

Evolving Therapy for *Helicobacter pylori* Infection: Efficacy and Economic Impact in the Treatment of Patients with Duodenal Ulcer Disease

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Abstract

Helicobacter pylori infection is present in most patients with duodenal ulcer disease, and cure of *H pylori* infection has been shown to dramatically reduce ulcer recurrence. Therapeutic strategies for duodenal ulcer disease have rapidly evolved over the past several years in an effort to consistently cure *H pylori* infection in a safe, cost-efficient manner. This paper reviews the effectiveness of treatments for *H pylori* infection in patients assessed with duodenal ulcer disease. The impact of clinical success on economic effectiveness has been determined in a recent prospective outcomes trial. Treatments with clarithromycin plus omeprazole or clarithromycin plus ranitidine-bismuth-citrate (RBC) provide consistent cure of *H pylori* infection, with eradication rates of 70% to 80%. Recent studies suggest that higher rates of eradication are possible with triple combination therapy (eg, clarithromycin plus a second antibiotic and a proton pump inhibitor or RBC), but the optimal triple therapy regimen (including the combination of drugs, dosage, and duration of treatment) has not yet been defined. A recent 1-year prospective outcomes trial has demonstrated that eradication therapy with clarithromycin and omeprazole, compared with standard antisecretory therapy, provides measurable savings in utilization of ulcer-related health-care resources. Combination therapy with clarithromycin plus omeprazole, clarithromycin plus RBC, or clarithromycin plus lansoprazole and amoxicillin have been approved for the treatment of *H pylori* infection in patients with duodenal ulcer disease. Economic analysis has confirmed that cure of *H pylori* infection not only contributes to the clinical resolution of duodenal ulcer disease, but also provides economic advantages by reducing costs associated with recurrence.

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Helicobacter *pylori* infection is found in 90% to 95% of patients with duodenal ulcer disease, and cure of this infection dramatically reduces ulcer recurrence.¹ Dual therapies with clarithromycin plus omeprazole and clarithromycin plus ranitidine-bismuth-citrate (RBC) are now approved as treatments for duodenal ulcer disease in the United States and many other countries. Regimens using clarithromycin plus omeprazole^{2,4} or clarithromycin plus RBC⁵⁻⁷ have been shown in large, well-controlled clinical trials to provide consistent cure of *H pylori* infection, with eradication rates of 70% to 80%. Recent preliminary studies have also suggested that it may be possible to achieve higher rates of eradication when treatment includes an additional antibiotic (ie, adding amoxicillin or a nitroimidazole to the clarithromycin-omeprazole regimen).⁸⁻¹⁴

The search for effective treatment of *H pylori* infection has also been spurred by the development of economic models which suggest that the rate of eradication is the most important predictor of cost-effective duodenal ulcer disease treatment.¹⁵⁻¹⁹ The results of a recent large, well-controlled, prospective, multicenter outcomes trial²⁰ have confirmed the economic benefits associated with treatment of *H pylori* infection in patients with duodenal ulcer disease. During a 1-year follow-up, initial treatment with clarithromycin plus omeprazole in patients with *H pylori* infection yielded significant economic savings (measured by utilization of healthcare resources and days of work lost to ulcer-related symptoms) compared with initial therapy with omeprazole alone or ranitidine alone.²⁰ These results emphasize the central importance of effective treatment of *H pylori* infection in minimizing the costs of duodenal ulcer disease.

Despite the demonstrated clinical and economic benefits of currently approved therapeutic regimens, there is a lack of consensus regarding the optimal therapy for *H pylori* infection. The purpose of this review is to discuss the progression of therapeutic strategies for treatment of patients infected with *H pylori* and to

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critically evaluate the clinical efficacy of established, as well as newer, combination therapies.

