two trials (generally including clarithromycin and metronidazole), different possibilities of 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 days, at least when 'rescue' therapy fails and third-line regimens are therefore prescribed [De Boer and Brody, 2000]. As several studies have underlined the relevance of metronidazole [Dore *et al.* 2000; Houben *et al.* 1999; Peitz *et al.* 1999; Van Der Wouden *et al.* 1999] and clarithromycin [Dore *et al.* 2000; Houben *et al.* 1999; Peitz *et al.* 1999; Tompkins *et al.* 1997] resistance, these two antibiotics should not be readministered, and several regimens have been evaluated in this scenario, outlined as follows.

Amoxicillin ± tetracycline-based regimens

In a recent study, patients with at least one treatment failure and 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 days, and the infection was cured in 76% of the cases [Miehlke *et al.* 2003]. This study suggests that, although the 'old-fashioned' dual combination of omeprazole plus amoxicillin is generally considered quite ineffective as first-line regimen, it may be associated with relatively good results if prescribed at high doses, even for *H. pylori* infection 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 [Chi *et al.* 2003]. 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 weeks and achieved eradication in 89% of the cases who had previously failed PPI, clarithromycin and tinidazole [Cudia *et al.* 1997].

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 [Nishizawa *et al.* 2009; Hsu *et al.* 2008; Rokkas *et al.* 2006; Gisbert *et al.* 2006a, 2006b, 2005a; Coelho *et al.* 2005; Gatta *et al.* 2005; Bilardi *et al.* 2004; Zullo *et al.* 2003a, 2001a]. As an example, a recent study by Zullo *et al.* [2003a] aimed to evaluate the efficacy of a levofloxacin-amoxicillin-PPI combination in patients who previously had failed two or more therapeutic attempts, and eradication rate was 83% (intention-to-treat analysis). More recently, Gisbert *et al.* [2006b] 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 alternatives of '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 10-day triple levofloxacin-based regimen is more effective than the same combination with rifabutin as a 'rescue' regimen [Gisbert *et al.* 2006b]. 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 [Akada *et al.* 1999; Heep *et al.* 1999; Brogden and Fitton, 1994]. 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 [Rossi, 1999]. 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 [Heep *et al.* 1999].

As summarized in Table 2, rifabutin-based 'rescue' therapy constitutes an encouraging strategy after multiple previous eradication failures [Gonzalez Carro *et al.* 2007; Navarro-Jarabo *et al.* 2007; Van Der Poorten and Katelaris, 2007; Borody *et al.* 2006; Miehlke *et al.* 2006; Gisbert *et al.* 2006b, 2003; Toracchio *et al.* 2005; Beales, 2001; Canducci *et al.* 2001; Bock *et al.* 2000; Perri *et al.* 2000]. As an example, Perri *et al.* [2000, 1998] used a 1-week 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 a eradication rate of 71% by intention-to-treat analysis. Gisbert *et al.* [2003], in a prospective multicenter study, included patients in whom a first eradication trial with PPI, clarithromycin and amoxicillin and a second trial with PPI, bismuth, tetracycline and metronidazole had failed. A third 14-day 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 [Gisbert *et al.* 2006b]. In the largest study up to now with rifabutin [Gonzalez Carro *et al.* 2007], 92 consecutive patients diagnosed with *H. pylori* infection resistant to two previous treatment regimens were treated with a PPI, rifabutin and amoxicillin for 10 days, 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 of 69%.

These findings suggest that new rifabutin-based combinations are effective for *H. pylori* strains resistant to antibiotics, and specifically to clarithromycin or metronidazole [Moayyedi *et al.* 2006; Miehlke *et al.* 2008]. Furthermore, rifabutin-based therapies have been compared with the widely used 'classic' quadruple therapy. Perri *et al.* [2001a] performed a randomized study where three groups of patients were treated for 10 days with pantoprazole, amoxicillin and rifabutin 150 mg once daily, or 300 mg once daily, 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 [Perri *et al.* 2001a].

Several concerns still remain, however, regarding rifabutin treatment. Firstly, this drug is very expensive. Secondly, severe leucopoenia and trombocytopenia have been reported in one patient treated with rifabutin, with myelotoxicity demonstrated by bone marrow aspirate [Canducci *et al.* 2001]. 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 rifabutin-based regimen [Gisbert *et al.* 2006b, 2003]. Finally, there is some concern about a widespread 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 [Bock *et al.* 2000]. 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).

Table 2. Rifabutin-based 'rescue' therapies (rifabutin-amoxicillin PPI) 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 [2001]	10	Rifabutin 300 mg o.d. Amoxicillin 1 g b.i.d. Omeprazole 20 mg b.i.d.	14	60
Bock *et al.* [2000]	25	Rifabutin 150 mg b.i.d. Amoxicillin 1 g b.i.d. Lansoprazole 30 mg b.i.d.	7	72
Borody *et al.* [2006]	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.* [2001]	10	Rifabutin 300 mg o.d. Amoxicillin 1 g b.i.d. Omeprazole 20 mg b.i.d.	10	70
Gisbert *et al.* [2003]	14	Rifabutin 150 mg b.i.d. Amoxicillin 1 g b.i.d. Omeprazole 20 mg b.i.d.	14	79
Gisbert *et al.* [2006b]	20	Rifabutin 150 mg b.i.d. Amoxicillin 1 g b.i.d. Omeprazole 20 mg b.i.d.	10	45
Gonzalez Carro [2007]	92	Rifabutin 150 mg b.i.d. Amoxicillin 1 g b.i.d. Pantoprazole 40 mg b.i.d	10	61
Miehlke *et al.* [2006]	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.* [2007]	45	Rifabutin 150 mg b.i.d. Amoxicillin 1 g b.i.d. Omeprazole 20 mg b.i.d.	7	44
Perri *et al.* [2000]	41	Rifabutin 300 mg o.d. Amoxicillin 1 g b.i.d. Pantoprazole 40 mg b.i.d.	7	71
Toracchio *et al.* [2005]	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.* [2007]	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: 69%. o.d., once daily; b.i.d., twice daily; t.i.d., three times per day.

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 [Xiao *et al.* 1990], and the majority of first-line furazolidone-based combination therapies revealed eradication rates above 80% [Xia *et al.* 2002]. Primary resistance to furazolidone is virtually absent [Megraud *et al.* 2003; Kwon *et al.* 2001; Haas *et al.* 1990], and its potential to develop resistance is as low as for bismuth compounds or amoxicillin [Treiber *et al.* 2002b]. Moreover, this drug has no cross-resistance potential to metronidazole [Haas *et al.* 1990]. Triple therapy in which furazolidone is used instead of metronidazole achieves high eradication rates, even in populations with a high prevalence of nitroimidazole resistance [Eisig *et al.* 2005; Nijevitch *et al.* 2005; Xiao *et al.* 2001; Ebrahimi-Dariani *et al.* 2003]. 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) [Isakov *et al.* 2002]. A few years ago, some authors tested a quadruple combination of furazolidone, bismuth, tetracycline and PPI as second-line eradication therapy, and reported encouraging results [Sotoudehmanesh *et al.* 2001]. More recently,

Treiber *et al.* [2002a] and Sanches *et al.* [2008] investigated whether this quadruple regimen containing furazolidone could be effective as third-line therapy in patients with *H. pylori* treatment failure after first-line (clarithromycin-metronidazole ± amoxicillin) and/or second-line (PPI-bismuth-tetracycline-metronidazole) regimens, and *H. pylori* infection was cured in >90% of the cases. Furthermore, 7-day 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 [Qasim *et al.* 2005].

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 [Buzas and Jozan, 2007]. 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. However, some aspects related with the use of furazolidone as a rescue therapy for *H. pylori* infection should be remarked, especially regarding its potential oncologic risk [De Francesco *et al.* 2009]. Furthermore, furazolidone is not available worldwide.

