

Review: Quadruple therapies appear to be more effective than triple therapies for eradicating single-drug-resistant *Helicobacter pylori*

Fischbach L, Evans EL. Meta-analysis: the effect of antibiotic resistance status on the efficacy of triple and quadruple first-line therapies for *Helicobacter pylori*. *Aliment Pharmacol Ther*. 2007;26:343-57.

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

QUESTIONS

What is the effect of drug resistance on therapies for *Helicobacter pylori* infection? Which therapies are most effective for eradicating nitroimidazole (NTM)- or clarithromycin (CTM)-resistant *H. pylori*?

METHODS

Data sources: MEDLINE (to February 2007) and bibliographies of relevant reviews. **Study selection and assessment:** English- or Spanish-language studies evaluating triple or quadruple therapies for eradicating *H. pylori* in patients who were either all sensitive or all resistant to CTM or NTM. Studies had to include ≥ 4 patients per treatment group with *H. pylori* infection at baseline. Studies of monotherapy or dual therapies were excluded. 93 randomized controlled trials (RCTs) ($n = 10\ 178$) met the selection criteria; 68% of treatment groups came from RCTs, 67% of patients had peptic ulcer disease, and 30% had nonulcer dyspepsia. {Individual study quality indicators were included in the metaregression model as suggested by Greenland.}* **Outcomes:** Eradication of *H. pylori* infection.

MAIN RESULTS

Meta-analysis showed that both NTM and CTM resistance reduced efficacy of triple therapies for eradicating *H. pylori* infection,

but CTM resistance reduced efficacy more than did NTM resistance (Table). Quadruple therapies appeared to be more effective than triple therapies for eradicating single-drug-resistant *H. pylori* infection (Table).

CONCLUSIONS

Clarithromycin resistance is associated with lower efficacy of triple therapies than is nitroimidazole resistance for eradicating *Helicobacter pylori* infection. Quadruple ther-

apies appear to be more effective than triple therapies for eradicating single-drug-resistant *H. pylori* infection.

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*Reference provided by author: Greenland S. Meta-analysis. In: Rothman KJ and Greenland S, eds. *Modern epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven; 1998:643-73.

Effect of drug resistance on triple or quadruple therapies for eradicating *Helicobacter pylori* infection†

Therapy	Number of studies (n)	Reduction in treatment efficacy (95% CI)		
		NTM resistance	CTM resistance	Dual resistance
AMX-NTM-BIS	6 (319)	38% (15 to 62)	—	—
NTM-TET-BIS	14 (711)	26% (14 to 38)	—	—
AMX-NTM-GAI	24 (1945)	30% (22 to 38)	—	—
CTM-NTM-GAI	34 (3128)	18% (13 to 23)	35% (25 to 45)	13% (–22 to 49)‡
AMX-CTM-GAI	24 (2556)	—	66% (58 to 74)	—
MTN-TET-BIS-GAI	16 (889)	14% (5 to 23)	—	—
CTM-MTN-BIS-RNT	5 (265)	1.5% (–1.7 to 4.7)‡	13% (–27 to 1.6)‡	44% (38 to 52)
AMX-CTM-MTN-GAI	2 (365)	Negligible	Negligible	Negligible

†AMX = amoxicillin; BIS = bismuth; CTM = clarithromycin; GAI = gastric acid inhibitor; MTN = metronidazole; NTM = nitroimidazole; RNT = ranitidine; TET = tetracycline. CI defined in Glossary.
‡Not significant.

COMMENTARY

First-line therapy for *H. pylori* eradication has been triple therapy with a proton-pump inhibitor (PPI), CTM, and amoxicillin (AMX) or metronidazole (MTN). The comprehensive meta-analysis by Fischbach and colleagues affirms the deleterious effect of CTM resistance on CTM-containing triple therapies and helps explain their declining efficacy.

MTN resistance seems to be less important than CTM resistance because it can be overcome to some extent. With the AMX-NTM-bismuth (BIS) triple therapy, a larger daily dose of NTM (1500 mg) can eradicate resistant strains. With NTM-tetracycline (TET)-BIS therapy, efficacy was better with MTN plus tinidazole, suggesting that the type of NTM used may be important. Adding a gastric acid inhibitor (GAI) improved efficacy of MTN-TET-BIS triple therapy. With CTM-NTM-GAI triple therapy, CTM resistance reduced efficacy by 35%, whereas MTN resistance reduced efficacy by only 18%; dosing both CTM and MTN twice daily improved efficacy. With AMX-CTM-GAI triple therapy, CTM resistance reduced efficacy by as much as 66%. Unfortunately, little can be done to overcome CTM resistance during eradication of *H. pylori*.

Quadruple therapy increased efficacy compared with triple therapies. The mean efficacy of PPI-MTN-TET-BIS on MTN-resistant strains

was high (79%). Better success was seen with ≥ 7 days of treatment and when certain PPIs were used. A quadruple therapy containing both MTN and CTM (AMX-CTM-MTN-GAI) was particularly effective, but too few patients were treated to be certain of its efficacy. Ranitidine bismuth citrate with CTM and MTN was particularly effective, but this drug is no longer available in most parts of the world. This is unfortunate, and perhaps it could be brought back.

It is costly and difficult to culture *H. pylori* and test antibiotic resistance, and assays are not routinely available. Furthermore, results do not necessarily predict clinical outcomes. In clinical practice, clinicians should avoid CTM-containing regimens in patients with prior exposure to macrolides. In patients with prior NTM use and patient populations with high baseline NTM resistance, this meta-analysis suggests that a first-line MTN-TET-BIS-GAI quadruple therapy for 7 to 14 days may be best. However, the large number of pills and complex dosing regimen may impair compliance.

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