‘Rescue’ Therapies for the Management of *Helicobacter pylori* Infection

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**Key Words**  
*Helicobacter pylori* infection · *Helicobacter pylori* eradication · Eradication failure · Failed eradication attempts · Rescue therapies

**Abstract**  
*Helicobacter pylori* infection is the main cause of gastritis, gastroduodenal ulcer and gastric cancer and should be considered as a major public health issue. According to several international guidelines, first-line therapy for treating *H. pylori* infection consists of proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC) with any two antibiotics of amoxicillin, clarithromycin or metronidazole given for 7–14 days. However, even with the recommended treatment regimens, approximately 20% of patients will fail to obtain *H. pylori* eradication. The proportion of patients with first-line *H. pylori* therapy failure may be higher in clinical practice and it may increase thanks to diffusion of *H. pylori* treatment. The recommended second-line therapy is the quadruple regimen composed by tetracycline, metronidazole, bismuth salts and a PPI. However, the efficacy of this regimen is limited by poor patient’s compliance due to its side effects, number of tablets per day, and long duration. Moreover, bismuth and metronidazole are not available in all countries. Alternatively, a longer-lasting (i.e. 10–14 days) PPI or RBC triple therapy with two antibiotics has generally been used. In an empirical strategy, the choice of second line depends on the treatment initially used. If a clarithromycin-based regimen was administered in first line, a quadruple regimen or PPI (or RBC) triple therapy with metronidazole and amoxicillin (or tetracycline) should be suggested as a second line. In case of second-line treatment failure, the patient should be evaluated by a case-by-case approach. A susceptibility-guided strategy, if available, is recommended in order to choose the best third-line treatment. Culture can reveal the presence of *H. pylori*-sensitive strains to clarithromycin (the best effective) or other antimicrobials (such as amoxicillin, metronidazole and tetracycline). Conversely, in an empirical strategy, a third-line not yet used therapy, can reach a high success rate. PPI or RBC, amoxicillin and a new antimicrobial (e.g. rifabutin, levofloxacin or furazolidone) could be used. Several studies have obtained relatively good results with triple therapy combining PPI, rifabutin, and amoxicillin, although a reversible myelotoxicity as leukopenia and thrombocytopenia has been described. Preliminary good results were also achieved with triples PPI regimens combining levofloxacin and amoxicillin without important adverse effects. Furazolidone has also shown efficacy for *H. pylori* eradication, although untoward reactions could limit its use, especially when high doses are employed. Finally, in more than one *H. pylori* treatment failure, non-antimicrobial add-on medications (such as lactoferrin, probiotics and others) could be used with the aim either to improve the eradication rate or to minimize side effects.
Introduction

*Helicobacter pylori* infection represents the main cause of gastritis, gastroduodenal ulcer and gastric cancer and should be considered as a major public health issue. It is one of the most common bacterial infections, affecting at least half the World population. Its prevalence depends on age, socioeconomic class and country of origin [1, 2].

First-line therapy for treating *H. pylori* infection consists of proton pump inhibitor (PPI) or ranitidine bismuth citrate (RBC) with any two antibiotics of clarithromycin, amoxicillin or metronidazole given for 7–14 days (table 1) as recommended by several international consensus conferences [3–6]. However, according to a number of recent meta-analysis [7, 8], even with the recommended regimens, approximately 20% of patients will fail to achieve eradication of the *H. pylori* infection and remain *H. pylori* positive. The percentage of patients with first-line *H. pylori* therapy failure may actually be higher in clinical practice [9, 10]. This issue is assuming an increasing importance because of the wide diffusion of *H. pylori* therapy prescription. The choice of best rescue therapy is always difficult due to development of secondary bacterial resistance [11–13] to antibiotics used as first-line treatment. On the other hand, retreatment is often limited by patient’s compliance, especially if the prescribed second-line therapy lasts longer and employs higher drug dosage.

In this paper, we will discuss the possible causes of *H. pylori* treatment failure and review the current literature on the several retreatment options available for patients with *H. pylori* infection resistant to one or more eradication attempts.

**Table 1.** Conventional doses of PPIs, bismuth compounds and antimicrobial agents commonly used in the *H. pylori* eradication regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitors</td>
<td></td>
</tr>
<tr>
<td>Omeprazole</td>
<td>20 mg twice daily</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>40 mg once or 20 mg twice daily</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>30 mg once or twice daily</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>20 mg once or twice daily</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>40 mg once or twice daily</td>
</tr>
<tr>
<td>Bismuth compounds</td>
<td></td>
</tr>
<tr>
<td>Bismuth subcitrate (BSC)</td>
<td>120 mg four times daily</td>
</tr>
<tr>
<td>Bismuth subsalicylate (BSS)</td>
<td>524 mg four times daily</td>
</tr>
<tr>
<td>Ranitidine bismuth citrate (RBC)</td>
<td>400 mg twice daily</td>
</tr>
<tr>
<td>Antimicrobial agents</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>1,000 mg twice daily</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>250 mg or 500 mg twice daily</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg twice or 250 mg four times daily</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>500 mg four times daily</td>
</tr>
<tr>
<td>Rifabutine</td>
<td>300 mg once or 150 mg twice daily</td>
</tr>
<tr>
<td>Levofl oxacin</td>
<td>250 mg or 500 mg once or twice daily</td>
</tr>
<tr>
<td>Furazolidone</td>
<td>200 mg twice daily</td>
</tr>
</tbody>
</table>

**Indications to Perform More than One Attempt to Eradicate**

More than one eradication attempts should be considered in all the conditions where this approach is strongly recommended [6] (table 2). In *H. pylori*-positive patients with peptic ulcer disease including both active, inactive and complicated disease as well as in those with low- and high-grade mucosa-associated lymphoid tissue lymphoma [14], *H. pylori* eradication is mandatory. In all these clinical conditions, the benefit of eradication largely outweighs any potential risk.

*H. pylori* treatment therapy is also suggested in patients with atrophic gastritis, following gastric cancer and in first-degree relatives of patients with gastric cancer, taking into account the close association between *H. pylori*, atrophic changes in the gastric mucosa, genetic factors and gastric cancer [15–17].
**Reasons for Unsuccessful Eradication**

Several factors could be responsible for *H. pylori* eradication failure and they are usually related to the microorganism, to the host or the regimens adopted.