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 complication. 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 [Moayyedi *et al.* 2006; Laine *et al.* 2001], 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 [Gisbert *et al.* 2008a, 2005b]. For example, in the study by Gasbarrini *et al.* [2000a], a total of 2606 patients were administered a PPI, tinidazole and clarithromycin for 1 week. Patients with continuing infection were then given a second 1-week 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-week quadruple scheme established on antibiotic sensitivity. Eradication rates after the first, second and third treatment, were 79%, 77% and 52%, respectively. This algorithm led to overall per-protocol eradication rates of 99%. Chan *et al.* [2000] 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 quadruple regimen, finally achieving a 99% cumulative eradication rate. Beales [2001] 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.* [2001a] reported an 83% cure rate in patients who had previously failed two courses of clarithromycin-amoxicillin and clarithromycin-tinidazole-based triple therapies. Gomollon *et al.* [2000a] studied the effectiveness of third-line treatment of *H. pylori* infection with 2-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.* [2002], 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.* [2002a]

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 second eradication trial, which gave a final eradication rate of 99%. In the study by Qasim *et al.* [2005], 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.* [2004] 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. Gisbert *et al.* [2008b] 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%. Finally, Rokkas *et al.* [2009] treated initially their patients with a triple regimen (omeprazole, amoxicillin and clarithromycin), and subsequently with a second-line quadruple. After two previous *H. pylori* eradication failures, patients received omeprazole, amoxicillin and levofloxacin, as a third-line empirical strategy. Out of 540 patients initially included in the study, *H. pylori* was finally eradicated in 90% (intention-to-treat) and in 98% (per-protocol) of them.

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 [Rokkas *et al.* 2009; Gisbert *et al.* 2008b, 2004; Qasim *et al.* 2005; Vicente *et al.* 2002; Treiber *et al.* 2002a; Beales, 2001; Zullo *et al.* 2001a; Chan *et al.* 2000; Seppala *et al.* 2000; Gasbarrini *et al.* 2000a; Gomollon *et al.* 2000a].

Furthermore, these encouraging (cumulative) results have been obtained when more than three consecutive treatments have been prescribed [Gisbert *et al.* 2008a, 2005b]. As an example, Seppala *et al.* [2000] 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 levofloxacin-based regimen can also be administered with good results

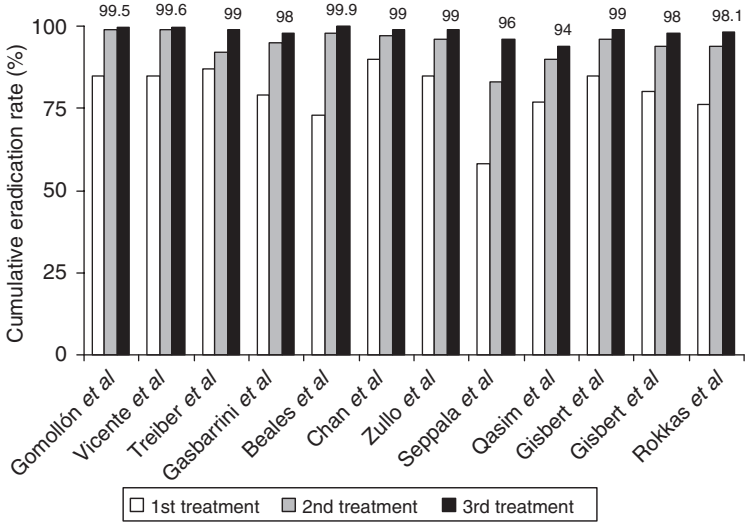

Figure 2. Cumulative *H. pylori* eradication rates with three consecutive eradication treatments.

after three previous eradication failures with antibiotics such as amoxicillin, clarithromycin, metronidazole, tetracycline and even rifabutin [Gisbert, 2005a]. Thus, we prospectively evaluated 10 patients with three consecutive *H. pylori* eradication failures (first treatment with PPI-clarithromycin-amoxicillin, second treatment with RBC-tetracycline-metronidazole, and third treatment with PPI-amoxicillin-rifabutin). A fourth eradication regimen with 10-day 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 four successive treatments was 99.5% [Gisbert *et al.* 2008b].

Finally, reports of 'ineradicable' *H. pylori* infection after more than four eradicating treatments failed have been recently published. Dore *et al.* [2003] 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.* [1999] reported their experience of 13 patients with at least five 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 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 [Zullo *et al.* 2001b].

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. Nowadays, apart from having to know well first-line eradication regimens, we must also be prepared to face treatment failures. Therefore, in designing a treatment strategy we should not focus on the results of primary therapy alone, but also on the final (overall) eradication rate.

The 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).

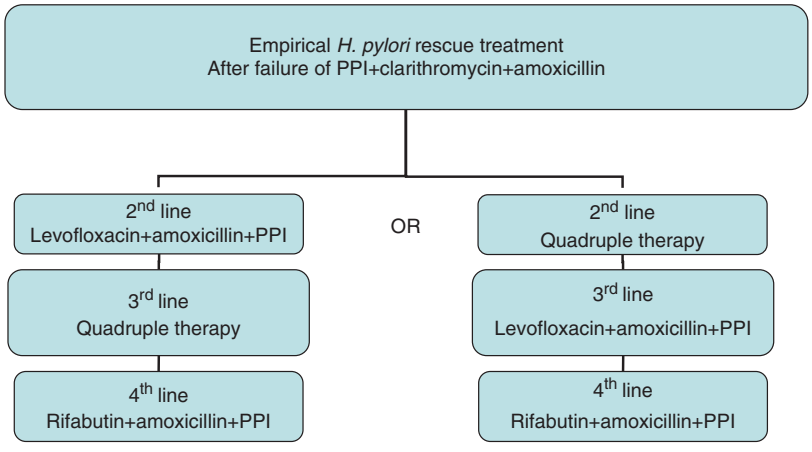

Figure 3. Choice of an empirical retreatment regimen, without culture and antimicrobial sensitivity testing, after failure of proton-pump inhibitor (PPI), amoxicillin and clarithromycin combination.
Note: quadruple therapy: combination of proton-pump inhibitor (PPI), bismuth, tetracycline and nitroimidazole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

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 [Gisbert, 1998].

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Conflict of interest statement

None declared.

References

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

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

Ali, A., Menegatti, M., Gatta, L., Landi, F., Ricci, C., Acciardi, C. *et al.* (1999) A Second-line anti-Helicobacter *pylori* therapy in patients with previously failed treatment. *Am J Gastroenterol* 94: 2321–2323.

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

Antos, D., Schneider-Brachert, W., Bastlein, E., Hanel, C., Haferland, C., Buchner, M. *et al.* (2006) 7-day triple therapy of *Helicobacter pylori* infection with levofloxacin, amoxicillin, and high-dose esomeprazole in patients with known antimicrobial sensitivity. *Helicobacter* 11: 39–45.

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

Axon, A. (2000) Quadruple therapy should be second-line treatment for *Helicobacter pylori* infection. In: Hunt, R.H. and Tytgat, G.N.J. (eds). Helicobacter pylori Basic Mechanisms to Clinical Cure, Kluwer Academic Publishers: The Netherlands, pp. 631–635.

Baena Diez, J.M., Lopez Mompo, C., Rams Rams, F., Garcia Lareo, M., Rosario Hernandez Ibanez, M. and Teruel Gila, J. (2000) Eficacia de una terapia secuencial en la erradicación de *Helicobacter pylori*: cuádruple terapia con omeprazol, metronidazol, tetraciclina y bismuto tras el fracaso de la combinación de omeprazol, claritromicina y amoxicilina. *Med Clin (Barc)* 115: 617–619.

Battaglia, G., Di Mario, F., Vigneri, S., Vianello, F., Benvenuti, M.E., Donisi, P.M. *et al.* (1998) Strategy for the retreatment of failed *Helicobacter pylori* eradication therapy: a case series. *Ital J Gastroenterol Hepatol* 30: 370–374.

