

Clinical Issues and Cost Effectiveness of Treating *H pylori*

Based on a presentation by M. Brian Fennerty, MD, FACP, FACG

Presentation Summary

Since 1987, an accumulating body of data has confirmed that patients in whom *H pylori* infection has been successfully eradicated have a better clinical outcome. In a managed care environment, better clinical outcome is only one of several treatment goals. Regimens to eradicate *H pylori* should be clinically effective, safe, and simple for both patient and provider, and promote compliance with therapy. In addition, treatment should heal or prevent symptoms and disease, avoid complications and maintain remission, and be cost effective.

Several regimens are available to eradicate *H pylori* in patients with peptic ulcer disease. They include dual-therapy regimens, consisting of an antisecretory agent plus an antibiotic, and triple-therapy regimens, consisting of a bismuth compound and/or an antisecretory agent plus one or two antibiotics.

At present, triple-therapy regimens with a proton pump inhibitor as the antisecretory agent are more efficacious, better tolerated, simpler,

and associated with better compliance than are other regimens.

Data regarding improved economic outcome first became available in 1995. Although these economic models indicate that patients with peptic ulcers (and perhaps those with dyspepsia as well) should be treated with antimicrobial regimens directed at eradication of *H pylori*, they do not address which regimen is preferable.

While the regimens may differ in their pharmacy costs, the key issue is which regimen is most cost effective in terms of disease management costs. Thus, a less expensive regimen that is also less effective clinically will be associated with more disease recurrence and ultimately result in significantly higher overall costs. Conversely, a more expensive regimen that is more effective clinically is associated with less recurrence and greater cost savings in the long run.

Although it has yet to be defined for all circumstances, the optimal regimen is the one with the greatest clinical efficacy, not the one that is least costly.

Since 1987, an accumulating body of data has confirmed that patients in whom *H pylori* infection has been successfully eradicated have a better clinical outcome, said M. Brian

Fennerty, MD, FACP, FACG, of the Oregon Health Sciences University in Portland.

For managed care organizations, the key to successful treatment is to iden-

tify, from among several commonly accepted and appropriate eradication therapies (Table 1), the regimen (or regimens) that combine(s) maximum clinical efficacy with maximum cost effectiveness, Dr. Fennerty pointed out.

Managed care organizations have many needs vis à vis *H pylori* eradication, including patient identification, guaranteed eradication, simpler regimens for patient and provider, favorable side effect profiles, increased quality, lower and predictable costs, and provider buy-in, he continued.

With these needs in mind, Dr. Fennerty reviewed the treatment goals of *H pylori* therapy and the efficacy of several regimens (Table 1) and described several economic models designed to determine the cost effectiveness of eradication therapy.

Treatment Goals

The treatment goals of eradication therapy are twofold: what the regimens themselves have to offer in terms of efficacy, tolerability, simplicity of use, and compliance; and what the regimens have to offer in terms of outcomes.

“The outcome is really the important part of treating any disease process, be it *H pylori*, hypertension, or diabetes,” he said. “We hope to treat or prevent symptoms and disease, to avoid complications

and maintain remission, and to make sure that the treatment is cost effective.”

In terms of treatment goals, triple-therapy regimens with proton pump inhibitors (PPIs) are more efficacious, better tolerated, simpler, and associated with better compliance than are other regimens. For example, of the FDA-approved regimens used to eradicate *H pylori*, those consisting of a PPI and two antibiotics have fewer side effects than either dual-therapy or bismuth-based triple therapy.

Regimen simplicity, however, remains a problem. Bismuth-based triple therapy, for example, requires that the patient take 224 pills over a 14-day period, while other regimens require between 70 and 119 pills over 14 days of therapy. Nevertheless, most regimens are simpler now than they had been in the past, he said.

Simplicity of regimen is an important issue since it affects compliance, and compliance clearly affects efficacy. In 1996, Laine showed that compliance decreases as the duration of therapy increases. He found that compliance was 100% with 7-day regimens, 94% with 10-day regimens, and 90% with 14-day regimens.¹

To improve compliance and help patients through 14 days of therapy, compliance packs have thus far been developed for bismuth-based triple therapy and for lansoprazole/amoxicillin/clarithromycin (LAC). “We will probably see more of this approach to these complex therapies for most of the regimens we use in clinical practice,” Dr. Fennerty said.