**Bacterial Resistance**

*H. pylori* resistance is an important factor leading to treatment failure [18]. Prevalence of *H. pylori* resistance to clarithromycin in European adults displays relevant regional differences: it is higher in southern (more than 20%) than in northern (about 3%) Europe [19–28]. In Canada and USA, it is estimated to be close to 4% [29] and 12%, respectively [30]. In Israel and Iran, it ranges from about 5% [31] to 17% [32]. In Japan, clarithromycin resistance is higher (13%) [33] than in Hong Kong (4.5%) [34] and Korea (5.4%) [35] (fig. 1).

The prevalence of *H. pylori* resistance to metronidazole ranges from 15 to 40% in Europe and USA, which is higher than in Japan (9–12%) [33, 36]. This prevalence is much higher in developing countries, ranging from 50 to 80% [37, 38] (fig. 2). However, the impact of resistance to clarithromycin or metronidazole on *H. pylori* treatment success is very different. Indeed, while a good correlation between bacterial resistance to clarithromycin and eradication failure does exist, this is not the case for metronidazole. As a matter of fact, a recent review [28] evaluating 20 studies from 1999 to 2003 pointed out a drop in the efficacy of the PPI-amoxicillin-clarithromycin regimen from 88 to 18% in the case of clarithromycin-resistant strains. In the case of metronidazole-resistant strains, however, success of the PPI-clarithromycin-metronidazole regimen decreased from 97 to 73%. Furthermore, the mean loss of efficacy of the metronidazole-based regimen could be less than 10% if this drug is prescribed in a quadruple 1-week therapy together with PPI, bismuth and tetracycline [39].

The majority of patients in whom first-line therapy failed developed secondary resistance to the prescribed antibiotics. An Italian study [23] enrolled 87 *H. pylori*...
positive patients neither harboring clarithromycin- nor metronidazole-resistant strains. 70% of the patients who failed first-line therapy got secondary antibiotic resistance, with resistance rates to clarithromycin and metronidazole of 64 and 35%, respectively. In another study, performed in Ireland, after failure of first-line therapy, the clarithromycin resistance rate increased from 3.4 to 58%. Even more importantly, resistance to both clarithromycin and metronidazole dramatically affected the efficacy of treatment [40].

**Patient-Related Factors (fig. 3)**

Factors related to the patients such as compliance, upper gastrointestinal diseases (e.g. functional dyspepsia or duodenal ulcer) and gastric acid secretion could influence the success of *H. pylori* eradication.

Poor compliance is one of the most important issues in treatment failure [41, 42]. The occurrences of adverse effects such as taste disturbance, nausea and loose stools discourage patients from completing a course of therapy [43]. Moreover, a treatment schedule consisting of many tablets per day and long duration, could also affect patient’s compliance [44]. On the other hand, a clear explanation that nearly all side effects are self-limiting and a strong encouragement to complete the treatment has dramatically reduced the discontinuation rates [45–47]. In a study of eradication failure, 30 *H. pylori*-positive outpatients were treated with a 7-day PPI triple therapy. Pa-
tient compliance was assessed by particular containers endowed with an electronic device recording the time of opening. In patients who took more than 60% of the established medications, the cure rate was significant higher (72%) than in those who took less than 60% of the prescribed pills [48].

Another important factor influencing the success of eradication is the clinical characteristics of the patients. In particular, patients affected by functional dyspepsia (FD) have been reported to have lower eradication rates than those with peptic ulcer disease (PUD), as already observed in the original meta-analysis by Huang and Hunt [49]. This was confirmed in a French study analyzing individual data of 2,751 H. pylori-positive patients included in 11 multicenter clinical trials given eradication treatment [50]. The reasons for this difference are not clear. It could be due to the different status of gastric mucosa or to the difference of infecting H. pylori strains, i.e. antibiotic resistance or Cag status. For instance, in patients with FD a resistance to clarithromycin higher than that observed in DU patients has been described [51]. Among the same lines, patients harboring Cag-A-positive strains, more frequent amongst DU patients, have a lower failure than those harboring Cag-A-negative strains [52].

Finally, the increase in gastric pH induced by antisecretory drugs is crucial in order to allow antibiotics exerting the best activity against H. pylori [53, 54]. PPIs display several pharmacological actions that give them a place in the eradication regimens (for review, see Scarpi­­nato and Pelosi [54]), that is:

1. they exert an antibacterial action against H. pylori;
2. by increasing intragastric pH, they allow the microorganism to reach the growth phase and become more sensitive to antibiotics such as amoxicillin and clarithromycin;
3. they increase antibiotic stability and efficacy, and
4. by reducing gastric emptying and mucus viscosity, they increase the gastric residence time and mucus penetration of antimicrobials.

However, not all the subjects have the same basal and stimulated gastric acid output or the same response to PPI. A small part of individuals may be acid hypersecretors with a large parietal cell mass. On the other hand, a genetic variation on hepatic metabolism of PPIs may also play a role [55, 56]. This class of drugs is indeed metabolized by cytochrome P450 isoenzyme 2C19 (CYP2C19) in the liver. There are genetic differences that affect the activity of this enzyme. The genotypes of CYP2C19 are classified into three groups: homozygous extensive metabolizer (homEM), heterozygous extensive metabolizer (hetEM) and poor metabolizer (PM). The pharmacokinetics and pharmacodynamics of PPIs differ among the different CYP2C19 genotype groups. Plasma PPI and intragastric pH levels during PPI treatment are the lowest in the homEM group and the highest in the PM group. These CYP2C19 genotype-dependent differences in pharmacokinetics and pharmacodynamics of PPIs are reflected in the cure rates for H. pylori infection with PPI-based therapies [57].

Recent evidence suggests that not only the increase in intragastric pH but also the duration of the antisecretory action could influence the eradication rate achieved with PPI-based regimens [58]. In addition, the duration of nocturnal acid breakthrough (NAB), frequently observed even with twice daily PPIs, can also affect the success of therapy [59].