Beales, I.L. (2001) Efficacy of *Helicobacter pylori* eradication therapies: a single centre observational study. *BMC Gastroenterol* 1: 7.

Bilardi, C., Dulbecco, P., Zentilin, P., Reglioni, S., Iiritano, E., Parodi, A. *et al.* (2004) A 10-day levofloxacin-based therapy in patients with resistant *Helicobacter pylori* infection: a controlled trial. *Clin Gastroenterol Hepatol* 2: 997–1002.

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

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

Borody, T.J., Pang, G., Wettstein, A.R., Clancy, R., Herdman, K., Surace, R. *et al.* (2006) Efficacy and safety of rifabutin-containing 'rescue therapy' for resistant *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 23: 481–488.

Brogden, R.N. and Fitton, A. (1994) Rifabutin. A review of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 47: 983–1009.

Buzas, G.M. and Jozan, J. (2007) Nitrofuran-based regimens for the eradication of *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 22: 1571–1581.

Cabrita, J., Oleastro, M., Matos, R., Manhente, A., Cabral, J., Barros, R. *et al.* (2000) Features and trends in *Helicobacter pylori* antibiotic resistance in Lisbon area, Portugal (1990–1999). *J Antimicrob Chemother* 46: 1029–1031.

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

Calvet, X., Gene, E. and Sanfeliu, I. (2001) Estrategias terapéuticas para la Infección por *Helicobacter pylori*. *Med Clin (Barc)* 116: 239.

Cammarota, G., Cianci, R., Cannizzaro, O., Cuoco, L., Pirozzi, G., Gasbarrini, A. *et al.* (2000) Efficacy of two one-week rabeprazole/levofloxacin-based triple therapies for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 14: 1339–1343.

Cammarota, G., Martino, A., Pirozzi, G., Cianci, R., Branca, G., Nista, E.C. *et al.* (2004) 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* 19: 789–795.

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

Carothers, J.J., Bruce, M.G., Hennessy, T.W., Bensler, M., Morris, J.M., Reasonover, A.L. *et al.* (2007) The relationship between previous fluoroquinolone use and levofloxacin resistance in *Helicobacter pylori* infection. *Clin Infect Dis* 44: e5–8.

Caselli, M., Zullo, A., Maconi, G., Parente, F., Alvisi, V., Casetti, T. *et al.* (2007) 'Cervia II Working Group Report 2006': guidelines on diagnosis and treatment of *Helicobacter pylori* infection in Italy. *Dig Liver Dis* 39: 782–789.

Cattoir, V., Nectoux, J., Lascols, C., Deforges, L., Delchier, J.C., Megraud, F. *et al.* (2007) 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* 29: 389–396.

Chan, F.K., Sung, J.J., Suen, R., Wu, J.C., Ling, T.K. and Chung, S.C. (2000) Salvage therapies after failure of *Helicobacter pylori* eradication with ranitidine bismuth citrate-based therapies. *Aliment Pharmacol Ther* 14: 91–95.

Chang, W.L., Sheu, B.S., Cheng, H.C., Yang, Y.J., Yang, H.B. and Wu, J.J. (2009) Resistance to metronidazole, clarithromycin and levofloxacin of *Helicobacter pylori* before and after clarithromycin-based therapy in Taiwan. *J Gastroenterol Hepatol* 24(7): 1230–1235.

Chi, C.H., Lin, C.Y., Sheu, B.S., Yang, H.B., Huang, A.H. and Wu, J.J. (2003) 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* 18: 347–353.

Chisholm, S.A. and Owen, R.J. (2009) Frequency and molecular characteristics of ciprofloxacin- and rifampicin-resistant *Helicobacter pylori* from gastric infections in the United Kingdom. *J Med Microbiol* Jul 9 [Epub ahead at print].

Choung, R.S., Lee, S.W., Jung, S.W., Han, W.S., Kim, M.J., Jeen, Y.T. *et al.* (2006) [Comparison of the effectiveness of quadruple salvage regimen for *Helicobacter pylori* Infection according to the duration of treatment]. *Korean J Gastroenterol* 47: 131–135.

Chung, S.J., Lee, D.H., Kim, N., Jung, S.H., Kim, J.W., Hwang, J.H. *et al.* (2007) Eradication rates of *Helicobacter pylori* infection with second-line treatment: non-ulcer dyspepsia compared to peptic ulcer disease. *Hepatogastroenterology* 54: 1293–1296.

Cianci, R., Montalto, M., Pandolfi, F., Gasbarrini, G.B. and Cammarota, G. (2006) Third-line rescue therapy for *Helicobacter pylori* infection. *World J Gastroenterol* 12: 2313–2319.

Coelho, L.G., Moretzsohn, L.D., Vieira, W.L., Gallo, M.A., Passos, M.C., Cindr, J.M. *et al.* (2005) New once-daily, highly effective rescue triple therapy after multiple *Helicobacter pylori* treatment failures: a pilot study. *Aliment Pharmacol Ther* 21: 783–787.

Cremonini, F., Di Caro, S., Covino, M., Armuzzi, A., Gabrielli, M., Santarelli, L. *et al.* (2002) Effect of different probiotic preparations on anti-*Helicobacter pylori* therapy-related side effects: a parallel group, triple blind, placebo-controlled study. *Am J Gastroenterol* 97: 2744–2749.

Croom, K.F. and Goa, K.L. (2003) Levofloxacin: a review of its use in the treatment of bacterial infections in the United States. *Drugs* 63: 2769–2802..

Cudia, B., Romano, M., Gioè, F.P., Barbera, N., Lo Gerfo, D. and Montalto, R. (1997) 'Rescue' therapy including ranitidine bismuth citrate + minocicline + amoxicillin for eradication of *Helicobacter pylori* in previous h.p. treatment failure. *Gut* 41(Suppl. 1): A103.

De Boer, W., Driessen, W., Jansz, A. and Tytgat, G. (1995) Effect of acid suppression on efficacy of treatment for *Helicobacter pylori* infection. *Lancet* 345: 817–820.

De Boer, W.A. and Borody, T.J. (2000) Treatment failures and secondary resistance to antibiotics. a growing concern in *Helicobacter pylori* therapy. *Dig Liver Dis* 32: 673–675.

De Boer, W.A., Driessen, W.M., Potters, V.P. and Tytgat, G.N. (1994) Randomized study comparing 1 with 2 weeks of quadruple therapy for eradicating *Helicobacter pylori*. *Am J Gastroenterol* 89: 1993–1997.

De Boer, W.A. and Tytgat, G.N. (2000) Regular review: treatment of *Helicobacter pylori* infection. *BMJ* 320: 31–34.

De Francesco, V., Ierardi, E., Hassan, C. and Zullo, A. (2009) Furazolidone therapy for *Helicobacter pylori*: is it effective and safe? *World J Gastroenterol* 15: 1914–1915.

Deltenre, M., Ntounda, R., Jonas, C. and De Koster, E. (1998) Eradication of *Helicobacter pylori*: why does it fail? *Ital J Gastroenterol Hepatol* 30(Suppl. 3): S326–328.

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

Di Caro, S., Assunta Zocco, M., Cremonini, F., Candelli, M., Nista, E.C., Bartolozzi, F. *et al.* (2002) Levofloxacin based regimens for the eradication of *Helicobacter pylori*. *Eur J Gastroenterol Hepatol* 14: 1309–1312.

Di Caro, S., Franceschi, F., Mariani, A., Thompson, F., Raimondo, D., Masci, E. *et al.* (2009) Second-line levofloxacin-based triple schemes for *Helicobacter pylori* eradication. *Dig Liver Dis* 41: 480–485.

Dore, M.P., Leandro, G., Realdi, G., Sepulveda, A.R. and Graham, D.Y. (2000) Effect of pretreatment antibiotic resistance to metronidazole and clarithromycin on outcome of *Helicobacter pylori* therapy: a meta-analytical approach. *Dig Dis Sci* 45: 68–76.

