Cost-Effectiveness of Abbreviated Regimens for *Helicobacter pylori* Eradication in Peptic Ulcer Disease

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- *Objective:* To compare the cost-effectiveness of abbreviated and conventional regimens for eradicating *Helicobacter pylori* infection in the treatment of peptic ulcer disease (PUD).
- *Design:* Cost-effectiveness analysis.
- *Patients:* Hypothetical cohort of persons with a diagnosis of PUD.
- *Methods:* A decision analytic model using the third-party payer perspective was created. Three abbreviated regimens (lansoprazole, azithromycin, and metronidazole [LAM]; omeprazole, clarithromycin, and metronidazole [OCM]; and bismuth, metronidazole, tetracycline, and omeprazole [BMT-O]) were compared to 3 regimens approved by the Food and Drug Administration (dual therapy with omeprazole and clarithromycin [OC]; triple therapy with lansoprazole, clarithromycin, and amoxicillin [LCA]; and quadruple therapy with bismuth, metronidazole, tetracycline, and famotidine [BMT-H_2RA]). Parameter estimates (compliance, eradication, and ulcer recurrence) were based on published meta-analyses, clinical trials, and review data. Average wholesale price was used for regimen costs. Effectiveness, based upon ulcer cure probability, was estimated using a clinician survey.
- *Measurements:* Expected incremental costs, effectiveness (ulcer cure rate), average cost-effectiveness, and incremental cost-effectiveness.
- *Results:* Expected costs ranged from $157 (BMT-O) to $436 (OC). Effectiveness was high in all regimens, ranging from 83% (OC) to 89% (BMT-O and OCM). BMT-O had the lowest average cost-effectiveness ratio ($176 per ulcer cured), dominating all regimens in incremental analysis. Sensitivity analyses demonstrated LAM's potential to surpass BMT-O in cost-effectiveness following subtle changes in eradication (Δ 3%) and compliance (Δ 7%) rates and average wholesale price (Δ 10%–11%).
- *Conclusions:* Abbreviated *H. pylori* eradication regimens warrant evaluation as potential treatments with effectiveness similar to conventional regimens and possible cost savings.

Helicobacter pylori, a gram-negative, urease-producing organism, is clearly involved in the pathogenesis of peptic ulcer disease (PUD) [1]. Its discovery is considered one of the past decade's most significant events in gastroenterology. Approximately 80% of gastric ulcers and 90% of duodenal ulcers are caused by *H. pylori* [2]. National guidelines now recommend treatment of *H. pylori* infection in the approximately 500,000 to 750,000 persons diagnosed with PUD in the United States each year [2–4]. The annual economic burden attributable to PUD is between $3 billion and $4 billion. Given these costs, value and cost-effectiveness are important considerations in *H. pylori* eradication therapy [3,5]. A number of regimens for eradication of *H. pylori* have been used successfully, and 7 currently exist based on the Food and Drug Administration (FDA)-approved labels in the 2002 *Physicians' Desk Reference* [6].

H. pylori eradication therapy in the United States typically consists of regimens that include combinations of a proton pump inhibitor (PPI) or bismuth preparation with 1 or 2 antibiotics that are taken for 10 days or more. The acceptance of abbreviated regimens in treatment guidelines is limited by the lack of evidence demonstrating eradication rates comparable to 10- to 14-day courses. However, the American College of Gastroenterology (ACG) recognizes bismuth-based triple therapy with the addition of a PPI for 1 week as an acceptable alternative [3].

Seven-day triple therapy consisting of a PPI, a macrolide antibiotic (eg, azithromycin, clarithromycin), and a nitroimidazole (eg, metronidazole, tinidazole) or β-lactam (eg,