Earlier Therapies for Treatment of *Helicobacter pylori* Infections

Bismuth-based combination therapies that include a nitroimidazole and a second antibiotic are effective treatments for *H pylori* infection; average eradication rates have been reported as 73% in studies using amoxicillin as the second antibiotic, and 82% in studies using tetracycline as the second antibiotic.¹⁴ The clinical efficacy of these regimens can be less than optimal in some patient populations due to several factors, including antibiotic resistance and lack of compliance (which may be related to the difficulty of adhering to complex dosing regimens or to a high incidence of unpleasant side effects). In particular, bismuth-based regimens that include a nitroimidazole (eg, metronidazole or tinidazole) show decreased efficacy against metronidazole-resistant *H pylori*.^{21,22} This has considerable impact on the efficacy of treatment, as metronidazole resistance is widespread and ranges from overall rates of 24% to 40% in the United States and Western Europe to more than 90% in developing countries where nitroimidazoles are routinely used in the treatment of other infectious diseases.^{22,23} Local metronidazole resistance rates may vary widely from overall rates; these variations can result from the demographics of local populations (eg, higher resistance rates among emigrants from Bangladesh in areas of London²³) or from widespread use of antimicrobial therapy with nitroimidazoles in individual communities. Metronidazole resistance may also be higher in smokers, who represent a large proportion of ulcer patients.^{24,25} Bismuth-based triple combination therapies can achieve eradication rates of more than 90% with sensitive organisms, but eradication rates may drop to 30% to 60% with resistant organisms. In addition, the rate of metronidazole resistance is increasing worldwide,²⁶ and this factor must be taken into account before using any newer treatment regimens that include metronidazole or other nitroimidazoles.

Bismuth-based combination therapies may also require the ingestion of 16 pills per day (usually for 2 weeks), and it has proven difficult to reliably achieve high levels of compliance with these complicated regimens in clinical practice. Efficacy depends on compliance²⁷⁻²⁹; for example, in one study,²⁷ eradication of *H pylori* fell from 96% among the patients who took more than 60% of their medication to 69% among the patients who took less than 60% of their medication. It is therefore not possible to predict the efficacy of these therapies in patient populations where compli-

ance is a recognized problem. Higher levels of compliance with some regimens may be obtained by improving patient education or by using combination packaging, which includes all the agents required for a course of *H pylori* eradication therapy. There are also difficulties associated with unpleasant side effects, which most commonly include headache, nausea, or diarrhea in up to 30% of the patients.³⁰ Other side effects may include black stools and black tongue, and there are potential serious interactions between metronidazole and alcohol. Although most of these side effects are not usually categorized as serious, their occurrence may negatively impact compliance and thus contribute to decreased effectiveness of the regimen; it is likely that compliance issues related to side effects are more frequent in the typical clinical setting as compared with clinical trials, in which both physicians and patients are more highly motivated.³¹

Attempts to treat *H pylori* infection with single antibiotics showed some success, but eradication rates were generally low and varied among antibiotics. In controlled trials, treatment with amoxicillin 1 g bid produced at best a 23% eradication rate.³² In contrast, treatment with clarithromycin 500 mg qid for 14 days resulted in a 54% cure rate of *H pylori* infection.³³ The efficacy of clarithromycin was dose dependent, ranging from 15% eradication when administered as 500 mg bid to 36% eradication when administered as 1000 mg bid to 54% eradication when administered as 500 mg qid.

To deal with issues of compliance and metronidazole resistance related to certain bismuth-based therapies and with the low efficacy of antibiotic monotherapy regimens, some subsequent strategies involved regimens that included clarithromycin or amoxicillin and a proton pump inhibitor. Proton pump inhibitors such as omeprazole and lansoprazole relieve symptoms and promote ulcer healing while enhancing the efficacy of some antibiotics against *H pylori*.^{21,39} Antimicrobial activity may be potentiated by any of several mechanisms, at least some of which are likely related to the increase in intragastric pH levels that occurs after treatment with proton pump inhibitors. These effects may include enhanced stability of acid-labile antibiotics or increased activity of certain antibiotics at more neutral pH levels, as well as enhanced immune response of the host to the *H pylori* infection.^{34,35}

Preliminary studies involving treatment of *H pylori* infection with amoxicillin plus omeprazole produced eradication rates of 80% to 85%, but these initial results (from studies carried out primarily in Germany³⁶⁻³⁸) were not reproducible in subsequent trials conducted in other parts of Europe and the United

States.³⁹ Although this combination can successfully deal with issues of compliance and antibiotic resistance, the wide variation in success rates (from 30% to 90%) has limited implementation of this combination. It is still not clear what factors contribute to the variability in the success rate of amoxicillin-omeprazole treatment. Environmental factors such as smoking have been shown to adversely affect efficacy,^{36,40,41} and it is possible that host factors present in certain patient populations may lead to variability in the efficacy of this regimen. The experience with amoxicillin and omeprazole provides a clear precedence for the failure of promising preliminary findings to translate into clinical success among diverse patient populations.

