# Test and treat strategies for *Helicobacter pylori* in uninvestigated dyspepsia: A Canadian economic analysis.

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**JK Marshall, D Armstrong, BJ O'Brien. Test and treat strategies for *Helicobacter pylori* in uninvestigated dyspepsia: A Canadian economic analysis. Can J Gastroenterol 2000;14(5): 379-388.**

**BACKGROUND:** Recognition of the pivotal role of *Helicobacter pylori* in the pathogenesis of peptic ulcer disease has revolutionized primary care approaches to dyspepsia. Decision analysis was used to compare the cost effectiveness of empirical ranitidine with a test and treat strategy using either *H pylori* serology or the $^{13}$carbon-urea breath test ($^{13}$C-UBT).

**PATIENTS AND METHODS:** A cohort of patients under age 50 years presenting with uninvestigated dyspepsia was evaluated. Three initial strategies were compared with respect to direct medical costs and effectiveness in curing *H pylori*-related ulcers – empirical ranitidine, *H pylori* serology and UBT. A one-year time horizon and third-party payer perspective were adopted in a Canadian health care setting.

**RESULTS:** UBT was more costly than either serology or ranitidine but was the most effective strategy and required the fewest endoscopies. No strategy demonstrated dominance over another in the base case. The incremental cost effectiveness ratio (ICER) of serology versus ranitidine was $118/cure, and sensitivity analysis induced dominance of serology in several plausible scenarios. The baseline ICER of UBT versus serology was $885/cure but showed substantial variation in sensitivity analysis. Each ICER was highly sensitive to variation in the cost of the tests themselves. At a serology cost of $25, UBT became dominant when its cost fell to $39.

**CONCLUSIONS:** In low risk patients with uninvestigated dyspepsia, testing for *H pylori* using serology appears to be economically attractive. $^{13}$C-UBT may be a cost effective alternative to serology if local conditions closely approximate the model parameters. Future changes in the costs of serology and $^{13}$C-UBT may determine the optimal approach.

**Key Words:** *Cost analysis; Cost effectiveness; Decision analysis; Dyspepsia;* Helicobacter pylori*; Serology; Urea breath test*

## Stratégies d'examen et de traitement des infections à *Helicobacter pylori* dans des cas de dyspepsie non investiguée : analyse économique canadienne

**CONTEXTE :** La découverte du rôle clé que joue *Helicobacter pylori* dans la pathogenèse des ulcères gastro-duodénaux a révolutionné l'approche des soins primaires à l'égard de la dyspepsie. On a eu recours à une analyse de décision pour comparer le rapport coût-efficacité du traitement empirique à la ranitidine à une stratégie d'examen et de traitement au moyen d'un test sérologique de dépistage de *H. pylori* ou d'un test respiratoire à l'urée marquée au carbone$^{13}$ ($^{13}$C-UBT).

**PATIENTS ET MÉTHODE :** On a évalué une cohorte de patients de moins de 50 ans souffrant de dyspepsie non investiguée. Trois stratégies

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initiales de traitement d'ulcères liés à *H. pylori* ont été comparées : le traitement empirique à la ranitidine, le test sérologique de dépistage de *H. pylori* et le test $^{13}$C-UBT, sous l'angle des coûts médicaux directs et celui de l'efficacité. La recherche, qui s'est déroulée dans un milieu de soins de santé au Canada, a duré un an et a adopté le point de vue d'un tiers payant.

**RÉSULTATS :** Le test $^{13}$C-UBT s'est avéré plus coûteux que le test sérologique ou la ranitidine mais s'est également avéré la stratégie la plus efficace qui exigeait le moins d'endoscopies. Aucune stratégie ne s'est montrée supérieure aux autres dans les cas de référence. Le rapport coût-efficacité différentiel (ICER) entre le test sérologique et la ranitidine était de 118 $/traitement et l'analyse de sensibilité a révélé la supériorité du test sérologique dans plusieurs scénarios plausibles. L'ICER de base entre le test $^{13}$C-UBT et le test sérologique était de 885 $/traitement mais a laissé voir des variations importantes dans l'analyse de sensibilité. Les ICER se sont tous montrés très sensibles à la variation du coût des examens eux-mêmes. Le test $^{13}$C-UBT s'est avéré supérieur au test sérologique lorsque le coût du premier tombait à 39 $ comparativement à 25 $ pour le deuxième.