Finally, smoking could have a negative impact on H. pylori eradication for reasons (such as increasing acid secretion or altering gastric mucus) not yet completely understood [60].

Treatment-Related Factors
The components, the dosage and the duration of a treatment play an important role in H. pylori eradication. PPI triple therapy is significantly more effective than dual therapy with two antibiotics or only one antibiotic combined with a PPI [61]. Twice daily PPIs are more effective than once daily administration. Two-week PPI-based triple therapy achieves better eradication rates than those observed after 1 week of treatment [62] (table 3).

‘Rescue’ Therapies

Rescue Therapy Options after First-Line Failure
(Second-Line Treatments)
H. pylori eradication after first-line therapy failure is considered more difficult, mainly due to selection of bacterial strains resistant to antibiotics used in the previous eradication attempt [63, 64]. For this reason, the best H. pylori rescue treatment is actually the right first-line therapy. As a general rule, geographical prevalence of antimicrobial resistance should influence the first-line regimen. If clarithromycin resistance rate is below 15–20%, treatment can start with a clarithromycin-based regimen [65]. Clarithromycin, in fact, with its high capacity to diffuse through gastric mucosa, represents the most effective bactericidal antibiotic against H. pylori [66]. However, after failure of a clarithromycin-based regimen, secondary resistance to this antibiotic is very frequent; range about
60–70% [23]. As a consequence, a significant decrease in clarithromycin efficacy is observed [28] when it is re-administered in a PPI triple second-line therapy, even prolonging the treatment to 14 days [67]. Thus, after failure of first-line clarithromycin-based regimens, a second-line therapy based on metronidazole should be adopted. The European Consensus Report [6] recommends a quadruple therapy for second-line treatment composed of: PPI b.i.d., bismuth salts (120 mg q.i.d.), metronidazole (500 mg three times daily) and tetracycline (500 mg q.i.d.). Many studies have reported good results with this quadruple schedule for 7–14 days with a mean eradication rate of 77% [68]. A pooled analysis on the efficacy of second-line therapies regimens, including 75 treatment arms, confirmed the efficacy of this regimen. In fact, the pooled eradication rates by PPI dual therapy, PPI triple therapy, RBC triple therapy and quadruple therapy were 45, 69, 80 and 75%, respectively [69], showing the superiority of both RBC triple and quadruple therapy. Quadruple therapy, however, could affect patient’s compliance due to the high incidence of adverse effects (up to 60%, although serious events are rare), and the great number of tablets per day (14 for 7–14 days) [64]. Furthermore, bismuth compounds are not available anywhere (as it is the case in the Asia-Pacific region and in some European countries such as France). In this case, the second-line treatment should use a PPI and two antibiotics (PPI triple therapy), the choice of which depends on the treatment initially used (see above).

### Treatment Options for Nonresponders to First-Line Treatment with Clarithromycin-Amoxicillin-Based Regimens (fig. 4; table 4)

After failure of a combination treatment with a PPI, clarithromycin and amoxicillin, taking into account the very low secondary resistance rate to amoxicillin [28], the first antibiotic should be replaced with a nitroimidazolic compound (metronidazole or tinidazole). The recommended treatment is the ‘classic’ quadruple therapy which reaches an eradication rate of 75–95% [9, 69–73]. However, a simpler PPI triple therapy with amoxicillin-metronidazole can achieve high success rates. Indeed, Nagahara et al. [67] obtained an eradication rate of 81% with a PPI schedule for 14 days in patients who failed first-line PPI-clarithromycin-amoxicillin therapy. More recently, other Japanese studies confirmed the good efficacy of PPI triple therapy with amoxicillin-metronidazole as second-line treatment. The eradication rate was higher than 80% when either rabeprazole (20 mg b.i.d.) or lansoprazole (30 mg b.i.d) were administered for 7–10 days with metronidazole (250 mg b.i.d.) and amoxicillin (750 mg b.i.d.). Similar results were also obtained in patients harboring metronidazole-resistant strains [74–76]. European trials, using doses of metronidazole higher than those employed in Japanese studies, confirmed the satisfactory eradication rate with this treatment for 7–14 days, although the efficacy dropped to about 60% in presence of metronidazole-resistant strains [77–79]. Furthermore, a French randomized open study compared the

### Table 3. Meta-analysis of the studies with PPI-based eradication regimens of 1 or 2 week duration. Forrest’s plot comparing the intention-to-treat eradication rates obtained with the two kinds of therapies (from Calvet et al., [62])

<table>
<thead>
<tr>
<th>Study</th>
<th>Exp, n/N</th>
<th>Ctr, n/N</th>
<th>Peto OR (95% CI fixed)</th>
<th>Weight</th>
<th>Peto OR (95% CI fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dal Bó, 1998</td>
<td>45/66</td>
<td>25/33</td>
<td></td>
<td>11.7</td>
<td>0.70 (0.28, 1.74)</td>
</tr>
<tr>
<td>Dammann, 1997</td>
<td>81/125</td>
<td>91/129</td>
<td></td>
<td>35.5</td>
<td>0.77 (0.46, 1.30)</td>
</tr>
<tr>
<td>Katicic, 1996</td>
<td>40/55</td>
<td>43/52</td>
<td></td>
<td>12.0</td>
<td>0.57 (0.23, 1.40)</td>
</tr>
<tr>
<td>Laine, 1996</td>
<td>43/50</td>
<td>46/50</td>
<td></td>
<td>6.3</td>
<td>0.55 (0.16, 1.90)</td>
</tr>
<tr>
<td>Louw, 1998</td>
<td>26/33</td>
<td>31/34</td>
<td></td>
<td>5.5</td>
<td>0.38 (0.10, 1.45)</td>
</tr>
<tr>
<td>Moayeddi, 1996</td>
<td>30/33</td>
<td>32/37</td>
<td></td>
<td>4.6</td>
<td>1.54 (0.36, 6.65)</td>
</tr>
<tr>
<td>Paoluzi, 1998</td>
<td>74/108</td>
<td>85/101</td>
<td></td>
<td>24.3</td>
<td>0.43 (0.23, 0.80)</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>339/470</td>
<td>353/436</td>
<td></td>
<td>100.00</td>
<td>0.62 (0.45, 0.84)</td>
</tr>
</tbody>
</table>

\[ \chi^2 4.13 \text{ (d.f. = 6) } Z = 3.03 \]
Fig. 4. Rescue regimens after PPI-clarithromycin-amoxicillin failure. PP = Per protocol analysis; PPI = proton pump inhibitor; RBC = ranitidine bismuth citrate.