Treatment of *Helicobacter pylori* Infection with Clarithromycin Plus Omeprazole or Ranitidine-Bismuth-Citrate

When administered concurrently, clarithromycin and omeprazole act synergistically to increase the plasma concentrations of both drugs and increase the tissue and mucus concentrations of clarithromycin.⁴² Combination therapy with clarithromycin 500 mg tid for 14 days and omeprazole 40 mg qd for 14 days (followed by omeprazole 20 mg qd for 14 days) has consistently given eradication rates of 70% to 80% and greater than 95% ulcer healing rates in several well-controlled clinical trials in North America and Europe.²⁻⁴ This therapy was well tolerated, and compliance with the regimen was not recognized as a problem.

Therapy with clarithromycin and RBC has also recently proven effective as a treatment for *H pylori* infection, with studies in the United States and Europe showing eradication rates of 70% to 84%. Therapy involves treatment with RBC at 400 mg bid plus clarithromycin 500 mg tid (United States) or 250 mg qid (Europe) for 14 days followed by RBC 400 mg bid for 14 days.⁵⁻⁷ Recently, one European study⁴³ also showed that treatment with RBC 400 mg bid and clarithromycin 500 mg bid was significantly more effective than treatment with RBC 400 mg bid and clarithromycin 250 mg qd (93% eradication vs 84% eradication, based on a per-protocol analysis, $P=0.014$).

Resistance of *H pylori* to clarithromycin has been reported, although overall primary macrolide resistance has been estimated at approximately 4% worldwide.⁴⁴ The rate of resistance to clarithromycin in France has remained steady, at less than 12%, for more than 10 years despite extensive use of macrolides in that country.⁴⁵ A recent study from Ireland reported a statistically nonsignificant increase in the annual primary resistance rate to clarithromycin from 5.3% to 8.6% over the past 3 years,⁴⁶ and a Belgian study

reported macrolide resistance to be stable at 7% from 1993 to 1996.⁴⁷ These studies are representative of worldwide observations which suggest that the rate of primary resistance to macrolides has remained relatively constant and should not be a primary concern when implementing therapy for *H pylori* infection.

Treatment of *Helicobacter pylori* Infection with Clarithromycin, Omeprazole or Lansoprazole, and Amoxicillin or a Nitroimidazole

Use of triple therapy regimens combining two antibiotics with a proton pump inhibitor has gained widespread attention over the past 3 years. Interest in such combination therapy was spurred by Bazzoli et al,⁸ who presented results suggesting that a 1-week treatment with clarithromycin, tinidazole, and omeprazole produced a 95% eradication rate of *H pylori* infection, with negligible side effects. Subsequent to the reported success of this therapeutic strategy, a number of abstracts have suggested that therapeutic regimens including clarithromycin and a proton pump inhibitor in combination with amoxicillin or a nitroimidazole achieve eradication rates against *H pylori* that may exceed 90%.^{9,12,13} Many of these regimens appear promising in preliminary trials. However, the absence of rigor in study design, methods, and data analysis, as well as significant variations in drug combinations, drug dosages, duration and timing of treatment, and entry criteria for trial subjects, leads to difficulty in interpreting the results of many studies. Some trials that included a treatment arm very similar or identical to the original protocol described by Bazzoli et al reported efficacy against *H pylori* that fell short of 95%.^{9,48} It is therefore appropriate to carefully evaluate new approaches to triple combination therapy and compare them with dual therapy before accepting any specific regimen into clinical practice.