**CONCLUSION :** Le test sérologique de dépistage de *H. pylori* semble intéressant du point de vue économique chez les patients à faible risque souffrant de dyspepsie non investiguée. Le test $^{13}$C-UBT peut s'avérer une solution de rechange acceptable, offrant un bon rapport coût-efficacité lorsque les conditions locales s'approchent sensiblement des paramètres du modèle. Si le coût du test sérologique ou du test $^{13}$C-UBT devait changer, cela pourrait avoir une incidence sur l'approche optimale.

By convention, the term 'dyspepsia' is used to describe a symptom complex of chronic or recurrent pain or discomfort in the upper abdomen that is attributable to the upper gastrointestinal tract. Although variably defined in the literature, dyspepsia imposes a substantial burden of illness. Population surveys suggest an annual prevalence of 25% to 29% (1-3), while practice audits reveal that dyspepsia accounts for 2% to 7% of primary care visits and 20% to 40% of gastroenterology consultations (4-7).

The new onset of dyspepsia in a previously asymptomatic individual can herald a variety of underlying organic disorders, including peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD) and gastric carcinoma. However, the majority of patients who develop upper abdominal discomfort have no endoscopic or radiographic evidence of peptic ulceration or reflux esophagitis, and are determined to have 'functional' or 'nonulcer' dyspepsia (NUD). Unfortunately, the precise character of an individual's dyspepsia correlates poorly with underlying pathology and cannot discriminate PUD reliably from NUD. As a result, traditional management strategies have mandated either an empirical trial of antisecretory medication (eg, an $H_2$-receptor antagonist) or early diagnostic imaging of the upper gastrointestinal tract (8).

Recent recognition of the pivotal role of *Helicobacter pylori* infection in the pathogenesis of PUD has revolutionized primary care approaches to patients with dyspepsia. Indeed, consensus guidelines published by several national and international organizations now endorse noninvasive testing for *H pylori* infection, with eradication therapy for those who test positive, as an initial intervention for low risk patients under age 45 or 50 years without 'alarm' symptoms such as bleeding or weight loss (9-11). The use of such 'test and treat' strategies is predicated on the reasonable assumption that gastric carcinoma is exceedingly rare in this subgroup (12).

Noninvasive testing for *H pylori* infection can be accomplished using either serology or urea breath tests (UBT). The former typically employs ELISA to measure qualitative or quantitative titres of immunoglobulin G to *H pylori*. Unfortunately, demonstrating antibodies to *H pylori* suggests prior exposure to the organism but does not prove active infection. A 50% drop in antibody titre correlates with eradication of the bacterium, but this approach is unreliable, takes at least six months and assumes that a baseline quantitative antibody titre has been measured (13-15).

UBT is considered by many to be the gold standard noninvasive test for the detection of active *H pylori* infection. After a 4 h fast, the patient ingests $^{13}$carbon- or $^{14}$carbon-labelled urea, which is metabolized to carbon dioxide by the *H pylori*-associated urease. The labelled carbon dioxide is then absorbed, and the increased concentration in expired air can be detected in a timed breath sample. When performed properly, the sensitivity and specificity of the UBT are well in excess of 95% (16). The widespread application of $^{14}$C-UBT has been limited, however, by its small attendant radiation exposure and the need for sample collection and analysis to be performed at appropriately licensed radioisotope storage facilities, which often are only available to tertiary care centres. In contrast, $^{13}$carbon is a naturally occurring nonradioactive isotope that constitutes about 1.1% of normal expired carbon dioxide. Thus, breath samples for the $^{13}$C-UBT can be collected locally and mailed to a central commercial laboratory for analysis using a mass spectrometer. Although such equipment is expensive, the impact of the initial capital outlay on unit cost can be diminished by using a central facility to process large numbers of samples from peripheral centres.

Due to the high prevalence of dyspepsia in the population, careful attention should be given to economic implications before endorsing a specific management strategy. Its high accuracy and relative convenience make $^{13}$C-UBT an appealing technology for the initial investigation of low risk individuals with dyspepsia. However, the relative cost effectiveness of a $^{13}$C-UBT strategy in achieving healing and eradication of *H pylori*-related PUD in a primary care setting has not been examined. This study was initiated to evaluate the costs and health outcomes of three common and reasonable approaches to patients with uninvestigated dyspepsia – an empirical four-week course of an $H_2$-receptor antagonist, *H pylori* testing using serology and *H pylori* testing using the $^{13}$C-UBT.