Table 4. Eradication therapies adopted in patients nonresponders to first-line PPI-clarithromycin-amoxicillin regimens

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Ref. No.</th>
<th>Patient population</th>
<th>Duration of therapy days</th>
<th>Second-line eradication therapy</th>
<th>Eradication rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ITT (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PP (95% CI)</td>
</tr>
<tr>
<td>Michopoulos et al., 2000</td>
<td>73</td>
<td>PU, FD</td>
<td>7</td>
<td>PPI-BSC-metronidazole 500 mg t.i.d.-tetracycline 500 mg t.i.d.</td>
<td>76 (62–91)</td>
</tr>
<tr>
<td>Boixeda et al., 2002</td>
<td>71</td>
<td>FD, PU</td>
<td>7</td>
<td>PPI-tetracycline-metronidazole 500 mg t.i.d.</td>
<td>82 (75–88)</td>
</tr>
<tr>
<td>Georgopoulos et al., 2002</td>
<td>72</td>
<td>FD, PU</td>
<td>7</td>
<td>omeprazole-BSC-metronidazole-tetracycline</td>
<td>84 (70–93)</td>
</tr>
<tr>
<td>Gomollon et al., 1999</td>
<td>70</td>
<td>PU</td>
<td>7</td>
<td>PPI-tetracycline-metronidazole 500 mg t.i.d.</td>
<td>95 (76–100)</td>
</tr>
<tr>
<td>Nagahara et al., 2004</td>
<td>67</td>
<td>PU, FD</td>
<td>10</td>
<td>omeprazole 20 mg o.d.-amoxicillin 500 mg b.i.d.-metronidazole 250 mg b.i.d.</td>
<td>81 (71–89)</td>
</tr>
<tr>
<td>Isomoto et al., 2003</td>
<td>74</td>
<td>PU, FD</td>
<td>7</td>
<td>rabeprazole 10 mg b.i.d.-amoxicillin 750 mg b.i.d.-metronidazole 250 mg b.i.d.</td>
<td>82 (72–92)</td>
</tr>
<tr>
<td>Murakami et al., 2003</td>
<td>75</td>
<td>PU, FD</td>
<td>7</td>
<td>PPI-amoxicillin 750 mg b.i.d.-metronidazole 250 mg b.i.d.</td>
<td>88 (80–95)</td>
</tr>
<tr>
<td>Miwa et al., 2003</td>
<td>76</td>
<td>PU or FD</td>
<td>10</td>
<td>PPI-amoxicillin 750 mg b.i.d.-metronidazole 250 mg b.i.d.</td>
<td>92 (79–98)</td>
</tr>
<tr>
<td>Lamouliatte et al., 2003*</td>
<td>78</td>
<td>PU, FD</td>
<td>14</td>
<td>PPI-amoxicillin-metronidazole</td>
<td>63 (50–75)</td>
</tr>
<tr>
<td>Perri et al., 2003</td>
<td>80</td>
<td>PU, FD</td>
<td>7</td>
<td>RBC-amoxicillin-tinidazole</td>
<td>85 (76–94)</td>
</tr>
<tr>
<td>Rinaldi et al., 1999</td>
<td>81</td>
<td>PU, FD</td>
<td>14</td>
<td>RBC-tetracycline-tinidazole</td>
<td>82 (75–97)</td>
</tr>
<tr>
<td>Zullo et al., 2001</td>
<td>82</td>
<td>PU, FD</td>
<td>14</td>
<td>RBC-tetracycline-metronidazole</td>
<td>96 (75–100)</td>
</tr>
</tbody>
</table>

FD = Functional dyspepsia; PU = peptic ulcer; PPI = proton pump inhibitor; BSC = bismuth subcitrate. Unless otherwise specified, PPIs and antimicrobials have been administered at their conventional antisecretory or antibacterial doses, given twice daily (see table 2).

* Included also patients (13% of the total) that failed to other first-line therapy regimens than PPI-clarithromycin-amoxicillin.

The eradication rate obtained with second-line therapy based on antibiotic susceptibility with that achieved by using empirical regimens. Of the 285 patients evaluated, 116 received different PPI-amoxicillin-clarithromycin regimens, 57 patients were treated with omeprazole (20 mg b.i.d.), metronidazole (500 mg b.i.d.) and amoxicillin (1 g b.i.d.) for 2 weeks, and 113 with a regimen based on susceptibility testing. The eradication rate was unacceptably low in the first subgroup of patients, it was 63% in the second, while in the group where the choice of treatment was guided by susceptibility testing, the eradication rate reached 74%; albeit no statistical difference was achieved between the two latter groups. The overall cure rate in patients with PPI-amoxicillin-metronidazole therapy was 80% in the metronidazole-sensitive strains and 60% in the metronidazole-resistant strains [78].

Good results were also observed when RBC triple therapy was administered as second-line treatment. Perri et al. [80] randomized 180 patients who failed first-line PPI-amoxicillin-clarithromycin, into one of the following 7-day treatments: (a) RBC (400 mg b.i.d.) with amoxicillin (1 g b.i.d.) and tinidazole (500 mg b.i.d.); (b) ‘classic’ quadruple PPI-bismuth-metronidazole-tetracycline therapy, and (c) PPI-amoxicillin and levofloxacin (500 mg o.d.). RBC triple therapy showed an eradication rate (85%) higher than the levofloxacin-based regimen (63%) and similar to the quadruple schedule (83%) but with less side effects. Encouraging results were also obtained with RBC.
triple therapy where tinidazole and tetracycline were added to the bismuth compound for 14 days. In fact, in two Italian studies this regimen, administrated as second-line therapy, achieved cure rates of 82% [81] and 96% [82], although 12% of patients complained of mild adverse effects. Moreover, one randomized Spanish study, including 60 patients, compared the efficacy of RBC (400 mg b.i.d.), tetracycline (500 mg q.i.d.) and metronidazole (250 mg q.i.d.) therapy to that of quadruple schedule consisting of omeprazole (20 mg b.i.d.), bismuth (120 mg q.i.d.), tetracycline (500 mg q.i.d.) and metronidazole (250 mg q.i.d.), both for 7 days. The triple RBC-based treatment achieved a higher eradication rate (86%) than the quadruple therapy (59%), with the advantage of being a simpler regimen with a lower number of tablets per day [83]. It is worth mentioning, however, that in this

**Fig. 5.** Rescue regimens after PPI-amoxicillin-nitroimidazole failure. PP = Per protocol analysis; PPI = proton pump inhibitor; RBC = ranitidine bismuth citrate.

