Cost effectiveness of alternative *Helicobacter pylori* eradication strategies in the management of duodenal ulcer

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B O'Brien, R Goeree, R Hunt, J Wilkinson, M Levine, A William. Cost effectiveness of alternative *Helicobacter pylori* eradication strategies in the management of duodenal ulcer. Can J Gastroenterol 1997;11(4):323-331. Published data and techniques for decision analysis were used to construct a model to estimate the cost effectiveness of nine alternative strategies for the management of patients diagnosed with uncomplicated duodenal ulcer. Two strategies of intermittent therapy with either ranitidine or omeprazole, one strategy of continuous maintenance treatment with ranitidine, and six strategies for ulcer healing and eradication of *Helicobacter pylori* infection were considered. Healing time curves were estimated by using published data, allowing for estimation of expected time for acute healing episodes. The expected number of weeks to heal per patient, in a one-year period, was estimated by combining healing time data with probability of ulcer recurrence. It was found that patients that underwent any of the six *H pylori* eradication regimens had fewer days with ulcer per year than those who underwent maintenance or intermittent ranitidine. Four eradication regimens had lower costs and better outcomes than ranitidine therapy. In comparing *H pylori* strategies, the two strategies of omeprazole plus one antibiotic (either amoxicillin or clarithromycin) are more costly than omeprazole plus two antibiotics (specifically amoxicillin and metronidazole or clarithromycin and metronidazole) and result in similar outcomes. Although omeprazole-based eradication regimens are more costly than ranitidine bismuth triple therapy, they are associated with fewer recurrences of ulcer and days of symptoms. A limitation of the analysis is that it did not incorporate issues of compliance and metronidazole resistance; however, the former concern may be less of an issue as *H pylori* regimens become simpler and shorter in duration.

Key Words: *Duodenal ulcer*, Helicobacter pylori, *Omeprazole*, *Ranitidine*

Analyse coût-efficacité d'une stratégie alternative d'éradication d'*Helicobacter pylori* en traitement de l'ulcère duodénal

RÉSUMÉ : Sur la base de données publiées et de techniques et d'analyses décisionnelles, un modèle a été construit pour analyser les rapports coût-efficacité de neuf stratégies thérapeutiques à l'intention de patients souffrant de l'ulcère duodénal non compliqué. Deux stratégies de traitement intermittent avec de la ranitidine ou de l'oméprazole, une stratégie de traitement continu à la ranitidine et six stratégies pour la guérison de l'ulcère et l'éradication d'*Helicobacter pylori* ont été envisagées. Les courbes de temps de guérison ont été calculées à l'aide des données publiées permettant une estimation du temps prévisible de guérison des épisodes aigus. Le nombre prévu de semaines de cicatrisation par patient sur une période d'un an a été calculé en combinant les données sur le temps de guérison et la probabilité de la récurrence d'ulcères. On a découvert que les patients qui prenaient l'un des six traitements d'éradication d'*H. pylori* présentaient un nombre de jours par année avec ulcère moindre que ceux qui prenaient un traitement d'entretien ou un traitement intermittent à la ranitidine. Quatre schémas d'éradication se sont révélés moins coûteux et leurs résultats, meilleurs qu'avec la ranitidine. En comparant les stratégies anti-*H. pylori*, on note que les deux stratégies à l'oméprazole plus un antibiotique (soit amoxicilline ou clarithromycine), sont plus coûteuses que l'oméprazole plus deux antibiotiques (précisément amoxicilline et métronidazole ou clarithromycine et métronidazole) et donnent des résultats semblables. Bien que les schémas d'éradication à base d'oméprazole soient plus coûteux que la trithérapie à la ranitidine et au bismuth, ils sont associés à un nombre moindre de récurrences de l'ulcère et de journées symptomatiques. Une lacune de l'analyse est qu'elle n'incorpore pas les problèmes de fidélité au traitement et de résistance au métronidazole. Toutefois, la question de la résistance revêt moins d'importance, puisque les schémas anti-*H. pylori* se simplifient et s'abrègent constamment.

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The association between gastric *Helicobacter pylori* infection and peptic ulcer disease (PUD) is well established (1) and many studies have shown that eradication of *H pylori* infection with various antimicrobial agents reduces ulcer recurrence (2,3). This has important implications for long term clinical management of PUD because traditional emphasis has been on acid suppressing drug therapy such as H_2 receptor antagonists (H_2RAs) (eg, ranitidine) and, more recently, proton pump inhibitors (PPIs) such as omeprazole. A recent consensus conference of the United States National Institutes of Health (NIH) noted that "nearly all patients with duodenal ulcer have *H pylori*" and that the association with gastric ulcer is "only slightly less strong". The NIH panel recommended treatment with antimicrobial agents for PUD patients with *H pylori* in addition to antisecretory drugs, whether on first presentation with the illness or on recurrence (4). Despite concerns about the cost implications of acid suppressing drug therapy in a chronic recurrent disease such as PUD (5), the economic implications of *H pylori* eradication compared with alternative drug therapies such as omeprazole have received little research attention.