Unlike previous economic evaluations of dyspepsia management strategies, this model acknowledges that patients

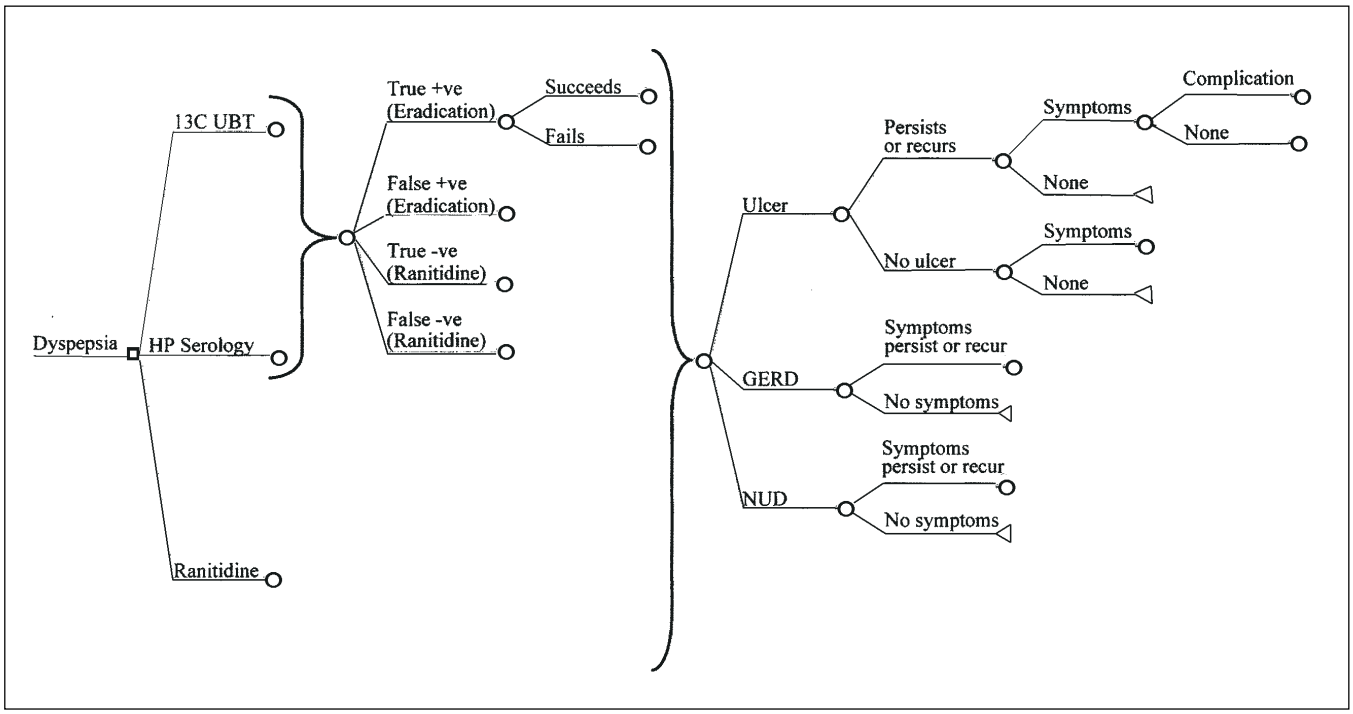


**Figure 1)** *Schematic summary of decision tree used for analysis. +ve Positive; -ve Negative; 13C UBT* $^{13}$*Carbon urea breath test; GERD Gastroesophageal reflux disease; HP* Helicobacter pylori; *NUD Nonulcer dyspepsia*

present with dyspepsia that may not be caused by *H pylori* or PUD and that, even if *H pylori* and PUD are cured, the dyspeptic symptoms may persist. However, cure of *H pylori* and PUD offers reassurance to patients and physicians that no significant underlying disease remains, and the substantial burden of illness imposed by PUD means that its cure remains an important aim. Although cure of PUD was chosen as our measure of effectiveness, it is important to recognize that the identification and cure of *H pylori* have management implications beyond pure considerations of costs and ulcer cure rates.