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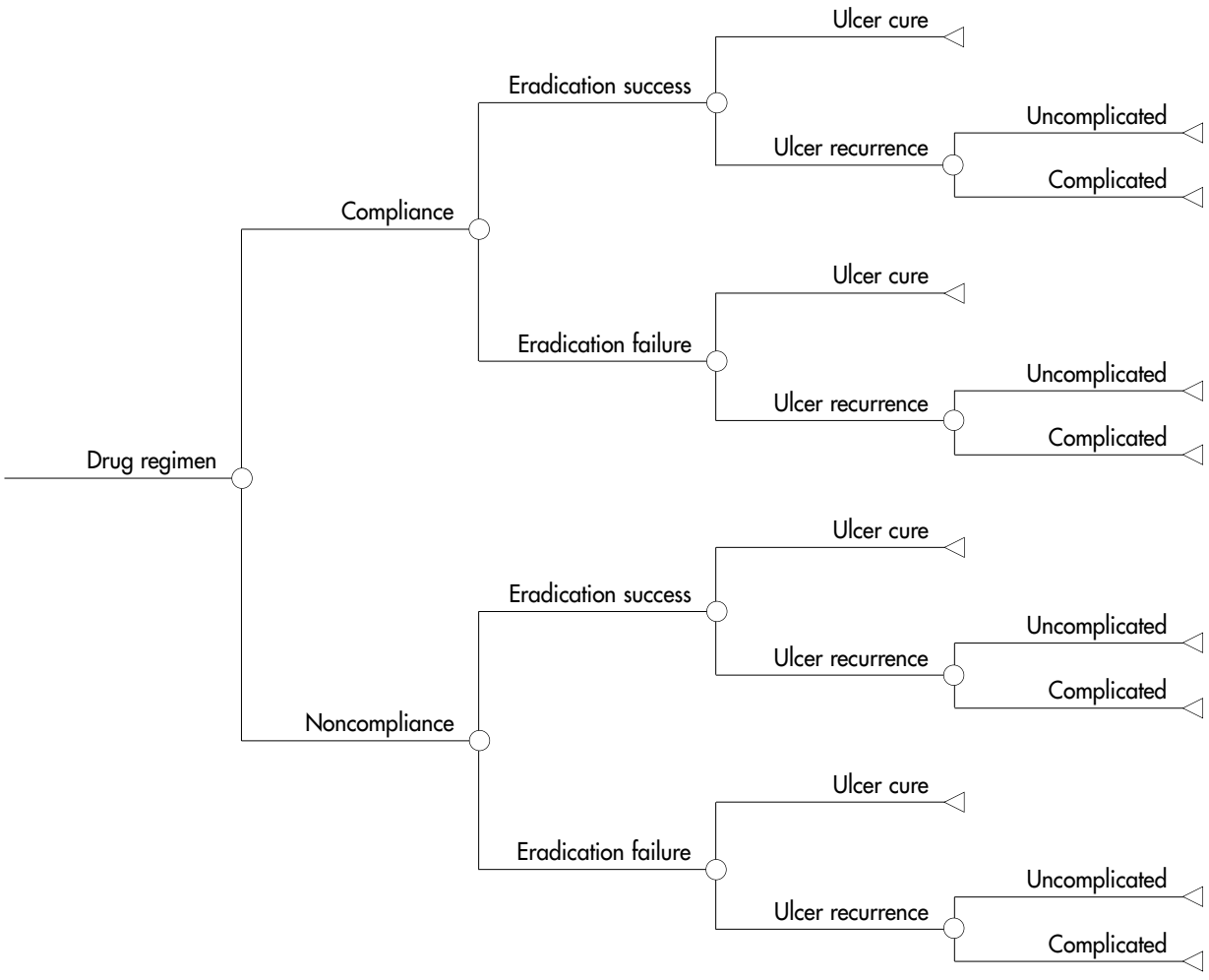

Figure 1. One of the 6 treatment regimen subtrees of the decision analytic tree.

amoxicillin) antibiotic has received increasing attention. A PPI and clarithromycin in combination with a nitroimidazole or β-lactam antibiotic for 7 days has been shown to have acceptable eradication rates (≥ 90% cure rate in per-protocol analysis and ≥ 80% cure rate in intent-to-treat analysis) [3,7]. Similarly, European studies have demonstrated the efficacy of azithromycin in triple-therapy regimens for *H. pylori* eradication. Azithromycin's long serum half-life (60 hours) and prolonged therapeutic concentration after 5 days of therapy offer potential for simplifying and shortening therapy [8]. Azithromycin prescribed for 5 days or less in combination with a PPI and another antibiotic has resulted in encouraging eradication rates [9].

Two reasons for considering abbreviated regimens are compliance and cost. If abbreviated regimens have comparable efficacy, are more acceptable to patients, and are less expensive, then they should be given serious attention. However, the relative cost-effectiveness of regimens of ≤ 7 days has not been established. This analysis evaluates the cost-effectiveness of 3 abbreviated regimens (ie, ≤ 7 days) in comparison with conventional treatments. Dual, triple, and quadruple treatment regimens currently approved by the FDA were chosen for comparison.