Clinical Efficacy

Efficacy rates for four FDA-approved regimens and three nonapproved regimens are shown in Table 2.¹⁻³ With the introduction of LAC, the first PPI triple-therapy regimen, efficacy rates finally reached 90%.⁴ “With the efficacy rates of the nonapproved PPI triple therapies also at about 90%, it is very difficult to recommend the first three FDA-approved regimens (OC, RBC-C, and

Table 1. *H pylori* Eradication Therapies

Dual Therapies	
LA	lansoprazole + amoxicillin
OC	omeprazole + clarithromycin
RBC-C	ranitidine bismuth citrate + clarithromycin
Triple Therapies	
BMT	bismuth subsalicylate + metronidazole + tetracycline
LAC	lansoprazole + amoxicillin + clarithromycin
MOC	metronidazole + omeprazole + clarithromycin
OAC	omeprazole + amoxicillin + clarithromycin
RBC-AC	ranitidine bismuth citrate + amoxicillin + clarithromycin

BMT) that we got used to using because they were on our formularies," Dr. Fennerty noted.

Elaborating on this point, he described several studies evaluating the efficacy of the PPI triple-therapy regimens shown in Table 2. In two of these studies, which involved 553 patients, 138 received LAC for 14 days; the per-protocol efficacy was 90%.⁴ In another study evaluating 14 days of LAC therapy, the per-protocol efficacy was 92% in 48 patients and 86% in 66 patients.⁴

In another study, which evaluated the efficacy of OAC in 150 patients, the intention-to-treat efficacy was 86% for 7 days of therapy, 90% for 10 days, and 92% for 14 days. Per-protocol efficacy was 86% for 7 days of therapy, 91% for 10 days, and 95% for 14 days.¹

"The efficacy between 7 days and 14 days of therapy is not much different, but we don't know if we can get by with treatment periods shorter than 10 days, although the 10-day data are pretty clean," he explained.

In a community effectiveness study involving 250 patients in Portland, Oregon, 137 received MOC therapy for 7, 10, and 14 days. Intention-to-treat efficacy was 91% for 7 days of therapy and 93% for 10 and 14 days, with the per-protocol efficacy rates also in the 90% range.² Similarly, in a study evaluating 14 days of therapy with RAC (RBC-AC), the per-protocol efficacy was 96%, and the intention-to-treat efficacy was 92%.³

"Thus, we have substantial data from very large, controlled studies conducted in the United States, as well as community effectiveness data, showing that PPI triple therapy in this country is far superior to the original FDA-approved regimens of OC, RBC-C, and BMT. This is not my bias. It's based on the literature, and it's truly evidence-based medicine," he emphasized.

Cost Effectiveness

By definition, cost effectiveness means optimizing the outcome while utilizing fewer dollars. However, in the past, the focus has been on using fewer

Table 2. *H pylori* Regimen Efficacy Rates

FDA-Approved Regimens	
OC	70%-75% per protocol
RBC-C	73%-84% per protocol
BMT	77%-82% per protocol
LAC	90% per protocol
Nonapproved Regimens	
MOC	91% per protocol*
OAC	91% per protocol [†]
	89% intention to treat*
RAC	96% per protocol [‡]
	92% intention to treat [‡]

*See reference 2.

[†]See reference 1.

[‡]See reference 3.

dollars and ignoring optimization of outcome.

"Not only is this approach inappropriate in clinical practice, but it also winds up being cost ineffective. When we focus on very limited aspects of the budget, such as the pharmacy budget, and make cuts there, we end up with dramatic cost increases elsewhere," Dr. Fennerty stressed.

Before describing several cost-effectiveness studies evaluating *H pylori* eradication, he noted that a number of assumptions were used in these economic models that probably markedly underestimated the true incidence of symptom and disease recurrence.

