

Sequential therapy boosts *H pylori* eradication rates

Antibiotics in sequence is a more formidable ally than the standard treatment regimen

Practice changer

Prescribe sequential therapy rather than the standard (concurrent) therapy to improve *H pylori* eradication rates, particularly in treatment-naïve patients.¹

Strength of recommendation

B: Based on a well-done meta-analysis with disease-oriented outcomes

Jafri NS, Hornung CA, Howden CW. Meta-analysis: sequential therapy appears superior to standard therapy for *Helicobacter pylori* infection in patients naive to treatment. *Ann Intern Med.* 2008;148:923-931.

ILLUSTRATIVE CASE

A 40-year-old woman with a peptic ulcer has been diagnosed with *Helicobacter pylori* infection, and schedules a visit to discuss treatment. You're aware of the declining eradication rates associated with standard therapy, and have heard that sequential therapy may be a more effective option. Should you offer it to this patient?

An estimated 30% to 40% of the US population is infected with *H pylori*,² a bacterium that plays a crucial role in the pathogenesis of peptic ulcer disease, chronic gastritis, and gastric cancer.¹ The triple-drug regimen (a proton-pump inhibitor [PPI] and clarithromycin with

amoxicillin, tinidazole, or another imidazole) is commonly used to treat *H pylori* in Europe and in the United States.³ Yet the eradication rate associated with this standard 3-drug regimen in this country is <80%, and appears to be on the decline. The likely problem: the increase in antibiotic-resistant strains of *H pylori*.²

Put amoxicillin first

In Italy, eradication rates of >90% have been reported with a sequential therapy: a PPI and amoxicillin for 5 days, followed by the PPI, clarithromycin, and tinidazole for an additional 5 days (**FIGURE**).⁴ (Because tinidazole is a relatively new drug in the United States and physicians may use other drugs in its class instead, we refer to the drug class—imidazoles—rather than a specific medication in the **FIGURE** and much of the text that follows.) Using amoxicillin before the other antibiotics weakens bacterial cell walls, preventing the formation of drug efflux channels that can inhibit clarithromycin and other antibiotics, according to 1 theory.¹ Thus, clarithromycin and an imidazole are more effective in the second phase of treatment.¹

Should US physicians adopt the Italian protocol and prescribe tinidazole? Would metronidazole or other imidazoles be equally effective?

Amanda Allmon, MD
James J. Stevermer, MD,
MSPH, Department of Family
and Community Medicine
University of Missouri-Columbia

PURLS EDITOR

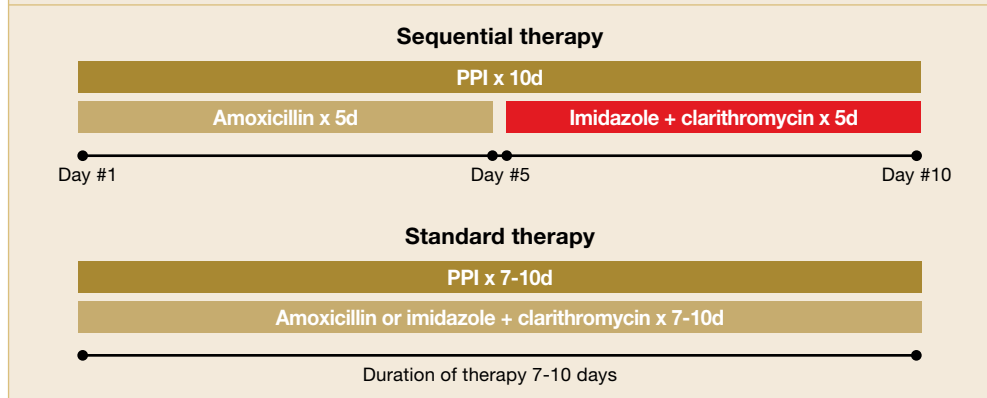
Bernard Ewigman, MD,
MSPH, Department of Family
Medicine, The University of
Chicago

FAST TRACK

Other antibiotics appear to be more effective when amoxicillin is taken first

CONTINUED

FIGURE

Sequential vs standard therapy: A comparison**STUDY SUMMARY****Sequential therapy is better on all counts**

This meta-analysis found 9 randomized controlled trials (RCTs) that compared *H. pylori* eradication rates with standard 7- to 10-day triple-drug therapy to 10-day sequential therapy; an additional small study used a 5-day triple-drug comparison group. The authors performed a thorough search and used standard meta-analysis methods for data synthesis and analysis. The patients were all *H. pylori* treatment naïve and had not used PPIs, histamine-2 receptor antagonists, or antibiotics in the month preceding the study. All patients (n=2747) had documented *H. pylori* infection based on fecal antigen test, histologic evaluation, biopsy urease test, or urea breath test.

All the trials were conducted in Italy, although 2 of the studies included patients from the United States. Nine RCTs compared a triple-therapy regimen with PPI to sequential therapy, 1 RCT compared a triple-drug regimen with ranitidine to sequential therapy, and 1 included only pediatric patients. Pooled eradication rates were 93.4% (95% confidence interval [CI], 91.3%-95.5%) for sequential therapy and 76.9% (CI, 71.0%-82.8%) for standard therapy, with a relative risk reduction of 71% (CI, 64%-77%).¹ The authors estimated that

for every 6.3 patients (95% CI, 5.2-7.1) treated with sequential therapy, there would be 1 additional cure compared to standard therapy. Standard 7- to 10-day triple therapy remained inferior to sequential therapy in all subgroup analyses, including patients with risk factors for eradication failure.