Methods

Model

A decision tree was constructed for the comparison of 6 drug regimens (**Figure 1**). A third-party payer perspective was taken. A 6-month time horizon was selected based upon estimates of ulcer recurrence for the period [10]. Each regimen was considered at the initial decision node for patients with definitive *H. pylori* and endoscopic confirmation of PUD. Four successive chance nodes incorporated compliance, eradication, ulcer recurrence, and hospitalization (complicated ulcer recurrence) rates. Pathway costs (treatment regimen, physician fees, and diagnostic tests) and ulcer status (cure,

Table 1. Drug Regimens

Regimen	Duration	Agents: Generic (Trade)	Class	Dosage	No. of Tablets	Cost, $
LAM	3/7 days	Lansoprazole (Prevacid)	Proton-pump inhibitor	30 mg qd x 7 days	19	64
		Azithromycin (Zithromax)	Macrolide antibiotic	500 mg qd x 3 days		
		Metronidazole (Flagyl)	Nitroimidazole antibiotic	250 mg bid x 3 days		
OCM	7 days	Omeprazole (Prilosec)	Proton-pump inhibitor	20 mg bid X 7 days	42	106
		Clarithromycin (Biaxin)	Macrolide antibiotic	500 mg bid x 7 days		
		Metronidazole (Flagyl)	Nitroimidazole antibiotic	500 mg bid x 7 days		
BMT-O	7 days	Bismuth subsalicylate (Pepto-Bismol)	Bismuth compound	525 mg qid x 7 days	119	73
		Metronidazole (Flagyl)	Nitroimidazole antibiotic	500 mg tid x 7 days		
		Tetracycline (Achromycin)	Tetracycline antibiotic	500 mg qid x 7 days		
		Omeprazole (Prilosec)	Proton-pump inhibitor	20 mg bid x 7 days		
OC	14–28 days	Omeprazole (Prilosec)	Proton-pump inhibitor	40 mg x 14 days, then 20 mg qd x 14 days	84	299
		Clarithromycin (Biaxin)	Macrolide antibiotic	500 mg tid x 14 days		
LCA	10 days	Lansoprazole (Prevacid)	Proton-pump inhibitor	30 mg bid x 10 days	60	144
		Clarithromycin (Biaxin)	Macrolide antibiotic	500 mg bid x 10 days		
		Amoxicillin (Amoxil)	β-lactam antibiotic	1000 mg bid x 10 days		
BMT-H_2RA	14–28 days	Bismuth subsalicylate (Pepto-Bismol)	Bismuth compound	525 mg qid x 14 days	252	122
		Metronidazole (Flagyl)	Nitroimidazole antibiotic	250 mg qid x 14 days		
		Tetracycline (Achromycin)	Tetracycline antibiotic	500 mg qid x 14 days		
		Famotidine (Pepcid)	Histamine-2 receptor antagonist	40 mg qhs x 28 days		

Note: Generic forms of metronidazole and amoxicillin were used in calculation of regimen costs. Azithromycin is available as 250-mg tablets, amoxicillin as 500-mg tablets, and Pepto-Bismol as 262-mg tablets. Therefore, 2 tablets of each would be prescribed.

uncomplicated recurrence, and complicated recurrence) were entered at the terminal nodes.

Inputs

Drug regimens. We analyzed 3 abbreviated (≤ 7 days) regimens (lansoprazole, azithromycin, and metronidazole [LAM]; omeprazole, clarithromycin, and metronidazole [OCM]; and bismuth, metronidazole, tetracycline, and omeprazole [BMT-O]) and 3 FDA-approved, conventional (10–28 days) regimens (dual therapy with omeprazole and clarithromycin [OC]; triple therapy with lansoprazole, clarithromycin, and amoxicillin [LCA]; and quadruple therapy with bismuth, metronidazole, tetracycline, and famotidine [BMT-H_2RA]) (**Table 1**).

Probability estimates. Point estimates were based on a MEDLINE database literature search and reference review for the years 1993 to 1999 (**Table 2**). For search criteria, we used a combination of the individual drugs comprising the treatment regimens and the terms "*Helicobacter pylori*" and "peptic ulcer disease." Estimated compliance rates were based on clinical trials evaluating *H. pylori* eradication regimens [11–15]. All trials used pill counts for compliance rates except 1 in which the method was unclear [15]. We defined compliance as the percentage of subjects reported taking ≥ 80% of their medication based on a dichotomy used for defining "poor" compliance [11]. For example, if 90% of the subjects took all of the medication in regimen A and 100% of the subjects took 80% of the medications of regimen B, we estimated compliances rates for regimen A to be 90% and for regimen B to be 100%.