**Fig. 6.** Rescue regimens after PPI-clarithromycin-metronidazole failure. PP = Per protocol analysis; PPI = proton pump inhibitor; RBC = ranitidine bismuth citrate.

**Table 5.** Eradication therapies adopted in patients non-responding to first-line PPI-nitroimidazole regimens with clarithromycin or amoxicillin

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Ref. No.</th>
<th>n</th>
<th>Patient population</th>
<th>Duration of therapy days</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ITT (95% CI) PP (95% CI)</td>
</tr>
<tr>
<td>PPI-nitroimidazole-amoxicillin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magaret et al., 2001</td>
<td>85</td>
<td>20</td>
<td></td>
<td>14</td>
<td>PPI-amoxicillin-clarithromycin</td>
<td>75 (56–94) 82 (64–100)</td>
</tr>
<tr>
<td>Lerang et al., 1997</td>
<td>84</td>
<td>18</td>
<td></td>
<td>10</td>
<td>PPI-amoxicillin 750 mg b.i.d.-clarithromycin</td>
<td>100 100</td>
</tr>
<tr>
<td>Magaret et al., 2001</td>
<td>85</td>
<td>28</td>
<td></td>
<td>14</td>
<td>PPI-BSC-metronidazole-tetracycline 250 mg q.i.d.</td>
<td>71 (54–88) 80 (64–96)</td>
</tr>
<tr>
<td>PPI-nitroimidazole-clarithromycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gisbert et al., 1999</td>
<td>83</td>
<td>10</td>
<td></td>
<td>7</td>
<td>PPI-BSC-metronidazole 250 mg b.i.d.-tetracycline</td>
<td>80 (44–97) 80 (44–97)</td>
</tr>
<tr>
<td>Zullo et al., 2001</td>
<td>82</td>
<td>16</td>
<td>PU, FD</td>
<td>14</td>
<td>RBC-tinidazole-tetracycline</td>
<td>88 (62–97) 88 (62–97)</td>
</tr>
</tbody>
</table>

FD = Functional dyspepsia; PU = peptic ulcer; PPI = proton pump inhibitor; BSS = bismuth subsalicylate; BSC = bismuth subcitrate.
study the eradication rate of the quadruple regimen was remarkably low, due to unknown reasons (likely different populations and/or *H. pylori* strains).

*Treatment Therapies for Nonresponders to Amoxicillin/Nitroimidazole-Based Regimens* (fig. 5; table 5)

After PPI-amoxicillin-nitroimidazole failure, retreatment with PPI-amoxicillin-clarithromycin for 7–10 days proved to be very effective with eradication rates ranging from 75% to 100%. [84, 85]. This second-line schedule appears to be the most logical, since there is often a low prevalence of clarithromycin resistance rate. On the other hand, classical quadruple therapy, potentially overcoming the impact of metronidazole resistance, could be also suggested. Margaret et al. [85] compared quadruple with PPI-clarithromycin-amoxicillin therapies in 48 patients who failed first-line metronidazole-based regimen. A satisfactory success rate (more than 70%) was found for both the regimens, without significant difference.

An alternative rescue regimen may be a similar one using a RBC instead of a PPI. In an observational study, involving a small number of patients who failed first-line eradication therapy, Beales [86] has shown an adequate eradication rate with RBC-amoxicillin-clarithromycin for 7 days.

*Treatment Options for Nonresponders to Clarithromycin/Nitroimidazole-Based Regimens* (fig. 6; table 5)

After failure of first-line therapy combining a PPI with clarithromycin and nitroimidazole, the theoretical choice would be dual therapy consisting of high-dose PPI and amoxicillin. However, controversial results [69, 87] have been obtained with this schedule, despite the early encouraging cure rate [88]. Thus, the best option remains a classic quadruple therapy which does not include clarithromycin and it is very effective also against metronidazole-resistant strains [69, 84, 89].

To simplify the latter schedule, Zullo et al. [82] employed RBC instead of PPI and bismuth and achieved good results. Indeed, in patients who fail a first *H. pylori* treatment with PPI-tinidazole-clarithromycin an eradication rate of 88% was obtained by using the RBC-tetracycline-tinidazole combination as a second-line treatment. In the countries where bismuth is not available, a PPI triple therapy with metronidazole and amoxicillin could be suggested, probably lasted for 14 days [78]. However, the success rate could drop to about 60% in presence of metronidazole-resistant strains [28].

*Alternative Antibiotics in Second-Line Therapy* (table 6, 7)

PPI triple therapies with antimicrobials not specifically used as components of eradication regimens (table 1), such as rifabutin, levofloxacin or furazolidone, could be administered as second-line treatment when a double resistance to both clarithromycin and metronidazole is suspected (like, for instance, in developing countries) and bismuth compounds are not available, or as alternative to quadruple therapy. Several studies have obtained relatively good results with triple therapy combining PPI, rifabutin, and amoxicillin for 7–14 days with satisfactory eradication rates [90–94]. Although a case of reversible myelotoxicity with leukopenia and thrombocytopenia has been reported [93], in the above studies the adverse effects were generally rare. Perri et al. [90] randomized 135 patients, who failed first-line therapy, into three groups for 10 days: quadruple therapy or PPI-amoxicillin-rifabutin triple therapy with two different dosage of rifabutin (150 or 300 mg o.d.). The group with rifabutin at high dosage obtained the highest eradication rate (86%), with fewer side effects than quadruple therapy. Toracchio et al. [94] evaluated 104 patients, who had failed one course of triple therapy. A 10-day triple therapy with pantoprazole, amoxicillin and rifabutin was administrated as second-line therapy, obtaining an eradication rate of 78.5% in patients harboring secondary resistance to clarithromycin and tinidazole.

