What’s the best secondary treatment for patients who fail initial triple therapy for *H pylori*?

**Evidence-based answer**

TREATING PATIENTS with *Helicobacter pylori* infection who have failed clarithromycin-based triple therapy (with amoxicillin and a proton pump inhibitor [PPI]) or a bismuth-based quadruple therapy produces cure rates of 75% to 81%. Ten-day regimens produce higher cure rates than 7-day regimens. Repeating the initial clarithromycin-based triple therapy cures fewer than half of patients (strength of recommendation [SOR]: A, meta-analyses of randomized controlled trials [RCTs]).

Treating with a metronidazole-based triple therapy (with amoxicillin and a PPI) also produces high (87%) cure rates (SOR: A, meta-analyses of RCTs in exclusively Japanese populations).

Selecting a secondary treatment regimen based on *H pylori* antibiotic susceptibility testing probably doesn’t improve cure rates over empiric antibiotic treatment (SOR: B, meta-analyses of RCTs with conflicting results). However, after 2 treatment failures it may be necessary (SOR: C, expert opinion-based guidelines).

Bismuth-based quadruple therapy has a more complex dosing regimen, and bismuth isn’t available in some countries. Rising rates of *H pylori* resistance to levofloxacin in certain areas could make levofloxacin-based triple therapy less effective in the future (SOR: C, expert opinion-based guidelines).

**Evidence summary**

A meta-analysis of RCTs evaluating levofloxacin-based triple therapy as a secondary treatment regimen for patients with *H pylori* infection who had failed initial clarithromycin-based triple therapy found cure rates averaging 76% (Table). Most of the regimens comprised levofloxacin (500 mg), amoxicillin (1 g), and a PPI (40 mg), all twice daily for 7 to 10 days. Ten-day regimens produced better cure rates than 7-day regimens (84% vs 69%; comparison statistic not supplied).

The meta-analysis also included RCTs evaluating bismuth-based quadruple therapy as secondary treatment, which found cure rates averaging 78%. The regimens varied, comprising bismuth salts (120-600 mg, 2-4 times daily), metronidazole (250-500 mg, 2-4 times daily), tetracycline (250-500 mg, 2-4 times daily), and a PPI (40 mg twice daily). Longer duration of therapy produced higher cure rates (7 days=76%; 95% confidence interval [CI], 0.72-0.80 in 29 RCTs with 2097 patients; 10 days=77%; 95% CI, 0.60-0.93 in 2 RCTs with 142 patients; 14 days=82%; 95% CI, 0.76-0.88 in 12 RCTs with 831 patients).

Repeating the original clarithromycin-based triple therapy (8 RCTs, 265 patients) produced low cure rates (46%).

Metronidazole-based therapy has high cure rate in a homogeneous population

A meta-analysis of 24 RCTs (1611 patients) that evaluated metronidazole-based triple therapy (mostly composed of amoxicillin 750 mg, metronidazole 250 mg, and any of
a number of PPIs, all dosed at 40 mg) twice daily for 7 days found cure rates averaging 87% in an exclusively Japanese study population.1

Comparable cure rates for levofloxacin- and bismuth-based therapy
Six RCTs with a total of 1057 patients compared cure rates for levofloxacin-based triple therapy with bismuth-based quadruple therapy and found no difference.1

Two earlier meta-analyses not included in the previously described study, comprising 8 RCTs with a total of 613 patients, produced conflicting results. The larger study (15 RCTs, 1462 patients) found no difference in cure rates.1 The smaller study (7 RCTs, 787 patients) favored quadruple therapy.3

Two secondary antibiotic regimens show similar cure rates
A meta-analysis of 4 RCTs (total 460 patients) that compared susceptibility-guided antibiotic secondary treatment (SGT) with empiric antibiotic secondary treatment found no difference in cure rates, although the largest single RCT (172 patients) favored SGT.4

Recommendations
The Maastricht IV/Florence Consensus Report (a periodically updated European study group evaluating Helicobacter management) includes expert opinion-based guidelines for H pylori treatment that recommend using antibiotic susceptibility to select treatment regimens in the event of 2 treatment failures.2 The report also notes that bismuth-based quadruple therapy may not be available in all countries and has a more complex dosing regimen, and that local resistance to levofloxacin must be taken into account when prescribing levofloxacin-based triple therapy.5

References

#TABLE
Cure rates for secondary treatment of H pylori after failed initial triple therapy1

<table>
<thead>
<tr>
<th>Secondary treatment regimen</th>
<th>Number of RCTs (number of patients)</th>
<th>H pylori eradication*</th>
<th>95% CI</th>
<th>Heterogeneity of studies**</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin-based triple therapy (with PPI, amoxicillin)</td>
<td>19 (1997)</td>
<td>76%</td>
<td>72%-81%</td>
<td>Considerable</td>
<td>Consider another option if there is high quinolone resistance in region</td>
</tr>
<tr>
<td>Bismuth-based quadruple therapy (with PPI, tetracycline, metronidazole/tinidazole)</td>
<td>29 (2097)</td>
<td>78%</td>
<td>75%-81%</td>
<td>Considerable</td>
<td>Bismuth not available in all countries; regimens more complex</td>
</tr>
<tr>
<td>Metronidazole-based triple therapy (with PPI, amoxicillin)</td>
<td>24 (1611)</td>
<td>87%</td>
<td>84%-91%</td>
<td>Moderate</td>
<td>All RCTs done in Japanese population</td>
</tr>
<tr>
<td>Repeat initial clarithromycin-based triple therapy (with PPI, amoxicillin)</td>
<td>8 (265)</td>
<td>46%</td>
<td>34%-58%</td>
<td>Moderate</td>
<td>Failure of regimen probably caused by H pylori resistance to clarithromycin</td>
</tr>
</tbody>
</table>

CI, confidence interval; PPI, proton pump inhibitor; RCT, randomized controlled trial.

*Eradication confirmed by urea breath test, histology, rapid urease test, or monoclonal stool antigen.

**0-0.40=unimportant heterogeneity; 0.40-0.75=moderate heterogeneity; >0.75=considerable heterogeneity.