Eradication rate estimates were based on a meta-analysis [5] and supplemented by literature review [7,9]. We assumed the eradication rate for noncompliant individuals would be 66% of the actual estimate based on attenuated eradication rates observed in subjects who were noncompliant with triple therapy [16]. We estimated 6-month ulcer recurrence rates for subjects with and without successful eradication to be 20% and 86%, respectively [10,17]. Last, a 2% hospitalization rate for complicated ulcer recurrence was used [17].

Cost estimates. Drug regimen costs were calculated using 1999 average wholesale price (AWP) [18]. Other costs included the physician fee for a follow-up visit (CPT 99211) and urea

Table 2. Decision Tree Variables and Base-Case Point Estimates

Regimen*	Compliance Rate [11–15]	Eradication Rate [5,7,9,16]		Ulcer Recurrence Rate [10,17]	
		Compliant	Noncompliant	Eradication (+)	Eradication (–)
LAM	100 (50–100)	88 (84–92)	58 (54–62)		
OCM	100 (50–100)	91 (89–93)	60 (58–62)		
BMT-O	91 (50–100)	97 (96–98)	64 (62–66)	20 (15–25)	86 (80–90)
LCA	92 (50–100)	90 (86–94)	59 (54–64)		
OC	92 (50–100)	73 (69–77)	48 (43–53)		
BMT-H_2RA	70 (50–100)	89 (86–92)	59 (57–61)		

Note: Rates are shown as percentages; values in parentheses indicate ranges applied in one-way sensitivity analyses.

*See Table 1 for description of drug regimens.

breath test (CPT 83019) in the event of uncomplicated ulcer recurrence. Here, reimbursement for a follow-up clinic visit ($47), urea breath test ($53), and the cost of 14-day BMT-O therapy ($146) was accrued [3,7]. Physician costs were based upon the Medicare physician fee schedule for 1999 [19]. A one-time cost of $5449 for hospitalization (ICD-9 176) was added in the event of complicated ulcer recurrence. This hospitalization cost was obtained from the Healthcare Cost and Utilization Project's inpatient sample for 1997, the most current year for which cost data were available [20]. A global cost-to-charge ratio of 0.54 obtained from the American Hospital Association was used to convert hospital charge to cost [21]. The cost was then inflated to 1999 dollars using the medical care component of the consumer price index.

Value of outcome estimates. We defined effectiveness in the base case according to the probability of ulcer cure since ulcer-related mortality is rare and ulcer resolution is the treatment goal. In valuing outcomes, we assigned *cure* after initial treatment a value of 1 and *complicated ulcer recurrence* (hospitalization) a value of 0. We estimated the value of *uncomplicated ulcer recurrence* by surveying 15 clinicians (8 general internists and 7 gastroenterologists) using a one-question, visual analog scale to determine the preference-weighted effectiveness for the scenario of uncomplicated ulcer recurrence (failed initial treatment with resolution following re-treatment). This estimation was done because a comparable value was not available in the literature. We assigned uncomplicated ulcer recurrence resolving after 14-day re-treatment with BMT-O a value of 0.57, the mean response.

Analyses

Decision analyses were performed utilizing DATA 3.5 (TreeAge Software, Inc). Expected and incremental cost (in dollars), effectiveness (ulcer cure), average cost-effectiveness ratio (expected cost/effectiveness, ie, the relative efficiency with which a regimen achieves ulcer cure), and incremental cost-effectiveness ratio are reported for each regimen. One-way sensitivity analyses were performed on all base-case probability estimates and costs to evaluate uncertainties in these parameters and to test the robustness of the analysis results. Ranges for sensitivity analyses on eradication estimates were based upon bootstrap standard deviations reported in a probabilistic sensitivity analysis [22]. In additional sensitivity analyses, 50% ranges were used for drug costs and compliance rates, 10% for ulcer recurrence rates, and the survey standard deviation (0.24) for the estimates of uncomplicated ulcer recurrence. For comparison of abbreviated and conventional treatment groups, 9 additional cost-effectiveness analyses were performed after setting the abbreviated and conventional regimen groups at their respective low, base-case, and high eradication estimates.