Dore, M.P., Marras, L., Maragkoudakis, E., Nieddu, S., Manca, A., Graham, D.Y. *et al.* (2003) Salvage therapy after two or more prior *Helicobacter pylori* treatment failures: the super salvage regimen. *Helicobacter* 8: 307–309.

Ebrahimi-Dariani, N., Mirmomen, S., Mansour-Ghanaei, F., Noormohammadpoor, P., Sotodehmanesh, R., Haghpanah, B. *et al.* (2003) 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* 9: PI105–108.

Egan, B.J., Marzio, L., O'Connor, H. and O'Morain, C. (2008) Treatment of *Helicobacter pylori* infection. *Helicobacter* 13(Suppl. 1): 35–40.

Eisig, J.N., Silva, F.M., Barbuti, R.C., Rodriguez, T.N., Malfertheiner, P., Moraes Filho, J.P. *et al.* (2009) Efficacy of a 7-day course of furazolidone, levofloxacin, and lansoprazole after failed Helicobacter pylori eradication. *BMC Gastroenterol* 9: 38.

Eisig, J.N., Silva, F.M., Rodriguez, T.N., Hashimoto, C.L. and Barbuti, R.C. (2005) A furazolidone-based quadruple therapy for *Helicobacter pylori* retreatment in patients with peptic ulcer disease. *Clinics* 60: 485–488.

Elizalde, I.R., Borda, F., Jara, C., Martínez, A., Rodríguez, C. and Jiménez, J. (1998) Eficacia de dos tratamientos consecutivos en la erradicación de *Helicobacter pylori*. *Anales Sis San Navarra* 21(Suppl. 2): 83–88.

European *Helicobacter pylori* Study Group. The Maastricht Consensus Report. (1997) Current European Concepts in the Management of *Helicobacter pylori* Infection. Gut 41: 813.

Gasbarrini, A., Ojetti, V., Armuzzi, A., Branca, G., Canducci, F., Torre, E.S. *et al.* (2000a) Efficacy of a multistep strategy for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 14: 79–83.

Gasbarrini, A., Ojetti, V., Pitocco, D., Armuzzi, A., Silveri, N.G., Pola, P. *et al.* (2000b) Efficacy of different *Helicobacter pylori* eradication regimens in patients affected by insulin-dependent diabetes mellitus. *Scand J Gastroenterol* 35: 260–263.

Gatta, L., Zullo, A., Perna, F., Ricci, C., De Francesco, V., Tampieri, A. *et al.* (2005) A 10-day levofloxacin-based triple therapy in patients who have failed two eradication courses. *Aliment Pharmacol Ther* 22: 45–49.

Giannini, E.G., Bilardi, C., Dulbecco, P., Mamone, M., Santi, M.L., Testa, R. *et al.* (2006) 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* 23: 281–287.

Gisbert, J.P. (1998) [The attitude in a failure to eradicate *Helicobacter pylori*: surrender or fight?]. *Med Clin (Barc)* 111: 778–782.

Gisbert, J.P. (2005a) Rescue therapy with levofloxacin after multiple *H. pylori* treatment failures. *Aliment Pharmacol Ther* 22: 653–654; author reply 654–655.

Gisbert, J.P. (2008a) 'Rescue' regimens after *Helicobacter pylori* treatment failure. *World J Gastroenterol* 14: 5385–5402.

Gisbert, J.P., Bermejo, F., Castro-Fernandez, M., Perez-Aisa, A., Fernandez-Bermejo, M., Tomas, A. *et al.* (2008c) Second-line rescue therapy with levofloxacin after *H. pylori* treatment failure: a Spanish multicenter study of 300 patients. *Am J Gastroenterol* 103(1): 71–76.

Gisbert, J.P., Boixeda, D., Bermejo, F., Nieves Rincon, M., Jesus Higes, M., Angeles Arpa, M. *et al.* (1999a) Re-treatment after *Helicobacter pylori* eradication failure. *Eur J Gastroenterol Hepatol* 11: 1049–1054.

Gisbert, J.P., Calvet, X., Bujanda, L., Marcos, S., Gisbert, J.L. and Pajares, J.M. (2003) 'Rescue' therapy with rifabutin after multiple *Helicobacter pylori* treatment failures. *Helicobacter* 8: 90–94.

Gisbert, J.P., Calvet, X., Gomollon, F. and Sainz, R. (2000a) [Treatment for the eradication of *Helicobacter pylori*. Recommendations of the Spanish Consensus Conference]. *Med Clin (Barc)* 114: 185–195.

Gisbert, J.P., Castro-Fernandez, M., Bermejo, F., Perez-Aisa, A., Ducons, J., Fernandez-Bermejo, M. *et al.* (2006a) Third-line rescue therapy with levofloxacin after two *H. pylori* treatment failures. *Am J Gastroenterol* 101: 243–247.

Gisbert, J.P., Dominguez-Munoz, A., Dominguez-Martin, A., Gisbert, J.L. and Marcos, S. (2005b) Esomeprazole-based therapy in *Helicobacter pylori* eradication: any effect by increasing the dose of esomeprazole or prolonging the treatment? *Am J Gastroenterol* 100: 1935–1940.

Gisbert, J.P., Fernandez-Bermejo, M., Molina-Infante, J., Perez-Gallardo, B., Prieto-Bermejo, A.B., Mateos-Rodriguez, J.M. *et al.* (2007b) First-line triple therapy with levofloxacin for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 26: 495–500.

Gisbert, J.P., Fuentes, J., Carpio, D., Tito, L., Guardiola, J., Tomas, A. *et al.* (2005c) 7-Day rescue therapy with ranitidine bismuth citrate after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther* 21: 1249–1253.

Gisbert, J.P., Gisbert, J.L., Marcos, S., Gravalos, R.G., Carpio, D. and Pajares, J.M. (1999b) Seven-day 'rescue' therapy after *Helicobacter pylori* treatment failure: omeprazole, bismuth, tetracycline and metronidazole vs. ranitidine bismuth citrate, tetracycline and metronidazole. *Aliment Pharmacol Ther* 13: 1311–1316.

Gisbert, J.P., Gisbert, J.L., Marcos, S., Jimenez-Alonso, I., Moreno-Otero, R. and Pajares, J.M. (2008b) Empirical rescue therapy after *Helicobacter pylori* treatment failure: a 10-year single-centre study of 500 patients. *Aliment Pharmacol Ther* 27: 346–354.

Gisbert, J.P., Gisbert, J.L., Marcos, S., Moreno-Otero, R. and Pajares, J.M. (2006b) Third-line rescue therapy with levofloxacin is more effective than rifabutin rescue regimen after two *Helicobacter pylori* treatment failures. *Aliment Pharmacol Ther* 24: 1469–1474.

Gisbert, J.P., Gisbert, J.L., Marcos, S., Moreno-Otero, R. and Pajares, J.M. (2007c) Levofloxacin- vs. ranitidine bismuth citrate-containing therapy after *H. pylori* treatment failure. *Helicobacter* 12: 68–73.

Gisbert, J.P., Gisbert, J.L., Marcos, S., Olivares, D. and Pajares, J.M. (2005e) *Helicobacter pylori* first-line treatment and rescue options in patients allergic to penicillin. *Aliment Pharmacol Ther* 22: 1041–1046.

Gisbert, J.P., Gisbert, J.L., Marcos, S. and Pajares, J.M. (2004) Empirical *Helicobacter pylori* 'rescue' therapy after failure of two eradication treatments. *Dig Liver Dis* 36: 7–12.

Gisbert, J.P., Gonzalez, L. and Calvet, X. (2005d) Systematic review and meta-analysis: proton pump inhibitor vs. ranitidine bismuth citrate plus two antibiotics in *Helicobacter pylori* eradication. *Helicobacter* 10: 157–171.

Gisbert, J.P., Gonzalez, L., Calvet, X., Garcia, N., Lopez, T., Roque, M. *et al.* (2000b) Proton pump inhibitor, clarithromycin and either amoxycillin or nitroimidazole: a meta-analysis of eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 14: 1319–1328.