Adherence rates were similar in both groups. Sequential therapy resulted in a median adherence rate of 97.4% (range, 90.0%-98.9%), with standard therapy at 96.8% (range, 93.0%-100%).¹ Reported side effects were also similar in both treatment groups.¹

WHAT'S NEW?**This meta-analysis reduces doubt**

The latest American College of Gastroenterology guidelines on the management of *H. pylori* infection acknowledge that sequential therapy has shown promise in Europe, but the organization has not supported a change from the standard regimen to sequential therapy as first-line treatment. The standard triple-therapy regimen is approved by the US Food and Drug Administration, and is the most commonly used *H. pylori* treatment in the United States.¹ This is the first meta-analysis based solely on RCTs, and it clearly demonstrates that sequential therapy increased eradication rates.

FAST TRACK

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PURLs methodology

This study was selected and evaluated using FPIN's Priority Updates from the Research Literature (PURL) Surveillance System methodology. The criteria and findings leading to the selection of this study as a PURL can be accessed at www.jfponline.com/purls.

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PATIENT HANDOUT

How to take your medicine for *H pylori* infection

Helicobacter pylori (called *H pylori* for short) is a type of bacteria that can cause an ulcer (sore) to develop within the lining of your stomach and intestines. Ulcers can cause pain and bleeding, so it is important to get rid of this bacteria. To do this, you will need to take 4 different medicines over the next 10 days. They must be taken in a certain order, exactly as your doctor has prescribed.

One of the drugs you will be taking (for the entire 10-day period) is a proton pump inhibitor (called a PPI), a medicine that helps reduce the amount of acid in your stomach. _____ is the name of the PPI your doctor has ordered. Take it twice a day, once in the morning and once in the evening, for 10 days.

You will also take 3 different kinds of antibiotics to eliminate the *H pylori* bacteria. For the first 5 days,

you will take amoxicillin twice a day (2 pills in the morning and 2 in the evening), along with the PPI.

After 5 days, all the amoxicillin pills should be gone, and you will switch to 2 other antibiotics: clarithromycin AND _____. For the next 5 days, you will take 1 PPI plus 1 clarithromycin and 1 _____ every morning AND every night.

These medications may cause nausea, diarrhea, and a bad taste in your mouth. These side effects are usually not serious, but if they bother you so much that you cannot continue to take the medicine, it is important to call our office right away.

To remember to take each of the medicines in the morning AND evening on the correct day, use this chart to follow along. Put a check mark in the morning box or the evening box every time you take your medicine.

DAY	AM	PM
1	3 pills: 1 PPI (_____) 2 amoxicillin <input type="checkbox"/>	3 pills: 1 PPI (_____) 2 amoxicillin <input type="checkbox"/>
2	↓ <input type="checkbox"/>	↓ <input type="checkbox"/>
3	↓ <input type="checkbox"/>	↓ <input type="checkbox"/>
4	↓ <input type="checkbox"/>	↓ <input type="checkbox"/>
5	↓ <input type="checkbox"/>	↓ <input type="checkbox"/>
6	3 pills: 1 PPI (_____) 1 clarithromycin <input type="checkbox"/> 1 antibiotic (_____)	3 pills: 1 PPI (_____) 1 clarithromycin <input type="checkbox"/> 1 antibiotic (_____)
7	↓ <input type="checkbox"/>	↓ <input type="checkbox"/>
8	↓ <input type="checkbox"/>	↓ <input type="checkbox"/>
9	↓ <input type="checkbox"/>	↓ <input type="checkbox"/>
10	↓ <input type="checkbox"/>	↓ <input type="checkbox"/>

CAVEATS**■ Drug resistance, previous Tx could skew results**

This meta-analysis only included studies performed in Italy, although 2 of the trials did include US recruits. Drug resistance patterns may be different in this country, which could alter sequential therapy's eradication rates.

Because 3 antibiotics are used in sequential therapy, we may have fewer remaining options for patients who do not respond to this regimen, and we do not have information about patients with previous treatment failures. In addition, this meta-analysis only evaluated *H pylori* eradication rates in treatment-naïve patients, so we have no information about the effectiveness of this regimen in patients with previous treatment failures.

■ Would other sequential regimens—or drugs—work?

Patients who are allergic to amoxicillin would not be candidates for this sequential therapy protocol. While sequential therapy was compared with 7- to 10-day standard triple therapy, this study did not compare it with other regimens—eg, quadruple therapy or a 14-day course of standard triple-drug therapy.

Other drugs may also affect outcomes. The sequential therapy studies all used tinidazole, a relatively new agent in the United States; we don't know whether metronidazole or other imidazoles are as effective.

The authors of this meta-analysis also noted the possibility of publication bias, but we doubt that there are enough unpublished data to invalidate the findings. Also, the selected RCTs only addressed eradication rates and not patient-oriented outcomes. However, most patient-oriented outcomes, including cancer and ulcers, can take years, even decades, to develop.

CHALLENGES TO IMPLEMENTATION**■ Sequential therapy may be confusing**

While adherence rates were similar in the standard and sequential treatment groups in the meta-analysis, sequential therapy—which requires switching medications midway through treatment—might be more confusing for patients in actual practice. This has the potential to negatively affect adherence to the sequential regimen.

It will be important for physicians who prescribe sequential therapy to counsel patients on the importance of completing the treatment regimen exactly as prescribed and to provide clear instructions for doing so, ideally in the form of a patient handout like the one on page 653. Cost is not a problem; the price of sequential therapy is about equal to, or possibly less than, that of standard therapy.⁵ ■

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FAST TRACK

Cost is not a problem; the price of sequential therapy is about the same as that of standard therapy