One large well-controlled trial involving European patients, the MACH 1 study,¹⁰ reported a 91% eradication rate for *H pylori* (calculated as intent-to-treat) after 1 week of treatment with clarithromycin 500 mg bid, omeprazole 20 mg bid, and amoxicillin 1 g bid. In the same study, a 1-week treatment with clarithromycin 250 mg bid, omeprazole 20 mg bid, and metronidazole 400 mg bid gave 90% eradication of *H pylori* in contrast to 86% eradication using the same regimen with clarithromycin 500 mg bid. These eradication rates were similar, since the confidence intervals for each regimen overlap (with lower confidence limits ranging from 72% to 85%). It is possible that the reported eradication rates represent an overestimate of actual cure of infection, because *H pylori* eradication was evaluated using only the urea breath test; it has recently been

shown that the urea breath test alone (at 1 month post-treatment) can give an elevated estimate of eradication (approximately 7%) relative to the pooled results of two diagnostic tests at the same time point.⁴⁹ The absence of US sites in this multicenter study may also have influenced the results, as prior experiences^{21,39} with clarithromycin-omeprazole and amoxicillin-omeprazole trials suggest that high *H pylori* eradication rates observed in Europe and Canada may not translate to studies in the United States (due to as yet-unexplained host or environmental factors). No well-controlled large studies that include US sites have yet been published.

It is apparent from the preceding discussion that there is as yet no clearly established dosing regimen for clarithromycin that provides optimal results in triple combination therapy. One recent study suggested that, in combination with omeprazole and amoxicillin, clarithromycin 500 mg bid was more effective than clarithromycin 250 mg bid in a 1-week regimen⁹; this was consistent with the original observation regarding clarithromycin monotherapy, which indicated that efficacy in the eradication of *H pylori* infection was dose dependent.³³

The duration of triple combination therapy that provides optimal eradication of *H pylori* also requires adequate assessment. Two recent studies^{11,12} have addressed the efficacy of 7-day versus 10-day versus 14-day therapy with clarithromycin 500 mg bid, omeprazole 20 mg qd or bid, and amoxicillin 1 g bid. The eradication rates after 10 days of treatment ranged from 83% to 88%, although both studies demonstrated a trend toward higher efficacy with longer treatment. However, these studies suffered from a β error: There were too few patients included in each treatment arm to demonstrate a significant difference in efficacy even if such a difference actually existed. Graham et al⁵⁰ have noted that it is necessary to include 286 patients in each treatment group to reliably demonstrate a 10% difference in efficacy between two treatments (at a power of 0.9), emphasizing the importance of study design in trials comparing the efficacy of two or more therapeutic regimens. One recent large, well-controlled, European trial¹³ showed an *H pylori* eradication rate of 90% (calculated as intent-to-treat, and based on *H pylori* analysis by histology, culture, and urea breath test results) after 10 days of treatment with clarithromycin 500 mg bid, omeprazole 20 mg qd, and amoxicillin 1 g bid; this suggests that a 10-day treatment regimen may be effective in some patient populations.

Several recent studies have reported that treatment with lansoprazole, in combination with clarithromycin and amoxicillin, produced *H pylori* eradication rates

ranging from 70% to more than 90%; the eradication rates compared favorably with those obtained with regimens including omeprazole.^{9,13,14} In one recently reported double-blind, multicenter, US study,¹⁴ treatment with clarithromycin 500 mg bid, amoxicillin 1 g bid, and lansoprazole 30 mg bid for 14 days gave 86% cure of *H pylori* infection (calculated as intent-to-treat), based on negative histology and culture test results 4 to 5 weeks after treatment.

Therapeutic strategies for treatment of *H pylori* infection are evolving more quickly than the rate of publication of well-controlled clinical trials. Although it is likely that one or more of the combination therapies now being studied will provide efficient, predictable eradication of *H pylori* infection in patients with duodenal ulcer disease, it is important to effectively compare the results of newer therapies with those of established therapies.