Assumptions

First, uncomplicated ulcer recurrence resolves with 14-day BMT-O therapy based upon re-treatment recommendations [7]. Treatment concludes with hospitalization for complicated ulcer recurrence. Second, effectiveness acts as a categorical variable based upon cure after initial treatment, one-time re-treatment, or hospitalization. Compliance acts as a dichotomous variable, with the percentage of subjects taking ≥ 80% of their medications being assigned the unadjusted eradication estimate and the remainder the adjusted estimate. Last, we substituted antibiotics/PPIs when exact medications were not represented in trials cited in the calculation of 4 compliance estimates (omeprazole for lansoprazole, metronidazole for tinidazole or amoxicillin, and bismuth subsalicylate for colloidal bismuth subcitrate) and 1 eradication estimate (metronidazole for tinidazole).

Results

Expected Costs and Effectiveness

Abbreviated, 7-day BMT-O had the lowest expected cost at $157 (**Table 3**). Despite having the lowest AWP, LAM had only the second lowest expected cost, $162, with an

Table 3. Cost-Effectiveness Analysis

Regimen*	Expected Cost, $	Incremental Cost, $	Effectiveness, %†	Incremental Effectiveness Ratio	Average Cost-Effectiveness Ratio	Incremental Cost-Effectiveness
BMT-O	157		89		176	
LAM	162	5	88	−1	184	Dominated
OCM	197	40	89	0	221	Dominated
BMT-H_2RA	238	81	85	−4	280	Dominated
LCA	243	86	88	−1	276	Dominated
OC	436	279	83	−6	525	Dominated

*See Table 1 for description of drug regimens.
†Ulcer cure rate.

incremental cost of $5. At $197, OCM had the highest expected cost of the abbreviated regimens. The expected costs of conventional regimens were all greater than those of abbreviated regimens and ranged from $238 (BMT-$H_2$RA) to $436 (OC). While LCA was more effective than the other conventional regimens, its expected cost ($243) was greater than BMT-H_2RA. Comparing the conventional therapies to the BMT-O regimen, incremental costs range from $81 to $279.

Effectiveness was relatively high in all regimens, with estimated ulcer cure rates of at least 83% (Table 3). The most effective regimens were BMT-O and OCM (89%). LAM was nearly as effective (88%) as the other 2 abbreviated regimens. Conventional 10-day LCA was nearly identical in effectiveness (88%) to the abbreviated regimens. BMT-H_2RA and OC were the least effective regimens (85% and 83%, respectively). Effectiveness varied minimally: 1% among the abbreviated regimens, 5% among conventional regimens, and 6% across all regimens.

Cost-Effectiveness Ratios

As BMT-O had the lowest expected cost and tied OCM for highest expected effectiveness, it dominated all other strategies. Also, each of the abbreviated regimens dominated each of the conventional regimens. The cost-effectiveness plot comparing all regimens demonstrates the relative superiority of BMT-O (**Figure 2**). Although LAM's expected cost is nearly identical to BMT-O, its effectiveness is less. Similarly, while OCM therapy is more effective than LAM, it is more costly per treated patient on average. OC's high cost and limited effectiveness results in this regimen's inferiority to not only abbreviated but also conventional treatments. In contrast to effectiveness, expected costs varied significantly (difference of $279 between lowest and highest expected costs).

Cost-Minimization Analysis

In order to conservatively estimate the economic impact of abbreviated regimens, we carried out a cost-minimization analysis with the assumption that the effectiveness of abbreviated and conventional regimens was equal. Cost savings per patient between the BMT-O and LAM abbreviated regimens was only $8. The BMT-O and LAM abbreviated regimens provided some cost savings compared with the OCM regimen ($45 and $37, respectively). However, the costs of all the conventional regimens were considerably greater than all abbreviated regimens. Cost savings per patient comparing abbreviated to conventional regimens ranged from $60 to $349.

