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

EVIDENCE-BASED ANSWER

A/ TREATING PATIENTS with *Helicobacter pylori* infection who have failed clarithromycin-based triple therapy with either levofloxacin-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).¹ 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%.¹ 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%).¹

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

TABLE

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

Secondary treatment regimen	Number of RCTs (number of patients)	<i>H pylori</i> eradication*	95% CI	Heterogeneity of studies**	Comments
Levofloxacin-based triple therapy (with PPI, amoxicillin) twice daily for 7-10 days	19 (1997)	76%	72%-81%	Considerable	Consider another option if there is high quinolone resistance in region
Bismuth-based quadruple therapy (with PPI, tetracycline, metronidazole/tinidazole) for 7-14 days	29 (2097)	78%	75%-81%	Considerable	Bismuth not available in all countries; regimens more complex
Metronidazole-based triple therapy (with PPI, amoxicillin) twice daily for 7 days	24 (1611)	87%	84%-91%	Moderate	All RCTs done in Japanese population
Repeat initial clarithromycin-based triple therapy (with PPI, amoxicillin) twice daily for 7-14 days	8 (265)	46%	34%-58%	Moderate	Failure of regimen probably caused by <i>H pylori</i> resistance to clarithromycin

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.

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.² 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.⁵ 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. **JFP**

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