Economic Impact of *Helicobacter pylori* Eradication in Duodenal Ulcer Disease

In today's healthcare environment, it is necessary for therapeutic regimens to be cost-effective as well as efficacious and safe. Several recently published economic models predicted that *H pylori* eradication therapy was cost-effective compared with either intermittent or continuous antisecretory therapy for duodenal ulcer disease. One model predicted up to 10-fold savings over a 15-year period,¹⁵ while other models, projected over periods of up to 5 years, suggested more modest economic benefit.¹⁶⁻¹⁹ In all cases, initial eradication therapy was predicted as the preferable treatment on the basis of cost-effectiveness. The calculation of economic benefit (particularly over long periods of time) can also be impacted by the use of generic as compared with brand-name drugs. Although small economic savings can be realized based on the selection of drugs, dosage, and duration of treatment for *H pylori* eradication therapy, most models indicate that frequency and severity of ulcer recurrence are the principal determinants of costs after treatment of the infection. Within this context, calculations of cost savings are sensitive to factors that influence treatment success, including antibiotic resistance, compliance, and the likelihood of translating success in preliminary studies to success in the clinical setting. For example, one model predicted cost-effectiveness of triple combination therapy only when metronidazole resistance was less than 36% and compliance was greater than 53% in the patient population undergoing treatment.¹⁸

The recent results from a randomized, double-blind, multicenter, prospective, 1-year study²⁰ have

now validated the previously published predictions of models with respect to the positive economic impact of *H pylori* eradication therapy. This study showed that treatment of active duodenal ulcer with clarithromycin and omeprazole resulted in reduced utilization of healthcare resources (both total and ulcer-related) as compared with initial therapy with ranitidine or omeprazole alone. It is particularly noteworthy that the results of this study support the premise that eradication of *H pylori* is crucial for curing duodenal ulcer disease and gaining the economic benefits associated with the long-term prevention of ulcer recurrence.

Selection of Patients for Treatment of *Helicobacter pylori* Infection

There is considerable evidence for the association of *H pylori* infection with both duodenal and gastric ulcer diseases.¹ It is clear that cure of the bacterial infection results in greatly decreased gastroduodenal ulcer recurrence and thereby reduces the risk for ulcer rebleeding. Patients with either active or previously diagnosed gastric or duodenal ulcers, whether associated with gastrointestinal bleeding or not, should be evaluated for the presence of *H pylori* and treatment given to those found to be infected. Rubin et al⁵¹ recently published a decision analysis model in which they evaluated the costs and outcomes associated with several approaches to the management of patients with peptic ulcer disease. They concluded that a management strategy of serologic testing followed by combination antimicrobial/antisecretory therapy for patients found to be infected with *H pylori* was the least expensive baseline option.

Gastric B-cell mucosa-associated lymphoid tissue (MALT) lymphoma is an indolent tumor of the stomach that has been associated with *H pylori* infection. Several investigators have demonstrated that this tumor frequently goes into remission after cure of *H pylori* infection,^{52,53} although the long-term effects on the progression of the disease are not yet clear. On the basis of this evidence, patients with low-grade MALT lymphoma should be screened for *H pylori* infection, and those who have positive results should be treated.

The evidence linking *H pylori* infection to the occurrence and severity of dyspepsia is less compelling, and at this time there is insufficient evidence to support screening and treatment of all patients with these diagnoses. Patients with dyspepsia can certainly be tested for *H pylori* infection on an individual basis, but it is important for the practitioner to be prepared to treat any patients in whom *H pylori* infection is then detected.

... CONCLUSIONS ...

Treatments with clarithromycin and omeprazole or RBC have proven consistently effective for the cure of *H pylori* infection in patients with duodenal ulcer disease.^{2,7} In addition to the clinical benefits of these therapies, a recent 1-year prospective study¹³ has demonstrated that *H pylori* eradication therapy with clarithromycin and omeprazole provides measurable savings in utilization of ulcer-related healthcare resources as compared with standard antisecretory therapy. Cure of *H pylori* infection has now been shown to contribute to the clinical resolution of duodenal ulcer disease and to provide the economic advantages associated with the absence of ulcer recurrence. Newer therapies for treatment of *H pylori* infection, which include clarithromycin and a proton pump inhibitor plus amoxicillin or a nitroimidazole, show promise for improved rates of *H pylori* eradication.

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