Growing pressure on limited drug budgets forces provincial formularies to face difficult decisions about formulary listing of new, more effective but higher priced drugs. Economic evaluation offers a way to synthesize the available data on costs and outcomes associated with alternative treatment strategies so that formulary decisions can be based on the best evidence regarding value for money.

In this paper, we summarize a project commissioned by the Canadian Coordinating Office of Health Technology Assessment (CCOHTA), investigating the economics of drug treatment for PUD and reflux disease. Details of methods and results are available elsewhere (6).

A BRIEF LITERATURE REVIEW

One of the earliest applications of economic appraisal to ulcer therapy was by Culyer and Maynard (7) who demonstrated the cost advantages of cimetidine over surgery in duodenal ulcer (DU). Much of the contemporary research has focused on comparisons between intermittent or maintenance therapy and H_2RA and omeprazole. More recently, these comparisons have also included combination antibiotic regimens to eradicate *H pylori*. For example, Jonsson et al (8) compared strategies of intermittent ranitidine versus omeprazole in the United Kingdom, including both direct and indirect costs (ie, value of time lost from work), and found that omeprazole therapy resulted in fewer symptomatic days and was lower in cost, over either a one-year or five-year period in most model assumptions. Sintonen and Alander (9) reached a similar conclusion from a study in Finland. Walan and Eriksson (10), using only direct health care costs, found that omeprazole therapy resulted in fewer day of symptoms and lower overall cost than H_2RA.

Following the NIH Consensus Conference on *H pylori* (4) a number of studies have examined the costs and outcomes of antibiotic therapy to eradicate *H pylori* as an alternative to either intermittent or maintenance acid suppression with an H_2RA or PPI. For example, Sonnenberg and Townsend (11) used a Markov model over 15 years to demonstrate that a combined strategy of healing the ulcer with H_2RA and eradicating *H pylori* with antibiotics is superior (lower cost and less time with ulcer symptoms) to maintenance or intermittent acid suppression with an H_2RA or vagotomy. Similarly, using a decision analysis model, Imperiale et al (12) concluded that treatment with H_2RA and bismuth triple therapy is less costly and more effective than treatment with an H_2RA alone. Unge et al (13), in a modeling analysis from Sweden over five years, compared treatment of duodenal ulcer with either omeprazole or an *H pylori* eradication regimen of omeprazole plus amoxicillin, and concluded that, despite higher initial costs, the eradication strategy is less costly and more effective than acid suppression alone.

Our own previous work (14) structured the economic problem as a comparison among three global treatment strategies for DU that were unrelated to nonsteroidal anti-inflammatory drug use: intermittent acid suppression (H_2RA or PPI); maintenance acid suppression (H_2RA); or *H pylori* eradication with either H_2RA and bismuth triple therapy or omeprazole plus amoxicillin. It was concluded that eradication strategies were least costly and most effective (fewer symptomatic recurrences); however, there was insufficient evidence to determine which of the *H pylori* regimens offered best value for money.

In 1995 we were commissioned by the CCOHTA, a federal/provincial government agency, to further develop our model to evaluate a number of different *H pylori* strategies. This paper summarizes our findings.

STUDY OBJECTIVES

Three global therapeutic strategies for the management of uncomplicated PUD were compared, and a number of therapeutic permutations were nested within each strategy for comparison. Details of doses and duration for each strategy are summarized in Tables 1 and 2. The chosen set of comparators enabled comparison of broad treatment strategies such as intermittent versus maintenance acid suppression and *H pylori* eradication, but also permitted comparison of costs and outcomes among various *H pylori* eradication regimens.

MATERIALS AND METHODS

Overview of analytic approach: There are three key components to understanding the analytic approach. First is the structuring of the therapeutic decision problem in terms of principles of clinical decision analysis. This is a conventional approach to clinical economic modeling (15), which structures relevant strategies, clinical events and costs using a decision tree. Expected costs and outcomes were calculated by determining the probabilities of relevant clinical events (ie, ulcer healing rates, ulcer recurrence rates, *H pylori* eradication rates) using principles of quantitative literature review or meta-analysis. Search criteria were identified for retrieval of relevant published studies, and pooled rates of events reported in the studies were estimated for inclusion in the

