What regimens eradicate *Heliobacter pylori*?

EVIDENCE-BASED ANSWER

Fourteen-day triple therapy with a proton pump inhibitor (PPI) plus clarithromycin and either amoxicillin or metronidazole is superior to 7-day therapy in eradicating *Heliobacter pylori* (strength of recommendation [SOR]: **A**, high-quality meta-analysis).

Seven-day triple therapy with a PPI or ranitidine bismuth citrate plus clarithromycin and either amoxicillin or metronidazole is also effective (SOR: **A**, high-quality systematic review).

Three-day quadruple therapy with a combination of PPI, clarithromycin, bismuth subcitrate, and metronidazole or a combination of PPI, clarithromycin, amoxicillin, and metronidazole also appears to be effective (SOR: **B**, unblinded randomized controlled trial).

EVIDENCE SUMMARY

The ideal *H pylori* eradication regimen should reach an intention-to-treat cure rate of 80% (**Table**).[1] Effective regimens are:

Fourteen-day triple therapy of PPI + clarithromycin + metronidazole *or* amoxicillin. A meta-analysis of 13 studies found the eradication rate for 14-day therapy was 81% (95% confidence interval [CI], 77%–85%), compared with 72% (95% CI, 68%–76%) for 7-day therapy. The eradication rate for 10-day therapy (83%; 95% CI, 75%–89%), however, was not significantly better than that for 7-day therapy (80%; 95% CI, 71%–86%).[2] Side effects were more frequent in the longer therapies, but did not lead to discontinuation of therapy.

Seven-day triple therapy of PPI + clarithromycin + metronidazole or amoxicillin. A high-quality systematic review of 82 studies using 7-day triple therapy found clarithromycin 500 twice daily yielded a higher eradication rate than clarithromycin 250 mg twice daily when combined with a PPI and amoxicillin (87% vs 81%; P<.0001). When clarithromycin was combined with a PPI and metronidazole, the higher dose of clarithromycin did not yield significantly higher eradication rates (88% vs 89%, P=.259).[3]

Seven-day triple therapy of ranitidine bismuth citrate + clarithromycin + metronidazole or amoxicillin. For these therapies, a high-quality systematic review of 8 studies reported eradication rates of 81% (95% CI, 77%–84%) with amoxicillin and 88% (95% CI, 85%–90%) with metronidazole.[4,5] Side effects were not reported in a uniform manner for the 7-day therapies, but were noted to be mild and did not lead to significant discontinuation of therapy. Pooled dropout rates were similar among all regimens.[4]

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What is a Clinical Inquiry?

Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and individuals with particular expertise.

Questions chosen for Clinical Inquiries are those considered most important, according to results of web-based voting by family physicians across the U.S.

Answers are developed by a specific method:

- First, extensive literature searches are conducted by medical librarians.
- Clinicians then review the evidence and write the answers, which are then peer reviewed.
- Finally, a practicing family physician writes a commentary.

TABLE

Effective therapies for *Heliobacter pylori* eradication

Regimen	Dosage	Duration (days)	Cost ($)[b]	SOR
PPI[a] Clarithromycin Metronidazole amoxicillin	 500 mg twice daily 500 mg twice daily *or* 1000 mg twice daily	14	210	A
PPI Clarithromycin Amoxicillin	 500 mg twice daily 1000 mg twice daily	7	105	A
PPI Clarithromycin Metronidazole	 500 mg twice daily 500 mg twice daily	7	105	A
Ranitidine bismuth citrate Clarithromycin Amoxicillin	400 mg twice daily 500 mg twice daily 1000 mg twice daily	7	85	A
Ranitidine bismuth citrate Clarithromycin Metronidazole	400 mg twice daily 250 mg twice daily 500 mg twice daily	7	82	A
PPI Clarithromycin Metronidazole Bismuth subcitrate	 500 mg twice daily 400 mg twice daily 240 mg twice daily	3	46	B
PPI (5 days) Clarithromycin Amoxicillin Metronidazole	 250 mg twice daily 1000 mg twice daily 400 mg twice daily	3	60	B

a. PPI: standard twice-daily dosing—eg, lansoprazole 30 mg or omeprazole 20 mg
b. Approximate cost of entire course of therapy from www.drugstore.com, August 2003.
PPI, proton pump inhibitor; SOR, strength of recommendation (for an explanation of evidence ratings, see page 779)

Three-day quadruple therapy of PPI + bismuth + clarithromycin + metronidazole *or* PPI+ clarithromycin + amoxicillin + metronidazole. An otherwise high-quality but unblinded randomized clinical trial of 234 patients demonstrated that 2 days of pretreatment with lansoprazole followed by 3 days of lansoprazole with clarithromycin, amoxicillin, and metronidazole yielded eradication rates comparable with 5-day treatment (81% vs. 89%; $P<.05$).[6]

Another randomized clinical trial of 118 patients, blinded to investigators but not patients, showed that quadruple 3-day therapy with lansoprazole + bismuth + clarithromycin + metronidazole was as effective as 7 days of lansoprazole + clarithromycin + metronidazole (87% vs 86%; $P=.94$), and had significantly shorter duration of side effects (2.6 vs 6.2 days; $P<.001$). Eradication rates were similar in isolates that were resistant or sensitive to either metronidazole or clarithromycin.[7]