Rifaximin is a synthetic rifamycin derivative that shares with rifabutin its antibacterial activity against *H. pylori* [95–98]. Most importantly, no strain with primary rifaximin resistance has been reported as yet. This antibiotic is however poorly adsorbed and its administration is associated with very few, if any, side effects [99]. In this connection, some rifaximin-based eradication regimens have been attempted [for review, see 100], with a dual rifaximin-clarithromycin combination achieving a 70% eradication rate [101]. New antimicrobial combinations (with and without PPIs) need, of course, to be explored in well-designed clinical trials including a large cohort of *H. pylori*-infected patients before rifaximin be considered a suitable antibiotic for first- or second-line eradication therapy.

Preliminary good results were also reported with triple PPI regimens combining levofloxacin and amoxicillin for 7–10 days [102, 103], with only mild side effects (such as glossitis [104]). Nista et al. [103], in a randomized trial, enrolled 280 patients, who failed first-line PPI-amoxicillin-clarithromycin, and randomized them to four groups: two PPI triple therapies for 10 days with rabeprazole...
levofloxacin (500 mg o.d.) and tinidazole (500 mg b.i.d.) and two classic quadruple therapies for 7 and 14 days. Success eradication was higher in the levofloxacin (about 90%) than in the quadruple regimens (ranging from 63 to 69%) with significantly less side effects. Bilardi et al. [105] randomized 90 patients, who had failed one or more eradication attempts, into pantoprazole (40 mg b.i.d.), amoxicillin (1 g b.i.d.) and levofloxacin (250 mg b.i.d.) regimen for 10 days or omeprazole (20 mg b.i.d.) for the first 1 week followed by a PPI-tetracycline-metronidazole-bismuth quadruple therapy in the second week. The former schedule showed a significant higher success cure (70%) than quadruple regimen (37%).
Interestingly enough, Wong et al. [106] compared the efficacy of PPI-levofl oxacin-rifabutin triple therapy with a classical quadruple therapy in a randomized trial involving 75 and 34 patients who failed various first-line and two or more courses of therapies, respectively. A very high eradication rate (up to 80%) was observed for the regimens also in patients harboring metronidazole- and/or clarithromycin-resistant strains.

Finally, furazolidone has also shown a good efficacy in eradicating *H. pylori*, although adverse events could limit its use. Potential furazolidone-related side effects include gastrointestinal symptoms, disulfiram-like reaction in patients taking alcohol, monoamine oxidase (MAO) inhibitor properties as well as glucose-6-phosphate dehydrogenase (G-6-PD) reduced activity. A detailed list of food or drugs with potential interactions is therefore mandatory for patients taking such antimicrobial [107, 108]. Isakov et al. [109] randomized duodenal ulcer patients, after failure first-line treatment and harboring metronidazole-resistant strains, to receive for 7 days: bismuth (240 mg b.i.d.), furazolidone (200 mg b.i.d.) and tetracycline (750 mg q.i.d.) or classic quadruple therapy. Eradication rates were 85 and 74% for the furazolidone-based regimen and quadruple therapy, respectively, with a significant lower rate of adverse events in the first group.

**Rescue Therapies after Two or More Failures** (table 7)

As recommended by European Guidelines [6], after failure of second-line regimen, primary care patients should be referred to a specialist setting and should perform third-line therapy according to susceptibility testing, if available. However, the best approach (empirical or susceptibility-guided) and the best therapy for patients with more than one failed eradication attempt remains controversial due to the lack of large randomized cohort studies and the lack of homogeneity of patients studied.

Beales [86], in a small observational study, treated 16 patients according to metronidazole and/or clarithromycin resistance into the following regimens: omeprazole-amoxicillin-rifabutin, RBC-clarithromycin-tetracycline or RBC-tinidazole-tetracycline. Alternatively, 4 patients with unknown resistance patterns underwent omeprazole-amoxicillin-rifabutin therapy. The overall success rate was higher (68%) in patients managed with susceptibility test strategy than in those treated by the empirical approach (50%).

Gomollón et al. [110] evaluated, in a small group of patients, the efficacy of 2-week quadruple, culture-guided combinations as third-line therapy. Different quadruple therapies with tetracycline-bismuth-omeprazole plus an additional antimicrobial (clarithromycin or amoxicillin or metronidazole or ciprofloxacin according to *H. pylori* susceptibility testing and allergy to penicillin) were studied. Overall eradication rate was unsatisfactory (less than 50%), with successful cure rate of 36% for the clarithromycin-based quadruple regimen and 67% for the amoxicillin-tetracycline-bismuth-omeprazole combination.

Cammarota et al. [111] managed 94 patients with persistent *H. pylori* infection after two treatment failures by a culture-guided approach. The majority of patients (89), harboring tetracycline- and amoxicillin-sensitive strains, received a 1-week quadruple drug combination consisting of: omeprazole (20 mg b.i.d.), bismuth (120 mg q.i.d.), amoxicillin (1 g b.i.d.) and doxycycline (100 mg b.i.d.). Four patients were given 1-week triple therapy with omeprazole-amoxicillin (1 g b.i.d.) and levofloxacin (500 mg b.i.d.) because of the presence of resistant strains to tetracycline but not to levofloxacin; 1 patient with resistant strains to tetracycline and levofloxacin but not to clarithromycin was treated with a standard PPI-amoxicillin-clarithromycin triple therapy. An overall eradication rate was obtained in 90%, showing the good efficacy of this approach and suggesting quadruple therapy with doxycycline as a possible option for third-line therapy.

Taking into account the low impact of metronidazole resistance in quadruple therapy [28, 112], this regimen could be suggested without culture. Dore et al. [113] reached an excellent success rate when quadruple regimen for 14 days was prescribed, in 42 patients, as a third-line therapy. This very good result was confirmed in a Chinese randomized controlled study involving a small number of patients harboring metronidazole- and/or clarithromycin-resistant strains [106].