For example, although *H pylori* eradication will cure ulcers in the overwhelming majority of patients whose ulcers are due to *H pylori* infection, it will not cure ulcer in those whose ulcers are due to NSAID use. Additionally, there will always be patients who require antisecretory therapy because of concomitant gastroesophageal reflux disease or nonulcer dyspepsia.

Scores of economic models evaluating *H pylori* eradication have been published recently. The first to be published, in 1995, was the Sonnenberg model, which presented the first cost analysis of *H pylori* eradication therapy.⁵

Using an extension of a previous Markov chain model for duodenal ulcer, Sonnenberg evaluated four treatment strategies (eradication, intermittent H₂ blockers, maintenance with H₂ blockers, and surgery) and provided 15-year cost estimates of both direct and indirect costs.

Direct per-patient treatment costs (including drug costs, endoscopy costs, and hospitalization) over a 15-year period were about \$1,000 for *H pylori* eradication, \$10,000 to \$11,000 for intermittent or maintenance therapy with H₂ blockers, and about \$18,000 for surgery.⁵

Sonnenberg later showed that indirect costs were dramatically reduced by eradication therapy in that patients so treated no longer had ulcer recurrence, bleeds, or perforations and missed fewer days from work.

While ulcer disease is an enormous public health problem in this country, it pales in comparison to dyspepsia, which can include gastric and duodenal ulcer, gastroesophageal reflux disease, gallbladder disease, and nonulcer dyspepsia. Most patients with dyspepsia are commonly treated with H₂ blockers or PPIs, often permanently and perhaps unnecessarily, Dr. Fennerty remarked.

Taking this clinical situation into account, Fendrick et al used a decision analytic model of suspected peptic ulcer disease to look at five different treatment strategies: immediate endoscopy for peptic ulcer and biopsy for *H pylori*; immediate endoscopy without biopsy; serologic test for *H pylori*; empiric treatment with an antisecretory agent; and empiric treatment with an antisecretory agent and antibiotics to eradicate *H pylori*. They provided a 1-year estimate of direct costs alone—ie, physician and pharmacy costs—for serology-directed treatment (\$894 per patient), empiric antisecretory treatment (\$952 per patient), and empiric *H pylori* eradication (\$818 per patient).⁶

Empiric *H pylori* therapy was found to be the most cost-effective approach, and this was of great interest to managed

care organizations because it represented a considerable savings in endoscopy costs, Dr. Fennerty pointed out.

Following the lead of Fendrick et al, Sonnenberg designed a decision analytic model of dyspeptic patients whose disease had not been definitively diagnosed. He found that if the symptoms responded to *H pylori* eradication in only 5% to 10% of this population, then eradication therapy was beneficial and cost effective.⁷

“What he was really describing was that some of these patients, perhaps as few as 5% to 10%, actually had ulcers when they presented. They represent the hidden ulcer population,” Dr. Fennerty noted.

The model found that eradication therapy was beneficial if ulcer prevention was associated with a more than \$4,000 benefit or if the ulcer prevalence was 10% or more in the dyspeptic population.⁷ In other words, the benefit of eradication in that population was so great that it would be cost effective even if the remaining 90% to 95% of the patients did not benefit, Dr. Fennerty explained.

The concept that it is cost effective to treat all patients who might have an ulcer to benefit only a few was confirmed by Ofman et al, who used a decision analytic model of direct costs over 1 year in patients who were seropositive for *H pylori*. They found that it was cost effective to treat *H pylori* if the probability of peptic ulcer disease is 10% or greater, even if there is no response in patients with nonulcer dyspepsia.⁸

Which Regimen to Use?

While economic models indicate that patients with peptic ulcer (and perhaps those with dyspepsia as well) should be treated with antibiotics directed at eradicating *H pylori*, they do not address which regimen is preferable. The key issue is not pharmacy costs, which may differ from regimen to regimen, but cost effectiveness in terms of overall disease management costs. As Dr. Fennerty

pointed out, "The most expensive regimen is the one that doesn't work."

Therefore, a less expensive regimen that is also less effective clinically will be associated with more disease recurrence and ultimately result in higher overall costs. Conversely, a more expensive regimen that is more effective clinically is associated with less recurrence and greater cost savings in the long run.