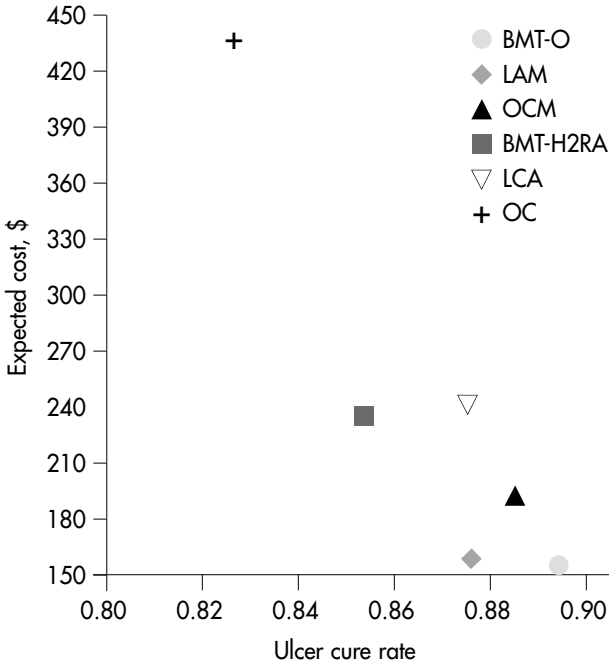

Figure 2. Cost-effectiveness analysis of *H. pylori* treatment options. The 6 treatment regimens are plotted by expected cost ($) versus effectiveness (ulcer cure rate), demonstrating the relative cost-effectiveness of each regimen.

One-way Sensitivity Analyses

Sensitivity analyses were performed on compliance, eradication, and ulcer recurrence rates as well as regimen AWP and the calculated effectiveness preference value. BMT-O lost its dominance over LAM in 3 circumstances: changes in eradication rates, AWP costs, and compliance. First, when LAM's eradication increased to 91% (from 88% baseline), its incremental cost-effectiveness ratio became positive; therefore, LAM was no longer dominated by BMT-O. At the high end of the plausible range of LAM eradication (92%), the incremental cost-effectiveness ratio for LAM versus BMT-O was $729 per additional ulcer cured. Second, a 10% increase in the AWP of BMT-O or an 11% decrease in the AWP of LAM caused BMT-O to lose its dominance; the incremental cost-effectiveness ratio for LAM versus BMT-O becomes $118 per additional ulcer cured. Third, BMT-O lost its dominance over LAM when its compliance decreased from 91% to 84% (LAM versus BMT-O incremental cost-effectiveness ratio is $37 per additional ulcer cured). Only 1 other significant outcome in sensitivity analyses was observed. OCM no longer was dominated by BMT-O when its AWP decreased by nearly 40% to $65 (OCM versus BMT-O incremental cost-effectiveness ratio is $113 per additional ulcer cured). BMT-O dominance and its relative position on the cost-effectiveness plane was otherwise unaffected by varying model parameters within their plausible ranges.

Abbreviated versus Traditional Regimens

We performed 9 additional analyses for comparison of the abbreviated and conventional regimens as groups. Analyses were performed after varying the abbreviated and conventional groups' eradication estimates at their low, base-case, and high values. The abbreviated regimen group remained dominant over the conventional regimen group, although there was variation within the abbreviated group. At the low and base-case estimates for the abbreviated regimens, BMT-O remained dominant. However, when the abbreviated group's eradication estimates were set to their respective high values, LAM equaled BMT-O in average effectiveness. Under no condition did a conventional regimen dominate all of the abbreviated regimens.

Discussion

We evaluated the cost-effectiveness of 3 "abbreviated" treatments for *H. pylori*-associated PUD. The purpose was not to imply superiority or propose the routine prescription of regimens not endorsed by practice guidelines or the FDA but rather to evaluate the utility of several abbreviated regimens being currently considered. We found expected costs to be less for the abbreviated regimens and effectiveness (the probability of ulcer cure) high for all regimens.

While intuitively the AWP of shortened regimens would be less, expected costs and effectiveness are worthy of attention. In cost-effectiveness analysis, expected costs were the result of the effects of regimen compliance, eradication, and ulcer recurrence estimate products upon the AWP. The proportion of the regimens' AWP contributing to the expected costs (AWP/expected cost) ranged from 40% to 67%. Therefore, even small changes in the pathway estimates had notable impact on the overall expected cost.

Effectiveness was high in all regimens (≥ 83%). If effectiveness is comparable among conventional and abbreviated regimens, then abbreviated regimens may become accepted as routine treatment. It should be noted that *effectiveness* calculated in analyses is not equal to *eradication* but rather the estimated probability of ulcer cure. The ACG currently recommends that *H. pylori* treatment regimens used have eradication rates greater than 80% (intention to treat) and 90% (per protocol) [3].