TABLE 1
Therapeutic strategies for patients with uncomplicated duodenal ulcer

'A' strategies: Heal ulcer and wait for recurrence	'B' strategy: Heal ulcer and start maintenance with H_2 receptor antagonist	'C' strategies: Heal ulcer and eradicate *Helicobacter pylori*
• A_1: Heal with ranitidine (150 mg bid, 8 weeks). No further treatment until ulcer recurrence, then heal with ranitidine (150 mg bid, 8 weeks)	• B_1: Heal ulcer with ranitidine (150 mg bid, 8 weeks) followed by continuous maintenance therapy with half-dose (150 mg/day) ranitidine. Recurrences treated with full-dose ranitidine (150 mg bid, 8 weeks)	• C_1: *H pylori* eradication with omeprazole and amoxicillin
• A_2: Heal ulcer with omeprazole (20 mg/day, 28 days). No further treatment until ulcer recurrence, then heal with omeprazole (20 mg/day, 28 days)		• C_2: *H pylori* eradication with omeprazole and clarithromycin
		• C_3: *H pylori* eradication with omeprazole, metronidazole and amoxicillin
		• C_4: *H pylori* eradication with omeprazole, amoxicillin and clarithromycin
		• C_5: *H pylori* eradication with omeprazole and clarithromycin and metronidazole
		• C_6: *H pylori* eradication with ranitidine and triple therapy

model. Finally, principles of cost effectiveness analysis were used to compare treatment strategies, and sensitivity analysis was used to explore key areas of uncertainty.

The viewpoint of this study is that of a governmental third-party payer for health care (ie, a provincial ministry of health) in Canada. Much of the cost information came from sources in the province of Ontario. Costs are reported in Canadian dollars from 1995.

Decision analysis model: Treatment alternatives are given in Tables 1 and 2 and are presented as a decision tree in Figure 1. A patient was diagnosed (by endoscopy) with uncomplicated DU, and the spectrum of treatment options was simplified into the three global strategies (Table 1).

Patients entering the model had confirmed and uncomplicated DU, which was necessary for two reasons. First, clinical data on the efficacy of alternative treatments for long term management of DU were from populations with diagnosed DU. It is recognized that, ideally, data on treatment effectiveness should be available on patients with dyspepsia indicative of ulcer, but such data are typically not available. Second, because the presence of DU on endoscopy is a highly sensitive and specific indicator of *H pylori* infection (2), our model did not involve additional diagnostic testing for the presence of *H pylori* or testing to confirm eradication. Therefore, this model addressed the question: "given that a patient has DU, what is the cost effectiveness of alternative clinical strategies?"

Expected costs and outcomes per patient were calculated for each therapeutic strategy, where 'expected' refers to a sum of items weighted by their probability of occurrence. Hence, the authors wished to capture both the 'up-front' costs of initial drug therapy (but excluding confirming endoscopy, which is common to all strategies) and any 'downstream' costs from management of ulcer recurrence in the 12-month interval. The model structure was simple because it was recursive in two six-month periods. Hence, probability of recurrence in the 12-month period was conditional upon recurrence or nonrecurrence in the first six months.

TABLE 2
***Helicobacter pylori* eradication regimens in 'C' strategies**

Regimen	Drugs	Dose	Days (range)
C_1	Omeprazole	20 mg bid	1-14
	Amoxicillin	1 g bid	1-14
	Omeprazole	20 mg/day	14-28
C_2	Omeprazole	20 mg bid	1-14
	Clarithromycin	500 mg tid	1-14
	Omeprazole	20 mg/day	14-28
C_3	Omeprazole	20 mg bid	1-14
	Metronidazole	500 mg bid	1-7
	Amoxicillin	1 g bid	1-7
	Omeprazole	20 mg/day	14-28
C_4	Omeprazole	20 mg bid	1-14
	Amoxicillin	1 g bid	1-7
	Clarithromycin	500 mg bid	1-7
	Omeprazole	20 mg/day	14-28
C_5	Omeprazole	20 mg bid	1-14
	Clarithromycin	500 mg bid	1-7
	Metronidazole	500 mg bid	1-7
	Omeprazole	20 mg/day	14-28
C_6	Ranitidine	150 mg bid	1-56
	Bismuth subsalicylate	151 mg qid	42-56
	Metronidazole	250 mg qid	42-56
	Tetracycline	500 mg qid	42-56

Outcome measures: Primary outcome of the model was time free from ulcer during the 12-month period. Data were pooled from ulcer healing trials for each regimen to estimate healing time curves. MEDLINE and other sources were searched to find randomized controlled trials in adults whose DU (larger than 5 mm diameter healing was determined by endoscopy at set intervals (eg, four weeks, eight weeks). Estimation of the area under the healing curve yields information on expected