Gisbert, J.P. and Morena, F. (2006c) Systematic review and meta-analysis: levofloxacin-based rescue regimens after *Helicobacter pylori* treatment failure. *Aliment Pharmacol Ther* 23: 35–44.

Gisbert, J.P. and Pajares, J.M. (2002) Review article: *Helicobacter pylori* 'rescue' regimen when proton pump inhibitor-based triple therapies fail. *Aliment Pharmacol Ther* 16: 1047–1057.

Gisbert, J.P. and Pajares, J.M. (2005) *Helicobacter pylori* 'rescue' therapy after failure of two eradication treatments. *Helicobacter* 10: 363–372.

Gisbert, J.P., Pajares, J.M. and Valle, J. (1999c) Ranitidine bismuth citrate therapy regimens for treatment of *Helicobacter pylori* infection: a review. *Helicobacter* 4: 58–66.

Gisbert, J.P., Pajares, R. and Pajares, J.M. (2007d) Evolution of *Helicobacter pylori* therapy from a meta-analytical perspective. *Helicobacter* 12(Suppl. 2): 50–58.

Gisbert, J.P., Perez-Aisa, A., Castro-Fernandez, M., Barrio, J., Rodrigo, L., Cosme, A. *et al.* (2009) *Helicobacter pylori* First-line treatment and rescue option containing levofloxacin in patients allergic to penicillin. *Dig Liver Dis* Jul 23 [Epub ahead of print].

Glocker, E., Stueger, H.P. and Kist, M. (2007) Quinolone resistance in *Helicobacter pylori* isolates in Germany. *Antimicrob Agents Chemother* 51: 346–349.

Gomollon, F., Ducons, J.A., Ferrero, M., Garcia Cabezudo, J., Guirao, R., Simon, M.A. *et al.* (1999) 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* 4: 222–225.

Gomollon, F., Sicilia, B., Ducons, J.A., Sierra, E., Revillo, M.J. and Ferrero, M. (2000a) Third line treatment for *Helicobacter pylori*: a prospective, culture-guided study in peptic ulcer patients. *Aliment Pharmacol Ther* 14: 1335–1338.

Gomollon, F., Valdeperez, J., Garuz, R., Fuentes, J., Barrera, F., Malo, J. *et al.* (2000b) Análisis coste-efectividad de dos estrategias de erradicación de *Helicobacter pylori*: resultados de un estudio prospectivo y aleatorizado en atención primaria. *Med Clin (Barc)* 115: 1–6.

Gonzalez Carro, P., Perez Roldan, F., De Pedro Esteban, A., Legaz Huidobro, M.L., Soto Fernandez, S., Roncero Garcia Escribano, O. *et al.* (2007) Efficacy of rifabutin-based triple therapy in *Helicobacter pylori* infected patients after two standard treatments. *J Gastroenterol Hepatol* 22: 60–63.

Graham, D.Y. (2009) Efficient identification and evaluation of effective *Helicobacter pylori* therapies. *Clin Gastroenterol Hepatol* 7: 145–148.

Graham, D.Y., Osato, M.S., Hoffman, J., Opekun, A.R., Anderson, S.Y., Kwon, D.H. *et al.* (2000) Metronidazole containing quadruple therapy for infection with metronidazole resistant *Helicobacter pylori*: a prospective study. *Aliment Pharmacol Ther* 14: 745–750.

Gumurdulu, Y., Serin, E., Ozer, B., Kayaselcuk, F., Ozsahin, K., Cosar, A.M. *et al.* (2004) Low eradication rate of *Helicobacter pylori* with triple 7–14 days and quadruple therapy in Turkey. *World J Gastroenterol* 10: 668–671.

Guslandi, M. (2001) Alternative antibacterial agents for *Helicobacter pylori* eradication. *Aliment Pharmacol Ther* 15: 1543–1547.

Haas, C.E., Nix, D.E. and Schentag, J.J. (1990) In vitro selection of resistant *Helicobacter pylori*. *Antimicrob Agents Chemother* 34: 1637–1641.

Hawkey, C.J., Atherton, J.C., Treichel, H.C., Thjodleifsson, B. and Ravic, M. (2003) 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* 17: 1065–1074.

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

Hojo, M., Miwa, H., Nagahara, A. and Sato, N. (2001) Pooled analysis on the efficacy of the

second-line treatment regimens for *Helicobacter pylori* infection. *Scand J Gastroenterol* 36: 690–700.

Houben, M.H., Van Der Beek, D., Hensen, E.F., Craen, A.J., Rauws, E.A. and Tytgat, G.N. (1999) A systematic review of *Helicobacter pylori* eradication therapy – the impact of antimicrobial resistance on eradication rates. *Aliment Pharmacol Ther* 13: 1047–1055.

Howden, C.W. and Hunt, R.H. (1998) Guidelines for the management of *Helicobacter pylori* infection. Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology. *Am J Gastroenterol* 93: 2330–2338.

Hsu, P.I., Wu, D.C., Chen, A., Peng, N.J., Tseng, H.H., Tsay, F.W. *et al.* (2008) Quadruple rescue therapy for *Helicobacter pylori* infection after two treatment failures. *Eur J Clin Invest* 38: 404–409.

Huang, J.Q. and Hunt, R.H. (1999) Treatment after failure: the problem of 'non-responders'. *Gut* 45(Suppl. 1): I40–44.

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

Isomoto, H., Inoue, K., Furusu, H., Enjoji, A., Fujimoto, C., Yamakawa, M. *et al.* (2003) 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* 18: 101–107.

Kahn, J.B. (2001) Latest industry information on the safety profile of levofloxacin in the US. *Chemotherapy* 47(Suppl. 3): 32–37, discussion 44–38.

Kearney, D.J. (2001) Retreatment of *Helicobacter pylori* infection after initial treatment failure. *Am J Gastroenterol* 96: 1335–1339.

Kim, J.J., Kim, J.G. and Kwon, D.H. (2003) Mixed-infection of antibiotic susceptible and resistant *Helicobacter pylori* isolates in a single patient and underestimation of antimicrobial susceptibility testing. *Helicobacter* 8: 202–206.

Kim, J.M., Kim, J.S., Kim, N., Kim, S.G., Jung, H.C. and Song, I.S. (2006) Comparison of primary and secondary antimicrobial minimum inhibitory concentrations for *Helicobacter pylori* isolated from Korean patients. *Int J Antimicrob Agents* 28: 6–13.

Kim, M.N., Kim, N., Lee, S.H., Park, Y.S., Hwang, J.H., Kim, J.W. *et al.* (2008) The effects of probiotics on PPI-triple therapy for *Helicobacter pylori* eradication. *Helicobacter* 13: 261–268.

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

Koksal, A.S., Parlak, E., Filik, L., Yolcu, O.F., Odemis, B., Ulker, A. *et al.* (2005) Ranitidine bismuth citrate-based triple therapies as a second-line therapy for *Helicobacter pylori* in Turkish patients. *J Gastroenterol Hepatol* 20: 637–642.

Krakowka, S., Ringler, S.S., Eaton, K.A., Green, W.B. and Leunk, R. (1996) Manifestations of the local gastric immune response in gnotobiotic piglets infected with *Helicobacter pylori*. *Vet Immunol Immunopathol* 52: 159–173.

Kumala, W. and Rani, A. (2006) Patterns of *Helicobacter pylori* isolate resistance to fluoroquinolones, amoxicillin, clarithromycin and metronidazoles. *Southeast Asian J Trop Med Public Health* 37: 970–974.

Kuo, C.H., Hu, H.M., Kuo, F.C., Hsu, P.I., Chen, A., Yu, F.J. *et al.* (2009) Efficacy of levofloxacin-based rescue therapy for *Helicobacter pylori* infection after standard triple therapy: a randomized controlled trial. *J Antimicrob Chemother* 63: 1017–1024.