## PATIENTS AND METHODS

**Decision tree:** The decision-analytic model was constructed using DATA software (TreeAge Software Inc, Williamstown, Massachusetts). A hypothetical cohort of 1000 patients under the age of 50 years who had presented to their primary care practitioner with a new complaint of dyspepsia and did not use nonsteroidal anti-inflammatory drugs was used. Three initial management strategies were compared – empirical treatment with a four-week course of oral ranitidine, *H pylori* testing using serology and *H pylori* testing using the $^{13}$C-UBT. Each strategy was evaluated with respect to costs and outcomes over a one-year period and from the viewpoint of a third-party payer for health care, considering only direct health care costs to the Ontario Ministry of Health. Health outcomes were quantified as the number of patients in whom *H pylori*-associated PUD was cured, in the sense that the ulcer was healed and the organism was eradicated.

In developing the path probabilities and management approaches applied to the model, three simplifying assumptions were made. First, it was assumed that gastric carcinoma would not develop in the hypothetical 'low risk' cohort. Second, it was assumed that endoscopy with antral biopsies for histology (including special stains for *H pylori*) and rapid urease testing was 100% accurate for the diagnosis of *H pylori* infection. Third, costs and outcomes up to and including only the first recurrence of symptoms were modelled, and the costs and consequences of subsequent episodes were not captured.

Within each arm, costs and consequences were modelled for six specific patient subgroups stratified by *H pylori* status (positive or negative) and underlying pathology (PUD, NUD or GERD). The model was designed to be entirely 'symptom-driven', with interventions determined by clinical response and/or recurrence rather than by endoscopic change. Thus, for example, no intervention was required for asymptomatic ulcer recurrences. Diagnoses also were not considered mutually exclusive, and patients who entered the model with PUD could develop NUD after cure of their ulcer.

The clinical management strategies followed in the model reflect recent Canadian consensus guidelines for the management of *H pylori* infection (10). Patients who initially tested positive for *H pylori* using the $^{13}$C-UBT or serology were given empirically an *H pylori* eradication regimen (Figure 1). Patients who tested negative were prescribed a four-week course of oral ranitidine. Only if symptoms persisted or recurred was the patient referred to a gastroenter-

**TABLE 1**
**Probabilities applied in the decision analysis model**

| Variable | Base case probabilities | Probability ranges for sensitivity analysis | Reference(s) |
|---|---|---|---|
| Prevalence of *Helicobacter pylori* | 0.30 | 0.10–0.50 | 17-21 |
| Prevalence of PUD if *H pylori*-positive | 0.35 | 0.20–0.50 | 22 |
| Prevalence of PUD if *H pylori*-negative | 0.03 | N/A | 22 |
| Sensitivity of $^{13}$C-UBT | 0.96 | 0.70–1.00 | 23-25 |
| Specificity of $^{13}$C-UBT | 0.98 | 0.70–1.00 | 23-25 |
| Sensitivity of serology | 0.85 | 0.70–0.95 | 26,27 |
| Specificity of serology | 0.79 | 0.70–0.95 | 26,27 |
| Effectiveness of *H pylori* eradication | 0.90 | 0.60–1.00 | 28,29 |
| PUD healing after four weeks of ranitidine | 0.70 | N/A | 30,31 |
| PUD healing after six weeks of omeprazole | 0.90 | N/A | 30,31 |
| PUD healing after one week of omeprazole | 0.85 | N/A | 30,31 |
| Recurrence rate of PUD over one year if *H pylori*-positive | 0.75 | 0.05–1.00 | 32,33 |
| Recurrence rate of PUD over one year if *H pylori*-negative | 0.04 | 0–0.20 | 32,33 |
| Proportion of ulcers with associated symptoms | 0.75 | N/A | 32 |
| Relapse rate of NUD | 0.65 | 0.00–1.00 | 37 |

*N/A Not assessed in sensitivity analysis; NUD Nonulcer dyspepsia; PUD Peptic ulcer disease; UBT Urea breath test*

ologist for consultation and endoscopy, which was assumed to include antral biopsies and rapid urease testing (RUT). In the ranitidine strategy, all patients whose symptoms persisted or recurred following the initial four-week course of ranitidine were referred for consultation and endoscopy.