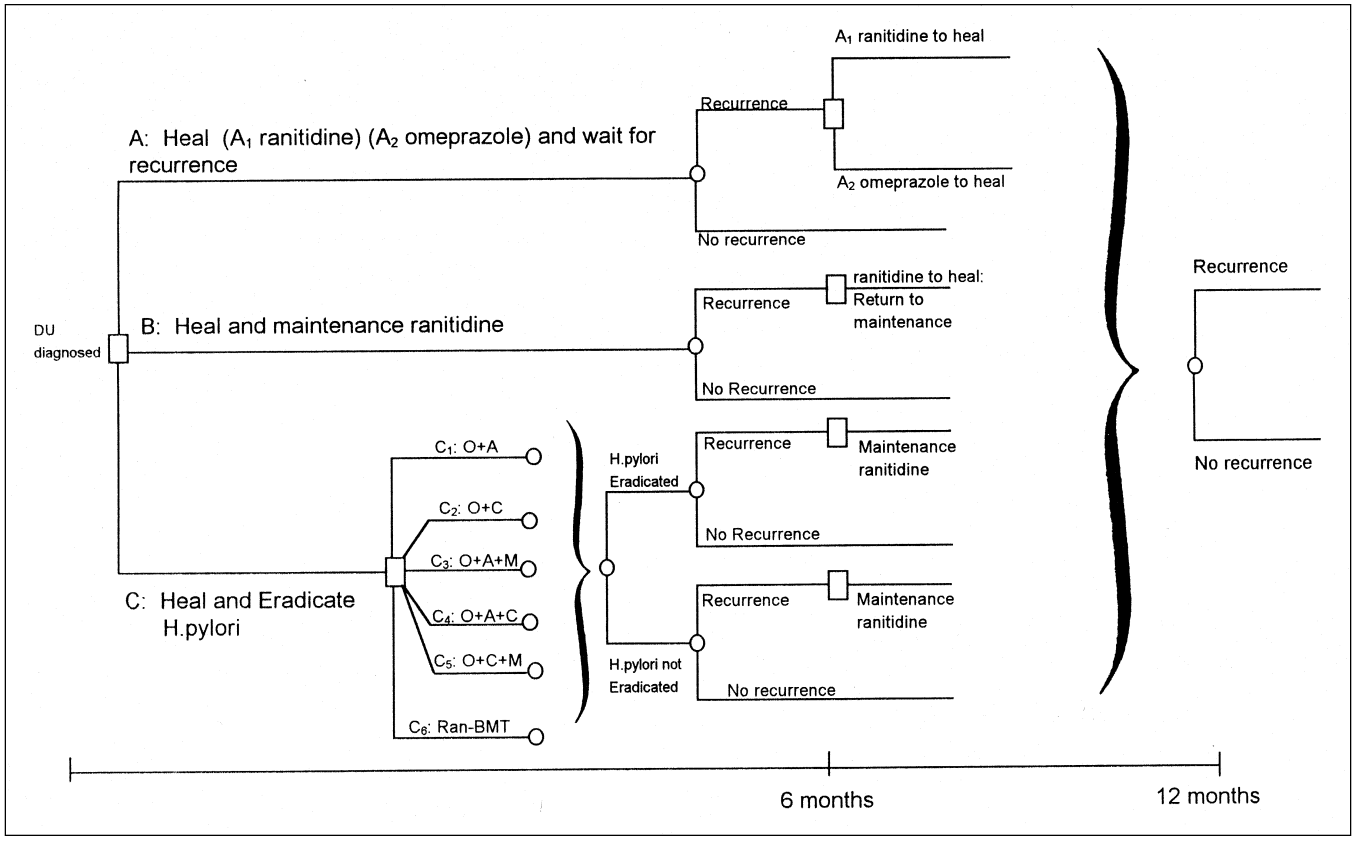

Figure 1) *Decision tree for management of persons with confirmed duodenal ulcer (DU). A Amoxixillin; BMT Bismuth subsalicylate, metronidazole and tetracycline; C Clarithromycin; M Metronidazole; O Omeprazole; Ran Ranitidine*

TABLE 3
Unit prices for pharmaceuticals, excluding dispensing fee

Drug	Dose (mg)	Cost per dose (CDN$)
Ranitidine (generic)	150	0.45*
Ranitidine (Zantac; Glaxo Wellcome)	150	1.20†
Cimetidine (generic)	400	0.15* (1)
Cimetidine (Tagamet; SmithKline Beecham)	400	0.64† (2)
Omeprazole (Losec; Astra)	20	2.57† (2)
Bismuth (Pepto-Bismol; Proctor & Gamble)	151	0.21† (2)
Amoxicillin (generic)	500	0.21* (1)
Amoxicillin (Amoxil; Wyeth-Ayerst)	500	0.41† (2)
Clarithromycin (Biaxin; Abbott)	500	3.57† (2)
Metronidazole (generic)	250	0.03* (1)
Metronidazole (Flagyl; Rhône-Poulenc Rorer)	250	0.05† (2)
Tetracycline (generic)	250	0.02* (1)
Tetracycline (Achromycin; Wyeth-Ayerst)	250	0.05* (2)

*Sources: *Ontario Drug Benefit Plan, plus 10% pharmacy upcharge; †Survey of local pharmacies*

time without (and with) ulcer during the acute healing treatment period. To determine total expected ulcer time over the period of the model, the duration healing of each acute ulcer was further weighted by the probability of ulcer recurrence (and retreatment) over the 12-month period, which varied among regimens.