Kwon, D.H., Lee, M., Kim, J.J., Kim, J.G., El-Zaatari, F.A., Osato, M.S. *et al.* (2001) Furazolidone- and nitrofurantoin-resistant *Helicobacter pylori*: prevalence and role of genes involved in metronidazole resistance. *Antimicrob Agents Chemother* 45: 306–308.

Laine, L., Fennerty, M.B., Osato, M., Sugg, J., Suchower, L., Probst, P. *et al.* (2000) Esomeprazole-based *Helicobacter pylori* eradication therapy and the effect of antibiotic resistance: results of three US multicenter, double-blind trials. *Am J Gastroenterol* 95: 3393–3398.

Laine, L., Schoenfeld, P. and Fennerty, M.B. (2001) Therapy for *Helicobacter pylori* in patients with nonulcer dyspepsia. a meta-analysis of randomized, controlled trials. *Ann Intern Med* 134: 361–369.

Laine, L., Suchower, L., Frantz, J., Connors, A. and Neil, G. (1998) 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* 93: 2106–2112.

Lam, S.K. and Talley, N.J. (1998) Report of the 1997 Asia Pacific Consensus Conference on the Management of *Helicobacter pylori* Infection. *J Gastroenterol Hepatol* 13: 1–12.

Lamouliatte, H., Megraud, F., Delchier, J.C., Bretagne, J.F., Courillon-Mallet, A., De Korwin, J.D. *et al.* (2003) Second-line treatment for failure to eradicate *Helicobacter pylori*: a randomized trial comparing four treatment strategies. *Aliment Pharmacol Ther* 18: 791–797.

Lee, J.H., Cheon, J.H., Park, M.J., Kim, N., Lee, D.H., Kim, J.M. *et al.* (2005) [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* 46: 94–98.

Lee, J.H., Hong, S.P., Kwon, C.I., Phyun, L.H., Lee, B.S., Song, H.U. *et al.* (2006a) [The efficacy of

levofloxacin based triple therapy for *Helicobacter pylori* eradication]. *Korean J Gastroenterol* 48: 19–24.

Lee, J.M., Breslin, N.P., Hyde, D.K., Buckley, M.J. and O'Morain, C.A. (1999) Treatment options for *Helicobacter pylori* infection when proton pump inhibitor-based triple therapy fails in clinical practice. *Aliment Pharmacol Ther* 13: 489–496.

Lee, Y.C., Wu, H.M., Chen, T.H., Liu, T.Y., Chiu, H.M., Chang, C.C. *et al.* (2006b) A community-based study of *Helicobacter pylori* therapy using the strategy of test, treat, retest, and re-treat initial treatment failures. *Helicobacter* 11: 418–424.

Lerang, F., Moum, B., Haug, J.B., Berge, T., Tolas, P., Sandvei, P.K. *et al.* (1997) Highly effective second-line anti-*Helicobacter pylori* therapy in patients with previously failed metronidazole-based therapy. *Scand J Gastroenterol* 32: 1209–1214.

Magaret, N., Burm, M., Faigel, D., Kelly, C., Peterson, W. and Fennerty, M.B. (2001) 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* 19: 174–178.

Malfertheiner, P., Megraud, F., O'Morain, C., Bazzoli, F., El-Omar, E., Graham, D. *et al.* (2007) Current Concepts in the Management of *Helicobacter pylori* Infection: The Maastricht III Consensus Report. *Gut* 56: 772–781.

Malfertheiner, P., Megraud, F., O'Morain, C., Hungin, A.P., Jones, R., Axon, A. *et al.* (2002) Current Concepts in the Management of *Helicobacter pylori* Infection – the Maastricht 2-2000 Consensus Report. *Aliment Pharmacol Ther* 16: 167-180..

Marko, D., Calvet, X., Ducons, J., Guardiola, J., Tito, L. and Bory, F. (2005) Comparison of two management strategies for *Helicobacter pylori* treatment: clinical study and cost-effectiveness analysis. *Helicobacter* 10: 22–32.

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

Matsuhisa, T., Kawai, T., Masaoka, T., Suzuki, H., Ito, M., Kawamura, Y. *et al.* (2006) 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* 11: 152–158.

Matsumoto, Y., Miki, I., Aoyama, N., Shirasaka, D., Watanabe, Y., Morita, Y. *et al.* (2005) Levofloxacin-versus metronidazole-based rescue therapy for *H. pylori* infection in Japan. *Dig Liver Dis* 37: 821–825.

Megraud, F. (2004) *H. pylori* antibiotic resistance: prevalence, importance, and advances in testing. *Gut* 53: 1374–1384.

Megraud, F. and Lamouliatte, H. (2003) Review article: the treatment of refractory *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 17: 1333–1343.

Michopoulos, S., Tsibouris, P., Bouzakis, H., Balta, A., Vougadiotis, J., Broutet, N. *et al.* (2000) Randomized study comparing omeprazole with ranitidine as anti-secretory agents combined in quadruple second-line *Helicobacter pylori* eradication regimens. *Aliment Pharmacol Ther* 14: 737–744.

Miehlke, S., Hansky, K., Schneider-Brachert, W., Kirsch, C., Morgner, A., Madisch, A. *et al.* (2006) 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* 24: 395–403.

Miehlke, S., Kirsch, C., Schneider-Brachert, W., Haferland, C., Neumeyer, M., Bastlein, E. *et al.* (2003) A prospective, randomized study of quadruple therapy and high-dose dual therapy for treatment of *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Helicobacter* 8: 310–319.

Miehlke, S., Schneider-Brachert, W., Kirsch, C., Morgner, A., Madisch, A., Kuhlisch, E. *et al.* (2008) One-week once-daily triple therapy with esomeprazole, moxifloxacin, and rifabutin for eradication of persistent *Helicobacter pylori* resistant to both metronidazole and clarithromycin. *Helicobacter* 13: 69–74.

Miwa, H., Nagahara, A., Kurosawa, A., Ohkusa, T., Ohkura, R., Hojo, M. *et al.* (2003) Is antimicrobial susceptibility testing necessary before second-line treatment for *Helicobacter pylori* infection? *Aliment Pharmacol Ther* 17: 1545–1551.

Miyachi, H., Miki, I., Aoyama, N., Shirasaka, D., Matsumoto, Y., Toyoda, M. *et al.* (2006) Primary levofloxacin resistance and gyra/B mutations among *Helicobacter pylori* in Japan. *Helicobacter* 11: 243–249.

Moayyedi, P., Soo, S., Deeks, J., Delaney, B., Harris, A., Innes, M. *et al.* (2006) Eradication of *Helicobacter pylori* for non-ulcer dyspepsia. *Cochrane Database Syst Rev* CD002096.

Murakami, K., Okimoto, T., Kodama, M., Sato, R., Miyajima, H., Ono, M. *et al.* (2006) Comparison of amoxicillin-metronidazole plus famotidine or lansoprazole for amoxicillin-clarithromycin-proton pump inhibitor treatment failures for *Helicobacter pylori* infection. *Helicobacter* 11: 436–440.

Murakami, K., Okimoto, T., Kodama, M., Sato, R., Watanabe, K. and Fujioka, T. (2008) Evaluation of three different proton pump inhibitors with amoxicillin and metronidazole in retreatment for *Helicobacter pylori* infection. *J Clin Gastroenterol* 42: 139–142.

Nagahara, A., Miwa, H., Kawabe, M., Kurosawa, A., Asaoka, D., Hojo, M. *et al.* (2004) Second-line treatment for *Helicobacter pylori* infection in Japan: proton pump inhibitor-based amoxicillin and metronidazole regimen. *J Gastroenterol* 39: 1051–1055.

Nagahara, A., Miwa, H., Ohkura, R., Yamada, T., Sato, K., Hojo, M. *et al.* (2001) Strategy for

retreatment of therapeutic failure of eradication of *Helicobacter pylori* infection. *J Gastroenterol Hepatol* 16: 613–618.