Our compliance estimates (all ≥ 90% except BMT-H_2RA, 70%) are higher than those seen in previous cost-effectiveness analyses. However, estimates cited previously have relied upon professional expertise or disease states requiring chronic prescription (eg, epilepsy) [5,17]. Those estimates may have limited generalizability to acute therapy such as *H. pylori* eradication treatment. Compliance estimates used in this analysis were based upon *H. pylori* regimen trials. Additional studies evaluating *H. pylori* treatment regimens (all less than 14 days) have observed compliance rates exceeding 90% [23–28]. Thus, we feel the estimates used were appropriate. Furthermore, sensitivity analyses performed on compliance rates demonstrated that only BMT-O estimates less than 85% affected the overall cost-effectiveness analysis outcome. It is likely that acceptable compliance with the majority of treatment regimens ≤ 14 days may be obtained. Certainly, if the patient has comorbid conditions requiring additional medications, minimizing the complexity of the regimen chosen would likely have benefit.

Although the BMT-O regimen was dominant in cost-effectiveness, azithromycin-containing triple therapy (LAM) was comparable and perhaps superior to BMT-O in sensitivity analyses. As a newer macrolide antibiotic, azithromycin's potential in combination therapy is encouraging. Azithromycin has been more extensively discussed in the European literature, where it has been declared not only equal to clarithromycin in efficacy but among the first-line treatment constituents [9,29]. One-way sensitivity analyses demonstrated LAM's potential to surpass BMT-O if eradication rates exceeded 91%. Therefore, azithromycin-containing regimens have marked potential for superiority if high eradication rates can be shown.

Among the 3 abbreviated regimens, OCM was limited primarily by the cost of the constituents, specifically omeprazole and clarithromycin. Of the 4 BMT-O constituents, 3 are available generically or over the counter, making this

regimen quite similar in cost to the least costly LAM regimen. Similarly, LCA was limited primarily by costs. While LCA was the most cost-effective of the conventional regimens ($276), prescription of the 14-day unit dose blister pack (Prevpac, AWP = $241) would result in a cost-effectiveness ratio ($386, data not shown) substantially greater than BMT-H_2RA ($280). Therefore, the benefit of using the more costly combination Prevpac form of LCA must be weighed against its higher costs.

Strengths of this analysis include consideration of regimens currently being evaluated in the literature as well as trial-based compliance estimates. In addition, azithromycin-containing regimens were included based upon European data. Few cost-effectiveness analyses or meta-analyses include azithromycin-based regimens. A limitation is the exclusion of adverse effects. However, we feel these are indirectly represented by compliance estimates. Additional cautions include the generalizability of results from controlled trials to the clinical setting and the limitations inherent in meta-analyses and reviews. Last, by nature of decision tree analyses, both compliance and eradication are treated as dichotomous variables when in fact they are likely continuous. We performed sensitivity analyses on both variables in an attempt to consider the impact of this dichotomization.

OC is included in analyses for comparative purposes across a broad range of treatment options. While the FDA approves dual regimens such as OC, their indications are limited and the ACG does not endorse use of dual therapy [3]. In addition, drug resistance was not addressed. Although metronidazole resistance has been more extensively described, resistance to the newer macrolide antibiotics exists. All warrant attention, particularly in the event of failed eradication.

The economic burden imposed by *H. pylori*-associated PUD in the United States is significant. If compliance and eradication rates on a population basis reflect those seen in the trials and meta-analyses, cost savings ranging from nearly $50 million to $250 million yearly may be realized by the use of abbreviated regimens. One may argue that not all diagnosed cases of PUD (approximately 750,000/year) receive treatment and that these savings are liberal. In fact, these estimates may be conservative. It has been suggested that up to 4 million individuals may benefit from *H. pylori* treatment [5].

Conclusions

Seven-day, quadruple therapy (BMT-O) dominated cost-effectiveness analysis of *H. pylori* eradication in PUD. An azithromycin-containing regimen (LAM) was comparable with lower AWP and regimen duration/tablet number. Abbreviated regimens have the potential for better compliance and lower costs. If they have eradication rates similar to those of conventional regimens, substantial cost savings may be gained by their use. The promise of abbreviated regimens warrants the undertaking of U.S.-based clinical trials evaluating LAM, OCM, BMT-O, and other abbreviated regimens that may become available to assess compliance, eradication, and ulcer recurrence rates. As *H. pylori* treatment options evolve rapidly, attention to the advantages of abbreviated regimens is warranted.

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