Costs: The primary source of drug price information for this study was Best Available Price from the Ontario Drug Benefit (ODB) Plan with a 10% pharmacy up-charge. For drugs such as omeprazole that are a nonformulary benefit and do not have the best available price on ODB, a small survey of local pharmacies was conducted to determine cost. These unit prices are presented in Table 3, and Table 4 shows the estimated costs for the regimens that were analyzed in this model. For example, an eight-week course of ranitidine, 150 mg bid, was $50.40 and a four-week supply of omeprazole, 20 mg per day, was $71.96. Drug costs are also presented for *H pylori* eradication strategies. These range from ranitidine plus triple therapy ($66.08) to omeprazole plus clarithromycin for two weeks ($257.88).

Information on clinical practice patterns and resource use (eg, diagnostic test ordering) and the prices of these resources were required to estimate costs associated with management of patients with symptoms of ulcer recurrence. No published data were available on how physicians manage ulcer recurrence in Canada. The authors therefore used data from the previous study, based on estimates by an expert phy-

TABLE 4
Costs of drug regimens used in the model, excluding dispensing fee

Regimen	Cost (CDN$)
Maintenance and intermittent acid suppression:	
• ranitidine (150 mg/day)	0.45 per day
• ranitidine (150 mg bid for eight weeks)	50.40
• omeprazole (20 mg/ day for 28 days)	71.96
Drug costs for eradication by strategy:	
• omeprazole + amoxicillin (omeprazole 20 mg bid for 14 days; amoxicillin 1 g bid for 14 days) + omeprazole 20 mg/day for 14 days	119.70
• omeprazole + clarithromycin (omeprazole 20 mg bid for 14 days; clarithromycin 500 mg tid for 14 days) + omeprazole 20 mg/day for 14 days	257.88
• omeprazole + amoxicillin + metronidazole (omeprazole 20 mg bid for 14 days; amoxicillin 1 g bid [500 mg x 2] for seven days; metronidazole 500 mg bid [250 mg x 2] for seven days) + omeprazole 20 mg/day for 14 days	114.66
• omeprazole + clarithromycin + metronidazole (omeprazole 20 mg bid for 14 days; clarithromycin 500 mg bid for seven days; metronidazole 500 mg bid [250 mg x 2] for seven days) + omeprazole 20 mg per day for 14 days	158.76
• omeprazole + amoxicillin + clarithromycin (omeprazole 20 mg bid for 14 days; amoxicillin 1 g [500 x 2 bid] for seven days; clarithromycin 500 mg bid for seven days) + omeprazole 20 mg/day for 14 days	163.80
• H_2 receptor antagonist triple therapy (ranitidine 150 mg bid for 56 days; bismuth 151 mg qid for 14 days; 250 mg metronidazole qid for 14 days; 500 mg tetracycline qid [250 x 2] for 14 days	66.08

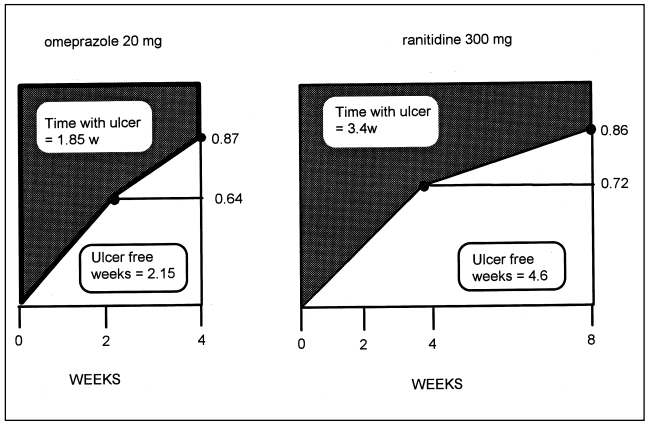

Figure 2) *Ulcer healing curves and time with ulcer (shaded area) for eight-week ranitidine regimen and four-week omeprazole regimen*