Alternatively, Miclhe et al. [87] observed in a prospective randomized study a similar and satisfactory success rate with both high-dose dual PPI-amoxicillin and quadruple therapy. A trend for a better compliance was reported in the previous regimen, although quadruple therapy consisted of a high metronidazole dose (2 g o.d.).

In an empirical management of patients who failed two or more eradication attempts, few prospective but not randomized or controlled studies have obtained good results employing PPI triple therapy with amoxicillin and an antibiotic not included in previous regimens (such as: rifabutin, levofloxacin or furazolidone) for 7–14 days. Perri et al. [114] evaluated the efficacy of 7-day triple therapy with pantoprazole (40 mg b.i.d.), amoxicillin (1 g b.i.d.) and rifabutin (300 mg o.d.) on 41 *H. pylori*-positive patients who failed more than two eradication treatments.

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Rescue Therapies for *Helicobacter pylori* Eradication

Dig Dis 2006;24:113–130
assuming both clarithromycin and nitroimidazolic compounds. A 71% success rate was obtained without reporting important adverse events (only 3% of patients had mild side effects such as diarrhea or nausea). In a multicenter Spanish pilot study [92], a similar, albeit longer, third-line therapy was prescribed to 14 patients in whom two eradication trials with the classical antibiotics (e.g., clarithromycin, metronidazole and tetracycline) failed. An eradication rate of 79% was achieved, although a higher percentage of patients complained of mild gastrointestinal side effects (36%) [92]. Alternatively, Zullo et al. [104] obtained a satisfactory success cure (83.3%) administering a 10-day schedule combining rabeprazole (20 mg b.i.d.), amoxicillin (1 g b.i.d.) and levofloxacin (250 mg b.i.d.) to 36 patients with persisting \textit{H. pylori} infection. The authors did not report important side effects, although 2 patients discontinued the treatment due to glossitis. Finally, Treiber et al. [108], in a pilot study, evaluated the efficacy of a 1-week quadruple regimen based on lansoprazole (30 mg b.i.d.), bismuth 240 mg (b.i.d.), tetracycline (1 g b.i.d.) and furazolidone (200 mg b.i.d.) as a third line. Success was observed in 9 of 10 (90%) patients who failed different first-line, clarithromycin-based therapies and a second-line quadruple therapy composed of PPI-bismuth-metronidazole and tetracycline, showing the efficacy of a furazolidone-based regimen even after the failure of ‘classic’ quadruple therapy. On the contrary, Qasim et al. [107] obtained an unsatisfactory success rate (13/34, 38%) with a 10-day course of rifabutin (300 mg o.d.), amoxicillin (1 g b.i.d.) and PPI (b.i.d.), employed as third-line therapy. On the other hand, a 1-week regimen with furazolidone (200 mg b.i.d.), amoxicillin (1 g b.i.d.) and PPI (b.i.d.) cured the \textit{H. pylori} infection in 60% of patients who failed first-, second- and third-line therapies with rifabutin, suggesting that furazolidone-based regimens could be effective also after failure of rifabutin-based therapies.

Gisbert et al. [115], in a prospective single-center study, managed 48 patients who failed two eradication attempts by an empirical strategy. In no case was the same schedule repeated (both in second- and third-line therapy). A new antibiotic (rifabutin) or the same antibiotic associated with PPI and bismuth (if with high risk of inducing resistant \textit{H. pylori} strains) was administered. An overall eradication rate of 71% was observed, suggesting that susceptibility testing could be not always necessary.

**Novel Agents** (table 8)

Eradication therapy with adjunctive nonantimicrobial agents could be useful either to increase the effectiveness of currently used antibiotics (e.g., altering bacterial micro-environmental and/or hindering the development of secondary bacterial resistance) or to reduce adverse effects.

Lactoferrin is a glycoprotein found in human and bovine milk and in several exocrine secretions (e.g., tears, bile and saliva) [116] that showed bacteriostatic and bactericidal effects [117, 118]. Human lactoferrin, as a single agent, does not eradicate \textit{H. pylori} infection as was demonstrated by a recent study performed in vivo in 9 patients [119]. Conversely, bovine lactoferrin could have synergistic actions if employed with PPI and antibiotics as showed in two clinical trials [120, 121]. In a multicenter prospective study, 119 consecutive patients, after failure of first-line PPI triple therapy, were enrolled. The patients were randomized in a 14-day quadruple therapy composed of esomeprazole (20 mg b.i.d.), bismuth (120 mg q.i.d.), amoxicillin (1 g b.i.d.) and tinidazole (500 mg b.i.d.) with or without bovine lactoferrin (200 mg b.i.d.). The eradication rate in the group taking lactoferrin was significantly higher than that of those who did not use the milk protein (80 vs. 64%) [122]. It is worth mentioning, however, that when lactoferrin was added to a standard 7-day regimen combining esomeprazole (20 mg b.i.d.) with clarithromycin (500 mg) and amoxicillin (1 g), all twice daily, no increase of eradication rate over the triple therapy alone has been observed [123]. These disappointing results were of course surprising, but the reasons for the discrepancy between this and the previous Italian studies [120, 121] are not clear. Since a difference in the prevalence of primary bacterial resistance to clarithromycin could be reasonably ruled out, other causes must be sought. A possibility is that lactoferrin and tinidazole may exert a synergistic effect against \textit{H. pylori},

**Table 8. Novel non-antimicrobial agents for \textit{H. pylori} eradication**

<table>
<thead>
<tr>
<th>Lactoferrin</th>
<th>Probiotics</th>
<th>N-acetylcysteine (NAC)</th>
<th>Pronase</th>
<th>Ecabet sodium</th>
<th>Repamipide</th>
<th>Ginger root</th>
<th>Broccoli sprouts</th>
<th>Propolis</th>
<th>Essential oils</th>
</tr>
</thead>
</table>

For references, see text.
while lactoferrin and amoxicillin do not. Such a hypothesis is supported by the observation that when lactoferrin is administered as monotherapy in the week before clarithromycin-tinidazole combination, it does not give any additive therapeutic effect [124]. Since lactoferrin can bind and disrupt some bacterial cell membranes [125], another possible explanation is that the antibacterial effect of lactoferrin – based on bacterial membrane damage of gram-negative bacteria – could be marginalized when amoxicillin is simultaneously administered. Indeed, amoxicillin too mainly acts interfering with microbial membrane structure. On the contrary, such an effect of lactoferrin could be useful when tinidazole is administered, a different mechanism being exploited by such antimicrobial. Whatever the reason, further studies are needed before recommending lactoferrin as add-on medication to eradication regimens in clinical practice.

