10-day sequential therapy was more effective than 10-day triple-drug therapy for eradicating *Helicobacter pylori* infection

Vaira D, Zullo A, Vakil N, et al. **Sequential therapy versus standard triple-drug therapy for *Helicobacter pylori* eradication: a randomized trial.** Ann Intern Med. 2007;146:556-63.

Clinical impact ratings: GIM/FP/GP ★★★★★☆☆ Gastroenterology ★★★★★★☆ Infectious Disease ★★★★☆☆☆

QUESTION

In patients with dyspepsia or peptic ulcer disease, is 10-day sequential therapy more effective than 10-day triple-drug therapy for eradicating *Helicobacter pylori* infection?

METHODS

Design: Randomized controlled trial.
Allocation: {Concealed}†.*
Blinding: Blinded (patients, investigators, {data collectors, outcome assessors, data analysts, and safety and monitoring committee}†).*
Follow-up period: 8 weeks.
Setting: 2 hospitals in Bologna and Rome, Italy.
Patients: 300 patients ≥ 18 years of age (mean age 49 y, 64% women) with dyspepsia or peptic ulcers who had never received treatment for *H. pylori* infection. Exclusion criteria included use of proton-pump inhibitors, H_2-receptor antagonists, bismuth preparations, or antibiotics in the past 2 weeks; concomitant use of anticoagulants or ketoconazole and glucocorticoids; the Zollinger-Ellison syndrome; surgery of the esophagus or upper gastrointestinal tract; severe or unstable cardiovascular, pulmonary, or endocrine disease; renal or hepatic disease or dysfunction; hematologic disorders; cancer in the past 5 years; Barrett esophagus or high-grade dysplasia; and severe psychiatric or neurologic disorders.
Intervention: Sequential (n = 150) or standard triple-drug therapy (n = 150). Sequential therapy consisted of pantoprazole, 40 mg, amoxicillin, 1 g, and placebo twice daily for 5 days; and pantoprazole, 40 mg, clarithromycin, 500 mg, and tinidazole, 500 mg, twice daily for the next 5 days. Standard therapy consisted of pantoprazole, 40 mg, clarithromycin, 500 mg, and amoxicillin, 1 g, twice daily for 10 days.
Outcomes: Eradication of *H. pylori* infection (negative results on 13^C-urea breath tests at 4 and 8 wk). Secondary outcomes were eradication of clarithromycin- or metronidazole-resistant *H. pylori* infection, treatment adherence (> 90% of medication taken), and adverse events.
Patient follow-up: 96% (100% included in the intention-to-treat analysis).

MAIN RESULTS

The sequential-therapy group had higher eradication rates for *H. pylori* and clarithromycin-resistant *H. pylori* infection than did the standard-therapy group (Table). Groups did not differ for eradication of metronidazole-resistant *H. pylori* infection (Table), treatment adherence, or incidence of major or minor adverse events. Adverse events included epigastric pain and mild diarrhea.

CONCLUSION

10-day sequential therapy was more effective than 10-day triple-drug therapy for eradicating *Helicobacter pylori* infection in patients with dyspepsia or peptic ulcer disease.

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*See Glossary.
†Information provided by author.

Sequential vs standard triple-drug therapy for *Helicobacter pylori* infection in patients with dyspepsia or peptic ulcers at 8 weeks‡

Outcomes	Sequential	Standard	RBI (95% CI)	NNT (CI)
Eradication of *H. pylori*§	89%	77%	16% (4.5 to 29)	9 (5 to 28)
Eradication of clarithromycin-resistant *H. pylori*‖	89%	29%	211% (54 to 558)	2 (2 to 5)
Eradication of metronidazole-resistant *H. pylori*‖	97%	91%	6.9% (–7.5 to 35)	Not significant

‡Abbreviations defined in Glossary. RBI, NNT, and CI calculated from data in article.
§Based on standard intention-to-treat analysis.
‖Based on per-protocol analysis.

COMMENTARY

H. pylori infection is an important cause of peptic ulcers and gastric cancer. Triple therapy comprising a proton-pump inhibitor (PPI) and 2 antibiotics has been the standard treatment for *H. pylori*, with an eradication rate of about 90%. However, widespread use of antibiotics has led to a dramatic increase in drug-resistant strains. A recent meta-analysis reported an eradication rate of about 80% with standard triple therapy (1).

Can we do better? For patients in whom triple therapy has failed once, quadruple therapy (bismuth, PPI, metronidazole, and tetracycline) or levofloxacin-based triple therapy can help a significant proportion. Nevertheless, re-treatment is inconvenient to patients, expensive, and involves repeated *H. pylori* tests. The study by Vaira and colleagues used an intention-to-treat analysis and found that 89% of patients who received sequential therapy had successful eradication compared with 77% of patients who received standard triple therapy. The benefits of sequential therapy stemmed mainly from the higher eradication rate of clarithromycin-resistant *H. pylori*. Side effect profiles of the 2 groups were similar.

Like many important studies, the trial by Vaira and colleagues brings more questions than answers. The study was conducted in Italy, a country with relatively low rates of metronidazole resistance and multidrug resistance. The high eradication rate achieved by sequential therapy in the subgroup with clarithromycin resistance was based on a small number of patients (n = 9). Whether similar success can be achieved in other countries still needs to be confirmed. Treatment failure also occurred in patients infected with susceptible strains. It would be useful to assess whether eradication rates could be increased further if either clarithromycin or tinidazole were given in the first 5 days in addition to the 2 drugs used in the current regimen. Moreover, the role of sequential therapy as salvage therapy for previous treatment failure should be explored.

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1. **Buzás GM, Józan J.** World J Gastroenterol. 2006;12:5311-9.