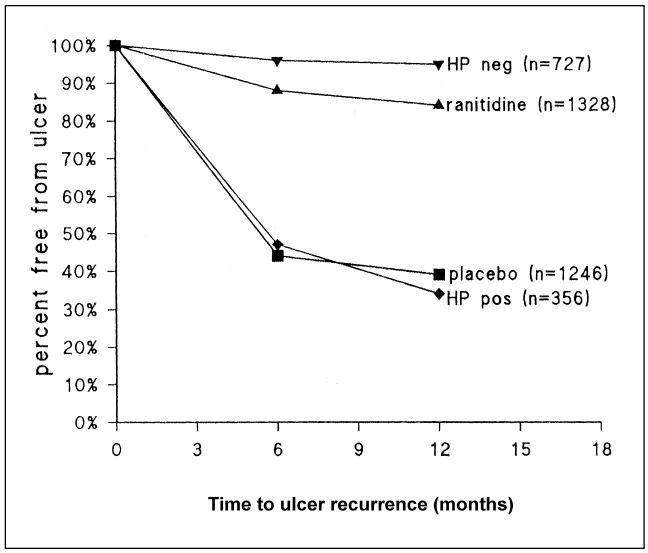

Figure 3) *Time to ulcer recurrence. HP neg* Helicobacter pylori *negative; HP pos* H pylori *positive*

sician panel (four gastroenterologists, two family doctors), and used a modified Delphi technique (16) to derive estimates and ranges of the percentage likelihood and volume of various services used when patients present with symptoms of ulcer recurrence. The panel was first mailed a questionnaire on resource use, based on a written scenario of DU recurrence, and then brought together in committee to discuss their estimates. The main focus was on the likelihood of use of expensive investigations such as urea breath test, upper gastrointestinal series or endoscopy.

In Ontario, hospitals receive global budgets, and physician services are reimbursed by the government health insurance plan on a fee-per-item-of-service basis. Prices (combined hospital and physician service costs) for procedures such as upper gastrointestinal endoscopy were estimated from two sources: a corporate cost model for Chedoke-McMaster hospitals in Hamilton, Ontario, which relates workload units assigned to procedures for managerial purposes (17-19) to hospital expenditures; and the physician fee schedule for Ontario (20), which itemizes allowable physician reimbursement by procedure under the provincial health insurance plan.

RESULTS

Ulcer healing probabilities: The authors found 26 ranitidine trials, either 150 mg bid or 300 mg per day, with 2641 patients of whom 1895 (72%) were healed at four weeks and 2278 (86%) by eight weeks. They found 24 omeprazole trials, 20 mg per day, reporting on 2633 patients of whom 1688 (64%) were healed at two weeks, and 2286 (87%) were healed at

TABLE 5
***Helicobacter pylori* eradication rates**

Regimen	Drug	Eradication rate (%)	Range for sensitivity analysis*	Source reference
C_1	Omeprazole and amoxicillin	61%	57-66	22
C_2	Omeprazole and clarithromycin			22
C_3	Omeprazole, metronidazole and amoxicillin	84%	79-90	22
C_4	Omeprazole, amoxicillin and clarithromycin	85%	75-96	22
C_5	Omeprazole, clarithromycin and metronidazole	91%	88-94	22
C_6	Ranitidine, bismuth subsalicylate, metronidazole and tetracycline	86%	80-92	23-25

**Range is 95% CI for C_1 to C_5 (22)*

TABLE 6
Expected cost, ulcer recurrences and weeks with ulcer: Base case

Strategy	Expected one-year cost per patient (CDN $)	Symptomatic ulcer recurrences per 100 patients	Expected weeks with ulcer per patient in one year
A: Heal and wait, treat duodenal ulcer recurrence with			
• A_1: ranitidine	306	69	5.7
• A_2: omeprazole	343	69	3.1
B: Heal and continuous maintenance with ranitidine	353	18	4.0
C: Heal and *Helicobacter pylori* eradication with			
• C_1: omeprazole and amoxicillin	387	28	2.4
• C_2: omeprazole and clarithromycin	482	22	2.3
• C_3: omeprazole, amoxicillin and metronidazole	292	14	2.1
• C_4: omeprazole, amoxicillin and clarithromycin	337	13	2.1
• C_5: omeprazole, clarithromycin and metronidazole	306	10	2.0
• C_6: ranitidine, bismuth subsalicylate, metronidazole and tetracycline	228	12	3.8

four weeks. Study curves and calculated expected time with and without ulcer are presented (Figure 2) to illustrate the distribution of healing time curves for regimens.

Ulcer recurrence probabilities: Using similar techniques for the quantitative summary of literature reviewed, the authors estimated rates of ulcer recurrence at six and 12 months. Ulcer recurrence probabilities are illustrated as a life table in Figure 3. There was a 56% rate of ulcer recurrence at six months in the placebo group compared with a 12% rate of recurrence in patients receiving continuous maintenance ranitidine. Patients who were positive for *H pylori* had a recurrence rate of 53%, similar to that of the placebo group. Endoscopically determined recurrence data, based on information from the literature on the proportion of symptomatic:asymptomatic recurrences, were adjusted for use in the model. Accordingly, an adjustment factor of 0.75 was used because 75% of ulcer recurrence is by endoscopy or symptomatic (for details see the authors' report [6]).