Probiotics could have inhibitory effect to H. pylori adherence [126] as well as antibacterial and immunomodulatory properties [127, 128]. However, first-line clinical trials [129–131] which administered probiotics as add-on medications to standard-PPI triple therapy have provided conflicting results. However, probiotic (Lactobacillus GG and Bifidobacteria) supplementation did achieve a significant reduction of the incidence of eradication regimen-related side effects [129–134].

N-acetylcysteine (NAC), being both a mucolytic and a thiol-containing antioxidant agent, could affect H. pylori micro-environment. Huynh et al. [135] demonstrated that NAC, in a dosage of 120 mg/day for 14 days, reduced the H. pylori load in mice by almost 1 log compared with sham treatment, but did not improve the severity of gastritis. Although devoid of in vitro activity against the microorganism, pronase has an additive effect in curing H. pylori infection [136]. In the patients who took pronase before surgery, the surface mucus gel layer was thinner than in the patients who did not take the proteolytic enzyme, and the structure of the mucus layer was markedly disrupted [136].

Ecabet sodium is a locally nonabsorbable antiulcer drug developed in Japan. Kim et al. [137] observed as it altered the inflammatory response in human gastric epithelial cell lines infected with CagA+ H. pylori, inhibiting the activation of NF-kB and in turn blocked both the transcription and expression of the IL-8 gene. Similarly, rebamipide which displays anti-inflammatory gastric properties and stimulates the synthesis of endogenous prostaglandins in the gastric mucosa [138], was shown to be capable of reducing mucosal inflammation even in the absence of H. pylori eradication [139]. Both these drugs therefore represent potential candidates as add-on medication to eradication regimens.

Finally, natural substances, like ginger root [140], broccoli sprouts [141], propolis [142] and essential oils [143], have all been shown an inhibitory effect on H. pylori growth in vitro and/or in vivo. Whether they could improve the eradication rate of first- and second-line eradication regimens remains to be established.

Conclusions

The best H. pylori rescue treatment is the right first-line therapy. Generally, the geographical prevalence of antimicrobial resistance should influence the first-line regimen. If the clarithromycin resistance rate is below 15%, treatment can start with a regimen based on clarithromycin. Alternatively, quadruple therapy, which has a similar success rate to a clarithromycin-based regimen but is not limited by primary or secondary resistance to both clarithromycin or metronidazole, could be used [112].

Whether it is better using a very effective first-line treatment despite adverse effects and poor compliance or starting with a simpler and better tolerated triple therapy is still matter of debate. In the case of first-line therapy failure with a clarithromycin-based regimen, the best option is ‘classic’ quadruple therapy adopting a PPI triple therapy with amoxicillin and metronidazole for 10–14 days where bismuth compounds are not available.

After failure of second-line treatment, the patients, if in primary care, should be referred to a specialist setting and should be evaluated, using a case-by-case approach, taking into account the eradication regimens attempted, the previous antimicrobial therapy and other comorbidities. The choice of third-line therapy should preferably be made according to susceptibility testing, or prescribing regimens containing new antimicrobials empirically.

In countries with a high resistance to metronidazole, quadruple therapy using furazolidone instead of metronidazole could be suggested, if available. Similarly, levofloxacin or rifabutin triple therapies could be adopted. Otherwise, if these new antimicrobials are not available and/or if the patient had previously performed one or more treatments with them (because of, for instance, respiratory infections), culture could give important information about the sensitivity of H. pylori strains to different antibiotics. Whether it is worth using add-on medications to increase the eradication rate or limit side effects is at present not well established.
Note Added in Proof

While this review was being submitted, Gisbert and De La Morena [144] published a meta-analysis outlining the high efficacy of levofloxacin-based rescue regimens. The eradication rate appears to be time-dependent since 10-day treatment was more effective than 7-day therapy. Besides being more effective than standard quadruple combination, levofloxacin-based regimens were also better tolerated, with a significantly lower incidence of adverse events. Some additional studies [145–147] confirmed the effectiveness of different levofloxacin combinations as a second- or third-line therapy, a feature shared by other quinolones, like for instance moxifloxacin [148]. Interestingly enough, Giannini et al. [147], by using a high-dose (500 mg b.i.d.) levofloxacin regimen, found no difference in eradication rate between a short (4-day) and the conventional 7-day treatment. In an attempt to make rifabutin-based regimens more effective and tolerated, Borody et al. [149] evaluated a high-dose amoxicillin (1.5 g t.i.d.) and pantoprazole (80 mg t.i.d.) plus a low-dose rifabutin (150 mg o.d.), all for 12 days, in 130 patients whose Helicobacter pylori infection proved to be resistant to standard clarithromycin-based triple therapy, achieving 96.6% eradication rate. Finally, it is worth mentioning that during the past United European Gastroenterology Week (UEGW), held in Copenhagen, October 15–19, 2005, the revised Maastricht Guidelines for Helicobacter pylori eradication, developed by the European Helicobacter pylori Study Group (EHSG), were presented [150]. Besides recommending two new indications for eradication, namely iron-deficiency anemia and idiopathic thrombocytopenia, these guidelines emphasized that bismuth-containing quadruple therapy still remains the best second-line eradication therapy, if available. In countries where bismuth-containing compounds are not on the market, the PPI-amoxicillin (or tetracycline)-metronidazole combination is recommended. After further failed eradication attempts, the treatment is however empiric, mainly based on the previous therapies and on the availability of microbial susceptibility testing.

References


Rescue Therapies for Helicobacter pylori Eradication


