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]

CONTINUED

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

CONTINUED

If used, knee braces should complement rehabilitative therapy and required surgery

posterior motion. Functional braces reduce abnormal movement under low load conditions but do not restore normal knee stability under high forces related to certain athletic activities. Physician and patient must guard against a false sense of security.[7]

The American Academy of Pediatrics says that functional braces may help prevent further injury to a previously injured knee. Their use is accepted clinically on the basis of subjective performance. If used, knee braces should complement rehabilitative therapy and required surgery.[8]

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CLINICAL COMMENTARY

Knee braces no substitute for rehabilitation, but patients say they help

A key question all clinicians must ask is who is being treated—the patient, yourself, or some third-party payer. While multiple studies on knee bracing after ACL reconstruction have not demonstrated improved knee stability or faster recovery times, many patients have reported subjective improvement in function.

As long as patients understand that a brace does not substitute for vigorous rehabilitation to improve strength, flexibility, and proprioception, I find no compelling reason to discourage its use after a patient is allowed to return to unrestricted activities.

Cost may then become the major deciding factor, but even off-the-shelf braces or neoprene sleeves may be sufficient to provide the subjective benefit.

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Does breastfeeding protect against viral GI infections in children <2 years old?

Several studies demonstrate that breastfeeding decreases the severity of rotavirus infection

EVIDENCE-BASED ANSWER

While breastfeeding protects against all-cause diarrhea in infants[1–5] (strength of recommendation [SOR]: **B**, based on cohort studies and 1 randomized controlled trial), no evidence shows that breastfeeding confers specific protection against viral gastrointestinal infections. Several studies demonstrate that breastfeeding does not prevent acquisition of rotavirus but does decrease the severity of its course (SOR: **B**, based on cohort, case-control studies, and a systematic review lacking homogeneity).[6–10]

EVIDENCE SUMMARY

Breastfeeding has been associated with decreased overall rates of diarrhea in infants in developed[2–4] and developing[1,5] countries. Many cases of gastroenteritis without a confirmed enteropathogen have viral causes. Rotavirus is a common viral pathogen in children aged <2 years, and much of the evidence about breastfeeding and viral gastroenteritis comes from studies about rotavirus infections.

Prospective cohort studies conducted in Canada[6] and the United States[7] showed no difference in the incidence of rotavirus gastroenteritis between infants up to 2 years of age who were breastfed and those who were not. Although differences were not found between either the incidence or the duration of rotavirus infections, these studies showed a significant decrease in the frequency of vomiting among breastfed infants.

A case-control study in Bangladesh suggests that breastfed infants have a higher incidence of rotavirus diarrhea, but selection of diarrhea patients as controls may have underestimated the protective effect.[8] Although breastfeeding was not found to provide overall protection from developing rotavirus gastroenteritis, exclusive breastfeeding appeared to protect against severe rotavirus diarrhea for infants aged <2 years.

Another US study showed that risk for rotavirus infection did not differ for infants who were exclusively breastfed, partially breastfed, or exclusively formula-fed.[10] However, the breastfed infants were more likely to have milder symptoms.

RECOMMENDATIONS FROM OTHERS

The American Academy of Family Physicians[11] and the American Academy of Pediatrics[12] recommend exclusive breastfeeding for a minimum of the first 6 months of life, and continuation of breastfeeding to supplement age-appropriate foods through the next 6 months. The World Health Organization[13] recommends exclusive breastfeeding for the first 4 to 6 months of life, and continuation of breastfeeding for 2 years of age or beyond.

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CLINICAL COMMENTARY
Another reason to encourage mothers to breastfeed

This review affirms that breast milk protects against diarrheal illness while questioning a specific effect in preventing rotavirus infections. Evidence that breast milk reduces severity of the world's major cause of diarrhea-associated death, however, is sufficient basis to support breastfeeding.

I educate expectant mothers about breast milk's disease-mitigating qualities and compliment breastfeeding mothers on giving this gift to their children. I discuss the impact of breastfeeding on incidence of otitis media, asthma, obesity, and all-cause diarrhea. I also counsel that breast milk may decrease severity of diarrhea because it is "easier on the digestive system" (lower osmolality) than formula.

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Which infants need lumbar puncture for suspected sepsis?