Time with ulcer per healing episode: Analysis of the area under the curve, for ranitidine and omeprazole, required to estimate time with and without ulcer per healing regimen is presented in Figure 2. Hence, of four weeks' treatment with omeprazole (20 mg), 2.15 were ulcer-free weeks. Eight weeks of ranitidine therapy (300 mg) yields four to six ulcer-free weeks.

***H pylori* eradication probabilities:** *H pylori* eradication rates were based on a recent meta-analysis by Chiba et al (21). This meta-analysis was based on a MEDLINE search for papers and abstracts reporting *H pylori* eradication rates for a number of the omeprazole combination regimens in this study. The meta-analysis was a per-protocol analysis of the number eradicated per number treated when assessed at four weeks posteradication therapy. Data from that study are presented in Table 5. For bismuth triple therapy, estimates vary (90%[22], 84%[23] and 89%[24]) so for the present study, a rate of 86% was assumed for the base case.

Cost effectiveness: Expected one-year cost per patient, symptomatic ulcer recurrences per 100 patients and expected weeks with ulcer per patient in one year are presented for each of the nine strategies (Table 6). These data indicate that both intermittent ranitidine and intermittent omeprazole have higher rates of symptomatic ulcer recurrence (69 per

100 patients) than other strategies. However, because the speed of healing was greater with omeprazole, the expected weeks with ulcer per patient in the one-year period was lower with intermittent omeprazole (3.1 weeks) than with intermittent ranitidine (5.7 weeks). Similarly, although continuous maintenance ranitidine results in a lower rate of symptomatic ulcer recurrence (18 per 100 patients), it is associated with four weeks of ulcer per patient in a one-year period because, when calculating expected ulcer duration, the lower recurrence rate is partially offset by slower healing time. All of the omeprazole-based *H pylori* eradication strategies were associated with approximately two weeks of ulcer per patient in a one-year period. In contrast, the time with ulcer is greater with ranitidine plus bismuth triple therapy as a *H pylori* regimen because of the longer duration of this regimen and the slower healing time associated with ranitidine.

When the costs of alternative regimens were considered, the six *H pylori* eradication strategies contained both the least costly strategy, ranitidine bismuth triple therapy (C_6) ($228), and the most costly regimen, omeprazole plus clarithromycin (C_2) ($482). The relatively high cost of the C_2 regimen is largely explained by the need to use brand name clarithromycin (Biaxin, Abbott) three times daily.

When costs and outcomes were considered together, it was apparent that strategies C_3 (omeprazole, amoxicillin and metronidazole) and C_5 (omeprazole, clarithromycin and metronidazole) were better than intermittent strategies (A_1 and A_2) and continuous maintenance ranitidine, having both lower costs and greater outcomes with fewer weeks of ulcer in a one-year period. For other *H pylori* regimens such as omeprazole with amoxicillin (C_1) or (C_2), there was a tradeoff because, relative to regimens such as intermittent or continuous maintenance ranitidine, these strategies offered better outcomes but at a higher cost.

To understand better the cost and outcome relationships among the alternatives, it was helpful to organize this information graphically. Figure 4 presents data on costs and expected weeks with ulcer per year using continuous maintenance ranitidine (B_1) as reference point (ie, every other point is presented relative to strategy B_1). It is clear that points lying above and to the left of B_1 at the origin (A_2, C_4, C_5, C_3 and C_6) offer increased effectiveness at reduced cost. All these strategies offer a definite improvement over maintenance ranitidine because they offer better outcome at a lower cost.

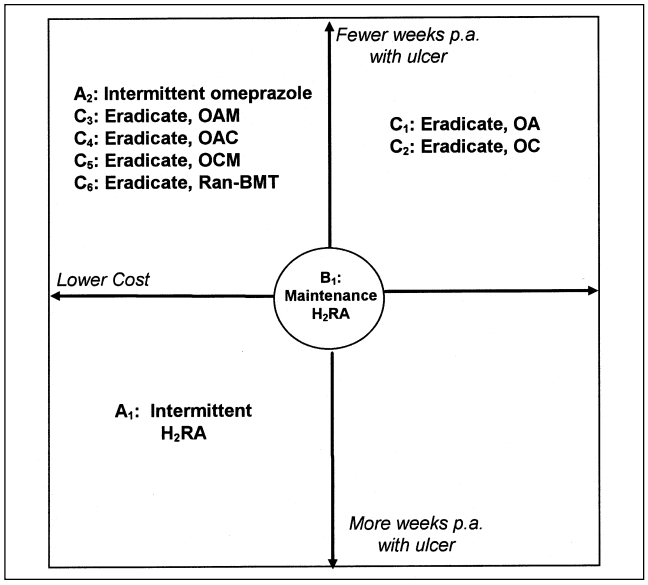

Figure 4) *Dominance and tradeoffs for all strategies relative to continuous maintenance ranitidine (B1). A Amoxicillin; C Clarithromycin; H_2RA H_2 receptor antagonists; M Metronidazole; O Omeprazole; pa Per annum; Ran Ranitidine*