The problems of emerging clarithromycin and metronidazole resistance have not been

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extensively studied. In 1 review, metronidazole-containing regimens eradicated metronidazole-sensitive strains more effectively than metronidazole-resistant strains (weighted difference, 15%; 95% CI, 8%–20%).[4] When an infection is resistant to metronidazole, amoxicillin should be used instead.[4] In areas of high clarithromycin and metronidazole resistance, a quadruple regimen might be more effective.[7]

RECOMMENDATIONS FROM OTHERS

The Maastricht Consensus of the European Heliobacter Study Group[1] recommends a 7-day triple regimen of PPI + clarithromycin + either metronidazole or amoxicillin or (if clarithromycin resistance is prevalent) PPI + amoxicillin 500 mg 3 times daily + metronidazole 500 mg 3 times daily.

The American College of Gastroenterology recommends 14-day therapy of one of the following options:[8]

- PPI + clarithromycin + (metronidazole or amoxicillin), or ranitidine bismuth citrate + clarithromycin + (metronidazole or amoxicillin). Tetracycline 500 mg twice a day can be substituted for amoxicillin or metronidazole
- PPI + bismuth subsalicylate 525 mg + metronidazole 500 mg 3 times daily + tetra-cycline 500 mg 4 times daily
- Bismuth subsalicylate 525 mg 4 times daily + metronidazole 250 mg 4 times daily + tetracycline 500 mg 4 times daily + H2 receptor antagonist in standard acid-suppression dose (eg, famotidine 20 mg twice a day for 4 weeks).

The Institute for Clinical Systems Improvement recommends as first-choice treatment a 7-day PPI/clarithromycin/amoxicillin combination, and as second choice a 7-day regimen of PPI, tetracycline 250 mg 4 times daily, metronidazole 500 mg twice daily, and bismuth subsalicylate 525 mg 4 times daily.[9]

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CLINICAL COMMENTARY

Patients beginning complex regimens require counseling

The most effective regimens (>80% eradication) for *H pylori* include a 10- to 14-day course of at least 2 antibiotics and an antisecretory agent. However, even optimal treatment regimens can fail in approximately 10% of patients. Poor compliance is among the most common reasons for treatment failure. Medication side effects can affect up to 50% of patients taking triple-agent regimens.

Treatment regimens with multiple medications administered several times daily can be difficult to follow. Convenient packaging containing all daily medications are available to optimize adherence.

Counseling points for patients should include how to take the medicine correctly, expected side effects, the importance of completing the entire therapy regimen, and warnings of specific interactions (eg, alcohol and metronidazole). Lastly, the patient should be made aware of the cost of the entire regimen, which ranges from $50 to $250.

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Does a knee brace decrease recurrent ACL injuries?

EVIDENCE-BASED ANSWER

After surgical anterior cruciate ligament (ACL) reconstruction, knee bracing does not significantly protect against injury during recovery or afterwards (strength of recommendation [SOR]: **C**, based on expert opinion). In addition, the use of a knee brace following ACL reconstruction does not improve stability or hasten rehabilitation, either immediately or for up to 2 years (SOR: **A**, based on randomized controlled trials with heterogenous results).

Patients wearing a knee brace after ACL reconstruction may report subjective enhanced performance, but measured performance is better without the brace (SOR: **B**, based on an individual case-control study).

We found no information specifically about functional bracing following ACL injuries that have been managed conservatively.

EVIDENCE SUMMARY

Functional braces are designed to provide stability for the unstable knee, but few trials report re-injury rates as an outcome. Cadaver studies show that braces limit tibial rotation and anterior translation. However, the mechanical effects of knee bracing in vivo are controversial.

> Patients wearing a knee brace feel they perform better, but measured performance improves without one

A study involving 5 patients with chronic unstable ACL injuries showed some limitation of movement with functional bracing, but it was accompanied by slowed muscle performance and used only low-stress forces.[1] Objective findings during physiologic stress loads are inconclusive.[2]

Three recent randomized controlled trials compared functional bracing with no bracing in rehabilitation after ACL reconstruction. In a prospective study of 62 patients, researchers found no benefit from using a postoperative knee brace at any stage (2 and 6 weeks; 3, 6, and 24 months) after surgery. Moreover, the brace did not contribute to a more stable knee during rehabilitation or 2-year follow-up.[3]

A similar study of 50 patients demonstrated no significant difference in function or laxity at 2 years.[4] A 2-year study comparing 30 braced with 30 nonbraced patients showed improved functional stability ($P<.05$) but increased thigh muscle atrophy ($P<.0001$) at 3-month follow-up in the braced group. However, no significant differences were seen at other follow-up intervals up to 2 years.[5]

One study evaluated running, jumping, and turning performance with and without a functional brace in 31 patients who had had an ACL reconstruction 5 to 26 months previously. They measured significantly better performance without bracing; however, more than half the group perceived enhanced performance with the brace.[6]

RECOMMENDATIONS FROM OTHERS

The American Association of Orthopaedic Surgeons believes that rehabilitative and functional knee braces can be effective in many treatment programs. Rehabilitative braces are more effective in protecting against excessive flexion and extension than against anterior and

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