Navarro-Jarabo, J.M., Fernandez, N., Sousa, F.L., Cabrera, E., Castro, M., Ramirez, L.M. *et al.* (2007) Efficacy of rifabutin-based triple therapy as second-line treatment to eradicate *Helicobacter pylori* infection. *BMC Gastroenterol* 7: 31.

Nijevitch, A.A., Shcherbakov, P.L., Sataev, V.U., Khasanov, R., Al Khashash, R. and Tuygunov, M.M. (2005) *Helicobacter pylori* eradication in childhood after failure of initial treatment: advantage of quadruple therapy with nifuratel to furazolidone. *Aliment Pharmacol Ther* 22: 881–887.

Nishizawa, T., Suzuki, H. and Hibi, T. (2009) Quinolone-based third-line therapy for *Helicobacter pylori* eradication. *J Clin Biochem Nutr* 44: 119–124.

Nista, E.C., Candelli, M., Cremonini, F., Cazzato, I.A., Di Caro, S., Gabrielli, M. *et al.* (2003) Levofloxacin-based triple therapy vs. quadruple therapy in second-line *Helicobacter pylori* treatment: a randomized trial. *Aliment Pharmacol Ther* 18: 627–633.

Orsi, P., Pinazzi, O., Aragona, G. and Di Mario, F. (2003) Rabeprazole/levofloxacin based triple therapy as a salvatage treatment after failure of *H. pylori* eradication with standard regimens. *Helicobacter* 8: 339–493.

Page Ii, R.L., Ferguson, D. and Cantu, M. (2007) An alternative salvage regimen for *Helicobacter pylori*-resistant patients with heart failure. *Cardiology* 110: 112–115.

Paoluzi, P., Iacopini, F., Crispino, P., Nardi, F., Bella, A., Rivera, M. *et al.* (2006) 2-week triple therapy for *Helicobacter pylori* infection is better than 1-week in clinical practice: a large prospective single-center randomized study. *Helicobacter* 11: 562–568.

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

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

Peitz, U., Sulliga, M., Wolle, K., Leodolter, A., Von Arnim, U., Kahl, S. *et al.* (2002) 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* 16: 315–324.

Perna, F., Zullo, A., Ricci, C., Hassan, C., Morini, S. and Vaira, D. (2007) Levofloxacin-based triple therapy for *Helicobacter pylori* re-treatment: role of bacterial resistance. *Dig Liver Dis* 39: 1001–1005.

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

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

Perri, F., Festa, V., Clemente, R., Villani, M.R., Quitadamo, M., Caruso, N. *et al.* (2001a) Randomized study of two 'rescue' therapies for *Helicobacter pylori*-infected patients after failure of standard triple therapies. *Am J Gastroenterol* 96: 58–62.

Perri, F., Festa, V., Merla, A., Barberani, F., Pilotto, A. and Andriulli, A. (2003) Randomized study of different 'second-line' therapies for *Helicobacter pylori* infection after failure of the standard 'Maastricht triple therapy'. *Aliment Pharmacol Ther* 18: 815–820.

Perri, F., Villani, M.R., Quitadamo, M., Annese, V., Niro, G.A. and Andriulli, A. (2001b) Ranitidine bismuth citrate-based triple therapies after failure of the standard 'Maastricht triple therapy': a promising alternative to the quadruple therapy? *Aliment Pharmacol Ther* 15: 1017–1022.

Pilotto, A., Franceschi, M., Rassu, M., Leandro, G., Bozzola, L., Furlan, F. *et al.* (2000) 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* 32: 667–672.

Qasim, A., Sebastian, S., Thornton, O., Dobson, M., McLoughlin, R., Buckley, M. *et al.* (2005) Rifabutin- and furazolidone-based *Helicobacter pylori* eradication therapies after failure of standard first- and second-line eradication attempts in dyspepsia patients. *Aliment Pharmacol Ther* 21: 91–96.

Reilly, T.G., Ayres, R.C., Poxon, V. and Walt, R.P. (1995) *Helicobacter pylori* eradication in a clinical setting: success rates and the effect on the quality of life in peptic ulcer. *Aliment Pharmacol Ther* 9: 483–490.

Rinaldi, V., Zullo, A., De Francesco, V., Hassan, C., Winn, S., Stoppino, V. *et al.* (1999) *Helicobacter pylori* eradication with proton pump inhibitor-based triple therapies and re-treatment with ranitidine bismuth citrate-based triple therapy. *Aliment Pharmacol Ther* 13: 163–168.

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

Rodriguez-Torres, M., Salgado-Mercado, R., Rios-Bedoya, C.F., Aponte-Rivera, E., Marxuach-Cuetara, A.M., Rodriguez-Orengo, J.F. *et al.* (2005) High eradication rates of *Helicobacter pylori* infection with first- and second-line combination of esomeprazole, tetracycline, and metronidazole in patients allergic to penicillin. *Dig Dis Sci* 50: 634–639.

Rokkas, T., Sechopoulos, P., Robotis, I., Margantinis, G. and Pistiolas, D. (2009) Cumulative *H. pylori* eradication rates in clinical practice by adopting first and second-line regimens proposed by the Maastricht

III consensus and a third-line empirical regimen. *Am J Gastroenterol* 104: 21–25.

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

Romano, M., Iovene, M.R., Russo, M.I., Rocco, A., Salerno, R., Cozzolino, D. *et al.* (2008) Failure of first-line eradication treatment significantly increases prevalence of antimicrobial-resistant *Helicobacter pylori* clinical isolates. *J Clin Pathol* 61: 1112–1115.

Rossi, G. (1999) [An update on the antibiotic therapy of tuberculosis]. *Recenti Prog Med* 90: 241–243.

Saad, R.J. and Chey, W.D. (2008) Persistent *Helicobacter pylori* infection after a course of antimicrobial therapy – what's next? *Clin Gastroenterol Hepatol* 6: 1086–1090..

Saad, R.J., Schoenfeld, P., Kim, H.M. and Chey, W.D. (2006) Levofloxacin-based triple therapy versus bismuth-based quadruple therapy for persistent *Helicobacter pylori* infection: a meta-analysis. *Am J Gastroenterol* 101: 488–496.

Sanches, B., Coelho, L., Moretzsohn, L. and Vieira, Jr G. (2008) Failure of *Helicobacter pylori* treatment after regimes containing clarithromycin: new practical therapeutic options. *Helicobacter* 13: 572–576.

Sanchez, J.E., Saenz, N.G., Rincon, M.R., Martin, I.T., Sanchez, E.G. and Martinez, M.J. (2000) Susceptibility of *Helicobacter pylori* to mupirocin, oxazolidinones, quinupristin/dalfopristin and new quinolones. *J Antimicrob Chemother* 46: 283–285.

Schrauwen, R.W., Janssen, M.J. and De Boer, W.A. (2009) Seven-day ppi-triple therapy with levofloxacin is very effective for *Helicobacter pylori* eradication. *Neth J Med* 67: 96–101.

Seppala, K., Kosunen, T.U., Nuutinen, H., Sipponen, P., Rautelin, H., Sarna, S. *et al.* (2000) Cure of *Helicobacter pylori* infection after failed primary treatment: one-center results from 120 patients. *Scand J Gastroenterol* 35: 929–934.

Shimoyama, T., Fukuda, S., Mikami, T., Fukushi, M. and Munakata, A. (2004) Efficacy of metronidazole for the treatment of clarithromycin-resistant *Helicobacter pylori* infection in a Japanese population. *J Gastroenterol* 39: 927–930.

Shirai, N., Sugimoto, M., Kodaira, C., Nishino, M., Ikuma, M., Kajimura, M. *et al.* (2007) 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* 63: 743–749.

Sicilia, B., Sierra, E., Lago, A., Villar, M., Garcia, S. and Gomollon, F. (2000) [High eradication rates in *Helicobacter pylori* infection in patients with duodenal ulcer who failed previous eradication therapy]. *Med Clin (Barc)* 115: 641–643.