DISCUSSION

We found that, relative to continuous maintenance therapy with ranitidine, intermittent omeprazole (A_2) and four of the *H pylori* eradication strategies (C_3, C_4, C_5, C_6) were all effective, having lower expected one-year costs with fewer weeks of ulcer in the one-year period. It was also found that intermittent ranitidine therapy had a lower cost, but was associated with more weeks of ulcer in the year, than continuous maintenance ranitidine. Finally, relative to the reference strategy (B_1), it was found that two of the *H pylori* eradication strategies (C_1 and C_2) offered a better outcome but at a higher cost. Therefore, the first general conclusion is that all of the *H pylori* eradication regimens offer better outcomes than either intermittent or maintenance ranitidine. However, there is differentiation between eradication regimens with respect to cost, with the combination of omeprazole with either amoxicillin or clarithromycin being the more costly eradication regimen.

In comparing *H pylori* eradication strategies, incremental cost effectiveness relative to ranitidine bismuth triple therapy was calculated. This analysis revealed that, among the eradication strategies, C_3 (omeprazole, amoxicillin, metronidazole) and C_5 (omeprazole, clarithromycin, metronidazole) offer the best value for money, with an incremental cost effectiveness of around $40 per ulcer-free week. The analysis was generally robust to alternative assumptions explored in sensitivity analysis. However, one-way sensitivity analyses on each of the eradication strategies by its assumed eradication rate suggest that the analysis is sensitive to alternate assumptions. For example, if the baseline eradication rate of 86% for bismuth triple therapy is decreased to 50%, then the strategy goes from being the least costly to the second most costly eradication strategy.

If it is assumed that many physicians are currently treating DU with either intermittent or maintenance H_2RAs, then one general conclusion from our analysis is that a move towards treatment targeted at *H pylori* eradication would both save money and improve health. Although bismuth triple therapy is the least costly of the eradication strategies, better outcomes for a modest increase in cost can be achieved with omeprazole plus two antibiotics given in a seven-day regimen, particularly strategies C_3 and C_5.

As with any modeling study, caveats and limitations arise,

primarily due to lack of available data. This model gives indications of relative costs and outcomes associated with management strategies, but future studies, directly comparing treatment regimens in terms of outcomes and costs, would be most useful. Assessments of health outcomes should be sufficiently comprehensive to capture not just ulcer recurrence and speed of healing but also any impacts on health-related quality of life associated with treatment side effects. A limitation of the present study is that we did not include any information on side effects. The NIH consensus conference concluded that side effects associated with *H pylori* regimens are minor and outweighed by the benefits of reduced ulcer recurrence (4), but quality of life or patient preference data on these outcomes would be valuable.

Another limitation of our model is that we have not considered the impact of patient noncompliance with antimicrobial drug regimens used for *H pylori* eradication. Noncompliance is known to be a problem when multiple drugs are to be taken at various times of the day, but reliable data relating compliance to efficacy (ie, ulcer recurrence and symptoms) were not available. A further limitation of our analysis is that we were not able to model the impact of metronidazole resistance on costs and outcomes. Again, this omission was due to limited available data on prevailing rates of resistance and how such resistance affects treatment regimens.

To what extent can the results of this analysis, based on clinical trial evidence, be generalized to patients seen in clinical practice? As with all models, it was necessary to make some simplifying assumptions. Consequently, we modeled expected costs and outcomes in patients known to have DU because it is in this population that the vast majority of evidence relating ulcer recurrence and healing to drug therapy is available.

An important question for primary care physicians is "what role should testing for *H pylori* have in the management of patients presenting with signs and symptoms of DU, but without diagnostic confirmation?" The NIH consensus recommendation was that treatment for *H pylori* should not be empirical. With the advent of simple office-based tests for *H pylori* (eg, urea breath tests) further study is warranted on the economics of *H pylori* testing and treatment in persons with unconfirmed DU.

A final criticism of our analysis is that some gastroenterologists may view our selection of *H pylori* regimens as outdated. The difficulty facing the analyst is that there is rapid evolution and progress in *H pylori* eradication. Our selection of *H pylori* regimens was based upon strategies prevailing when we undertook the work for the CCOHTA, and for which data were available. Inevitably, with such rapid change, new strategies are emerging each day. For example, the evidence from the Metronidazole Amoxicillin Clarithromycin *Helicobacter pylori* (MACH) 1 trial indicates high rates of eradication for seven-day regimens of omeprazole plus two antibiotics. If shorter regimens with lower drug acquisition costs can be as effective as earlier regimens, then the case for eradication becomes even more compelling. The research agenda is to collect more precise data on costs and outcomes to compare *H pylori* regimens to determine which of these approaches offers the best value for money.

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