EVIDENCE-BASED ANSWER

Evidence from prospective and retrospective clinical trials suggests that for infants <2 months old, only those at high risk for serious bacterial infection by standardized criteria (eg, Rochester classification) require lumbar puncture (strength of recommendation [SOR]: **B**, based on prospective and retrospective cohort studies). However, expert opinion suggests lumbar puncture on all infants aged 0 to 28 days with suspected sepsis, and all infants aged >2 months who are to receive empiric antibiotics (SOR: **C**, based on expert opinion).

EVIDENCE SUMMARY

Standardized clinical criteria (**Table**) exist to determine the risk of serious bacterial infection, which includes meningitis; of particular note, these criteria do not require cerebrospinal fluid examination. Infants aged <3 months who fall into the "high-risk" category or appear toxic have 21% probability of a serious bacterial infection, 10% probability of bacteremia, and 2% probability of bacterial meningitis.[1] The "low-risk" infants have a correspondingly lower incidence of serious bacterial infection: the negative predictive value of the Rochester classification is 98.9% (95% confidence interval [CI], 97.2–99.6%).[2]

The negative predictive value for bacterial meningitis (a subset of serious bacterial infection) is even greater. Five studies applied the standardized criteria to febrile infants and monitored them for the development of serious bacterial infection, including meningitis.

Two prospective cohort studies of outpatients aged 0 to 2 months used the Rochester criteria to assign infants to risk groups. They studied a total of 1294 infants; 659 (51%) were low-risk. None of the low-risk infants developed bacterial meningitis.[2,3]

TABLE

How to identify infants at low risk of serious bacterial infection: Rochester Classification

Febrile infants (temperature ≥38°C, 100.4°F) ≤60 days of age who meet *all criteria* are at low risk of serious bacterial infection:

General health	Born at ≥37 weeks' gestation Did not receive perinatal or antenatal antibiotics Was not treated for unexplained hyperbilirubinemia Was not hospitalized in the nursery longer than the mother Has had no hospitalization since discharge No diagnosed chronic or underlying illnesses
Physical findings	Appears well and nontoxic No evidence of skin, soft tissue, bone, or joint abnormalities, or otitis media
Laboratory findings	Peripheral total white blood cells 5,000–15,000/mm^3 Absolute band form leukocytes <1,500/mm^3 Spun urine sediment <10 white blood cells per high power field Fresh stool smear <5 white blood cells per high power field

One prospective cohort study of infants aged <1 month hospitalized for fever used a similar method for assessing risk, but added a C-reactive protein value <20 mg/L to criteria for low-risk. Of 250 infants studied, 131 (52%) were low-risk; none of these developed bacterial meningitis.[4]

A retrospective chart review of 492 infants aged <3 months who were hospitalized due to fever included 108 infants aged <1 month. Thirty percent (114) of the infants aged 1 to 3 months and 67% (72) of the younger infants underwent lumbar puncture at the discretion of the treating physician. All infants were retrospectively assigned to low- or high-risk groups for serious bacterial infection using the Rochester criteria. Of the 296 infants rated "low-risk," none developed bacterial meningitis. Ten of these infants subsequently developed evidence of another bacterial focus (predominantly urinary tract infection).[5]

RECOMMENDATIONS FROM OTHERS

The American Academy of Pediatrics has not issued a clinical practice guideline or clinical report addressing this issue. An evidence-based guideline developed at Cincinnati Children's Hospital Medical Center in 1998 recommends hospitalization and a full sepsis workup (including lumbar puncture) for infants aged <1 month, or infants aged 1 to 2 months who are high-risk.[6]

A clinical review-based guideline published in 1993 gives the same recommendations.[7] The expert panel that devised this guideline emphasized a full sepsis evaluation (including cerebrospinal fluid cultures) for infants <28 days of age "despite the low probability of serious bacterial infections in this age group and the favorable outcome of the children managed to date with careful observation." For low-risk infants aged 1 to 2 months, lumbar puncture is not necessary unless empiric antibiotics are given; having a cerebrospinal fluid culture prior to empiric antibiotics reduces the concern of partially treated meningitis in the case of clinical deterioration after hospital discharge.[6,7]

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CONTINUED

CLINICAL COMMENTARY

Evaluating fever in infants: judging the risks

The evaluation of the febrile infant is often fraught with anxiety. Physicians must balance the potentially devastating consequences of a missed serious bacterial infection with the desire to avoid unnecessary work-ups.