"The important thing is not what to use, but to recognize that the efficacy of the regimen determines its cost effectiveness, not the cost of acquiring the drugs," Dr. Fennerty reminded the audience.

He then described a "real world" community study in which he and a colleague, Nimish Vakil, tracked 38 gastroenterologists in Portland, Oregon, and their treatment of 250 patients over a 2-year period. Efficacy of five *H pylori* eradication regimens was evaluated, and the rates were rolled back into Vakil's previously reported decision analytic model to provide 2-year estimates of direct costs and to determine the costs per patient treated. Results are shown in Table 3.^{2,9}

Over the 2-year period, it was found that the least expensive regimen (triple therapy with BMT) cost nearly twice as much per patient treated than did triple therapy with an "expensive" PPI (MOC) because BMT was less effective, he said.

Conclusion

There is no doubt that both the clinical and economic outcomes are improved in patients with peptic ulcer disease who are treated with *H pylori* eradication therapy. Not to test and treat patients with ulcer disease borders on negligence, Dr. Fennerty said. Although such treatment probably does not improve the clinical outcome in patients with dyspepsia, it substantially improves economic outcome.

H pylori treatment and choice of regimen should be guided by regional or community effectiveness data. However, at this point, it appears that PPI-

Table 3. Efficacy and Cost-Effectiveness of Five Eradication Regimens in Community Outcomes Study

Regimen	Efficacy Rate	Cost per Patient Treated
MOC	93%	\$344
OBMT	76%	\$512
BMT	73%	\$613
OC	76%	\$732
OA	71%	\$641

See references 2 and 9

based triple therapy for 7-14 days is the optimal regimen in terms of efficacy and cost effectiveness.

"In the managed care environment," Dr. Fennerty concluded, "we should not let a small or finite portion of the overall disease management scheme—such as the pharmacy budget—get in the way of providing appropriate treatment and cost-effective therapy. And remember, cost effectiveness is determined by the effectiveness of the regimens, not the acquisition costs of the drugs themselves."

... REFERENCES ...

1. Laine L, Estrada R, Trujillo E, Fukunaga K, Neil G. Randomized comparison of differing periods of twice-a-day triple therapy for the eradication of *Helicobacter pylori*. *Aliment Pharmacol Ther* 1996;10:1029-1033
2. Fennerty M, Lieberman D, Magaret N, and GORGE Consortium. Effectiveness of *H pylori* treatment regimens in clinical practice: A community-based outcomes study (abstr). *Gastroenterology* 1997;112:A14.
3. Laine L, Estrada R, Trujillo M, Emami S. Randomized comparison of ranitidine bismuth citrate (RBS)-based triple therapies for *H pylori* (*Hp*) (abstr). *Gastroenterology* 1997;112:A192.
4. Fennerty M, Bianchi T, Rose P, et al. Triple therapy with lansoprazole, clarithromycin, and amoxicillin is highly effective in the eradication of *Helicobacter pylori* infec-

tion (abstr). *Gastroenterology* 1997;112:A116.

5. Sonnenberg A, Townsend W. Costs of duodenal ulcer therapy with antibiotics. *Arch Intern Med* 1995;155:922-928.

6. Fendrick AM, Chernew ME, Hirth RA, Bloom BS. Alternative management strategies for patients with suspected peptic ulcer disease. *Ann Intern Med* 1995;123:260-268.

7. Sonnenberg A. Cost-benefit analysis of testing for *Helicobacter pylori* in dyspeptic subjects. *Am J Gastroenterol* 1996;91:1773-1777.

8. Ofman JJ, Etchason JE, Fullerton S, Kahn KL, Soll AH. Management strategies for *Helicobacter pylori*-seropositive patients with dyspepsia: Clinical and economic consequences. *Ann Intern Med* 1997;126:280-291.

9. Vakil N, Fennerty M. Cost-effectiveness of treatment regimens for *H pylori* infection based on a community practice effectiveness study (abstr). *Gastroenterology* 1997;112:A47.