Sotoudehmanesh, R., Malekzadeh, R., Vahedi, H., Dariani, N.E., Asgari, A.A. and Massarrat, S. (2001) Second-line *Helicobacter pylori* eradication with a furazolidone-based regimen in patients who have failed a metronidazole-based regimen. *Digestion* 64: 222–225.

Tanaka, M., Isogai, E., Isogai, H., Hayashi, S., Hirose, K., Kimura, K. *et al.* (2002) Synergic effect of quinolone antibacterial agents and proton pump inhibitors on *Helicobacter pylori*. *J Antimicrob Chemother* 49: 1039–1040.

Thong-Ngam, D. and Mahachai, V. (2006) 14-day quadruple therapy with ranitidine bismuth citrate after *Helicobacter pylori* treatment failure in Thailand. *J Med Assoc Thai* 89(Suppl. 3): S119–125.

Tompkins, D.S., Perkin, J. and Smith, C. (1997) Failed treatment of *Helicobacter pylori* infection associated with resistance to clarithromycin. *Helicobacter* 2: 185–187.

Toracchio, S., Capodicasa, S., Soraja, D.B., Cellini, L. and Marzio, L. (2005) Rifabutin based triple therapy for eradication of *H. pylori* primary and secondary resistant to tinidazole and clarithromycin. *Dig Liver Dis* 37: 33–38.

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

Treiber, G., Wittig, J., Ammon, S., Walker, S., Van Doorn, L.J. and Klotz, U. (2002b) 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* 162: 153–160.

Tucci, A., Poli, L. and Caletti, G. (1999) Treatment of the 'ineradicable' *Helicobacter pylori* infection. *Am J Gastroenterol* 94: 1713–1715.

Ueki, N., Miyake, K., Kusunoki, M., Shindo, T., Kawagoe, T., Futagami, S. *et al.* (2009) Impact of quadruple regimen of clarithromycin added to metronidazole-containing triple therapy against *Helicobacter pylori* infection following clarithromycin-containing triple-therapy failure. *Helicobacter* 14: 91–99.

Usta, Y., Saltik-Temizel, I.N., Demir, H., Uslu, N., Ozen, H., Gurakan, F. *et al.* (2008) Comparison of short- and long-term treatment protocols and the results of second-line quadruple therapy in children with *Helicobacter pylori* infection. *J Gastroenterol* 43: 429–433.

Uygun, A., Ozel, A.M., Yildiz, O., Aslan, M., Yesilova, Z., Erdil, A. *et al.* (2008) 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* 23: 42–45.

Vaira, D., Ricci, C., Lanzini, A., Perna, F., Romano, A. and Corinaldesi, R. (2007) How to proceed in *Helicobacter pylori*-positive chronic gastritis refractory to first- and second-line eradication therapy. *Dig Dis* 25: 203–205.

Vakil, N. (2009) *H pylori* treatment: new wine in old bottles? *Am J Gastroenterol* 104: 26–30.

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

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

Van Der Poorten, D. and Katelaris, P.H. (2007) The effectiveness of rifabutin triple therapy for patients with difficult-to-eradicate *Helicobacter pylori* in clinical practice. *Aliment Pharmacol Ther* 26: 1537–1542.

Van Der Wouden, E.J., Thijs, J.C., Van Zwet, A.A., Sluiter, W.J. and Kleibeuker, J.H. (1999) The influence of in vitro nitroimidazole resistance on the efficacy of nitroimidazole-containing anti-*Helicobacter pylori* regimens: a meta- analysis. *Am J Gastroenterol* 94: 1751–1759.

Van Oijen, A.H., Verbeek, A.L., Jansen, J.B. and De Boer, W.A. (2000) Review article: treatment of *Helicobacter pylori* infection with ranitidine bismuth citrate- or proton pump inhibitor-based triple therapies. *Aliment Pharmacol Ther* 14: 991–999.

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

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

Watanabe, Y., Aoyama, N., Shirasaka, D., Maekawa, S., Kuroda, K., Miki, I. *et al.* (2003) Levofloxacin based triple therapy as a second-line treatment after failure of *Helicobacter pylori* eradication with standard triple therapy. *Dig Liver Dis* 35: 711–715.

Wong, W.M., Gu, Q., Chu, K.M., Yee, Y.K., Fung, F.M., Tong, T.S. *et al.* (2006) Lansoprazole, levofloxacin and amoxicillin triple therapy vs. quadruple therapy as second-line treatment of resistant *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 23: 421–427.

Wong, W.M., Gu, Q., Lam, S.K., Fung, F.M., Lai, K.C., Hu, W.H. *et al.* (2003) Randomized controlled study of rabeprazole, levofloxacin and rifabutin triple therapy vs. quadruple therapy as second-line treatment for *Helicobacter pylori* infection. *Aliment Pharmacol Ther* 17: 553–560.

Wu, D.C., Hsu, P.I., Chen, A., Lai, K.H., Tsay, F.W., Wu, C.J. *et al.* (2006) Randomized comparison of two rescue therapies for *Helicobacter pylori* infection. *Eur J Clin Invest* 36: 803–809.

Xia, H.H., Yu Wong, B.C., Talley, N.J. and Lam, S.K. (2002) Alternative and rescue treatment regimens for *Helicobacter pylori* eradication. *Expert Opin Pharmacother* 3: 1301–1311.

Xiao, S.D., Liu, W.Z., Hu, P.J., Ouyang, Q., Wang, J.L., Zhou, L.Y. *et al.* (2001) A multicentre study on eradication of *Helicobacter pylori* using four 1-week triple therapies in China. *Aliment Pharmacol Ther* 15: 81–86.

Xiao, S.D., Liu, W.Z., Xia, D.H., Jiang, S.J., Wang, R.N., Zhang, Z.H. *et al.* (1990) 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* 37: 503–506.

Yahav, J., Samra, Z., Niv, Y., Evans, C.T., Passaro, D.J., Dinari, G. *et al.* (2006a) Susceptibility-guided vs. empiric retreatment of *Helicobacter pylori* infection after treatment failure. *Dig Dis Sci* 51: 2316–2321.

Yahav, J., Shmuely, H., Niv, Y., Bechor, J. and Samra, Z. (2006b) In vitro activity of levofloxacin against *Helicobacter pylori* isolates from patients after treatment failure. *Diagn Microbiol Infect Dis* 55: 81–83.

Zou, J., Yang, Z.X. and Qin, Z.M. (2003) [Laboratory and clinical study of levofloxacin against *Helicobacter pylori*]. *Zhonghua Yi Xue Za Zhi* 83: 1778–1781.

Zullo, A., Hassan, C., Campo, S.M., Lorenzetti, R., Febbraro, I., De Matthaeis, M. *et al.* (2001a) A triple therapy regimen after failed *Helicobacter pylori* treatments. *Aliment Pharmacol Ther* 15: 1193–1197.

Zullo, A., Hassan, C., De Francesco, V., Lorenzetti, R., Marignani, M., Angeletti, S. *et al.* (2003a) A third-line levofloxacin-based rescue therapy for *Helicobacter pylori* eradication. *Dig Liver Dis* 35: 232–236.

Zullo, A., Hassan, C., Lorenzetti, R. and Morini, S. (2001b) *Helicobacter pylori* eradication: do we have another ace up our sleeve? *Dig Liver Dis* 33: 805–806.

Zullo, A., Hassan, C., Lorenzetti, R., Winn, S. and Morini, S. (2003b) A clinical practice viewpoint: to culture or not to culture *Helicobacter pylori*? *Dig Liver Dis* 35: 357–361.

Zullo, A., Perna, F., Hassan, C., Ricci, C., Saracino, I., Morini, S. *et al.* (2007) Primary antibiotic resistance in *Helicobacter pylori* strains isolated in Northern and Central Italy. *Aliment Pharmacol Ther* 25: 1429–1434.