In the past, guidelines have had an extremely conservative viewpoint, essentially grouping all infants by age, and recommended an extensive inpatient work-up regardless of clinical status. The Rochester Criteria have provided guidelines for clinical risk stratification in this age group, allowing a more rational approach to the workup. The above data provide further useful guidance for the appropriate use of lumbar puncture in evaluation of these infants.

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What medication best prevents migraine in children?

EVIDENCE-BASED ANSWER

Propranolol, valproic acid, and amitriptyline are effective prophylaxis for migraine in children to varying degrees, are widely available, and have a reasonable safety profile (strength of recommendation [SOR]: **B**, based on either single randomized controlled trial, prospective or retrospective cohort studies, or trials with conflicting evidence).

Flunarizine and nimodipine have the best evidence of benefit in children; however, availability, cost, and side effects limit their usefulness (SOR: **B**, based on multiple small randomized controlled trials).

EVIDENCE SUMMARY

Amitryptyline was moderately efficacious in 3 small nonblinded trials.[1,2] The largest and best-designed prospective cohort trial studied 192 children. Of the 146 patients available for the first follow-up visit, 84% noted subjective improvement of symptoms. Headache frequency decreased from 17.1 ± 10.1 to 9.2 ± 10.0 days/month ($P<.001$).[1]

Propranolol, although widely used in children, has conflicting evidence regarding effectiveness. One small randomized controlled trial showed reduced headache frequency in children when compared with placebo.[3] However, these results were not duplicated in a larger randomized controlled trial using slightly smaller doses.[4]

A comparative randomized controlled trial with multiple crossovers involving 33 children found that a self-hypnosis placebo decreased mean headache frequency from 13.3 per 3-month interval to 5.8 ($P=.045$), but found propranolol no different than placebo.[5] Propranolol was also studied in a 3-armed

randomized controlled trial in comparison with flunarizine—a drug likely to be efficacious—and placebo. Both drugs were equally efficacious and superior to placebo according to reviews; however, these results were not published in English and could not be critiqued by this author.[2]

In 2 small retrospective case studies, *valproic acid* demonstrated >50% improvement in symptoms in 65%[6] and 78%[7] of subjects. A single uncontrolled interventional trial of valproic acid in 10 children showed a significant trend of improvement in frequency (mean of 6 attacks/month to 0.8 attacks/month) and duration (mean 5.5 hours per attack to 1.1 hour).[8]

Two similar vasodilatory calcium channel blockers, *flunarizine* and *nimodipine*, have the best evidence as migraine prophylactics in children. Flunarizine was found to be effective in multiple well-designed randomized controlled trials and case series, as well as in multiple comparative trials with other agents.[2]

In a double-blinded, placebo-controlled randomized controlled trial of 48 children, flunarizine decreased mean headache frequency (3.0 attacks/3 months vs 6.5 [$P<.001$]).[9] A repeat randomized controlled trial in 70 children had similar outcomes.[10]

Nimodipine, in a single randomized controlled trial with crossover design in 37 children decreased headache frequency from a mean of ~2.7 attacks/month to ~1.9 vs. no change for placebo ($P<.05$).[11] A small, prospective, nonblinded comparative trial found that nimodipine and flunarizine have similar efficacy and are superior to placebo.[12]

Cyproheptadine is widely used in children but is not as effective as amitriptyline and propranolol.[2] In adults it is not considered a first-line agent due to lack of evidence of efficacy.[13] Nonsteroidal anti-inflammatory drugs have insufficient data to recommend them as prophylactic medications in children.[2]

RECOMMENDATIONS FROM OTHERS

Nelson Textbook of Pediatrics recommends propranolol as a first-line agent for prevention.[14]

A recent review article15 recommends cyproheptadine as an initial agent in children <10 years of age. This article also has a patient handout discussing nonpharmacologic prophylactics such as regular sleep, exercise, stress reduction, and avoiding certain foods.

UpToDate recommends propranolol, cyproheptadine, valproate, and amitriptyline as prophylactic options based on patient parameters such as age, sex, and comorbid conditions.[16]

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CLINICAL COMMENTARY

Propranolol has fewest side effects

Migraines in children are not as well studied as the same problem in adults. I like to stick with older medications known to have fewer side effects. Propranolol is my first choice for any age, since it has been well studied and has very few side effects. Amitriptyline would be second because it is well known, but it does have a sedating effect. If both of these fail to control the migraines, I would consider calcium channel blockers, which are newer in the prevention of migraines.

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