In each arm of the model, endoscopically proven peptic ulcers were treated with eradication therapy if associated with *H pylori* infection. Peptic ulcers without evidence of *H pylori* infection were treated with a four-week course of oral omeprazole 20 mg bid. Patients who underwent endoscopy and were found to have persistent *H pylori* infection without an ulcer were prescribed eradication therapy because it would not have been known whether they had an ulcer at entry into the model. Patients with isolated esophagitis at endoscopy were prescribed an eight-week course of oral omeprazole 20 mg bid, while those with normal mucosa and no *H pylori* received no new therapy.

In each arm, the first-line regimen for *H pylori* eradication was omeprazole 20 mg, clarithromycin 500 mg and metronidazole 500 mg bid for seven days (OCM). The second-line regimen, used for OCM failures, was omeprazole 20 mg bid, clarithromycin 500 mg bid and amoxicillin 1000 mg bid for seven days. When a third attempt at *H pylori* eradication was necessary, ranitidine 150 mg bid, bismuth subsalicylate 524 mg qid, metronidazole 250 mg qid and tetracycline 500 mg qid were prescribed for two weeks.

**Probability inputs:** Point estimates of path probabilities for the decision tree were extracted from a review of the published literature (Table 1). Articles were identified from computerized searches of the MEDLINE database (1966 to 1998) and from hand searches of recent review article bibliographies. For each probability, a plausible range of values for sensitivity analysis was chosen to reflect uncertainty in the literature. Where a necessary probability could not be found in the literature, a reasonable point estimate was chosen empirically and a wide range of plausible values was used for the sensitivity analysis.

The prevalence of *H pylori* infection among dyspeptic patients was assumed to be 30% (range 10% to 50%) (17-21). Among *H pylori*-positive patients, the prevalence of PUD was assumed to be 35% (20% to 50%) versus 3% among those without *H pylori* (22). The sensitivity and specificity of the $^{13}$C-UBT for detection of *H pylori* were estimated at 96% and 98%, respectively (70% to 100%) (11,23-25). The *H pylori* serology assay was assigned a sensitivity of 85% and a specificity of 79% (70% to 95%) based on a published meta-analysis and a third-party technical review (26,27).

The effectiveness of *H pylori* eradication therapy was assumed to be 90% (range 60% to 100%) (28,29). With successful eradication, 95% of ulcers were assumed to heal versus 76% if eradication failed. A four-week course of ranitidine was considered to heal 70% of ulcers, while a six-week course of omeprazole monotherapy healed 90% (30,31). *H pylori*-negative patients who were given eradication therapy in error because of a false-positive noninvasive test were assigned an ulcer healing rate of 85% because they had received a seven-day course of omeprazole (30,31).

The one-year recurrence rate of *H pylori*-positive PUD without maintenance therapy was assumed to be 70% (50% to 100%), while that following successful eradication of the organism was assumed to be 4% (0% to 20%) (32,33). Throughout the model, it was assumed that 75% of ulcers were symptomatic and 1% of new ulcers presented with complications such as bleeding or perforation (32).

Because no therapy has demonstrated conclusive efficacy in NUD, the symptomatic response rate of NUD to any therapy was considered equivalent to the placebo response rate reported in clinical trials. In particular, despite recent controversy, no benefit was assumed from *H pylori* eradication in *H pylori*-positive NUD (34-36). Hence, the one-year symptomatic relapse rate regardless of therapy was estimated to be 65% (0% to 100%) (37).

**Cost inputs:** Several sources were used to estimate locally relevant direct costs for the resources consumed in the model (Table 2). Wholesale drug costs were determined through a survey of local pharmacies including the Hamilton Health Sciences Corporation (McMaster Site) Outpatient Pharmacy, Hamilton, Ontario. A 10% pharmacy markup was added to the wholesale price, as well as a dispensing fee of $4.11 per prescription ($6.11 minus a copayment of $2.00). Costs for physician services were taken from the 1998 Ontario Ministry of Health Schedule of Benefits (38).

The costs of outpatient endoscopy, endoscopic biopsy and RUT were derived from the Hamilton Health Sciences Corporation costing model, developed in accordance with the Ontario Case Cost Project (OCCP). The latter is a joint venture of the Ontario Ministry of Health and the Ontario Hospital Association, wherein each of 13 participating institutions uses a standardized methodology to maintain a database of resource utilization and resource unit cost indexed by individual patient encounter (39). The cost of admission for management of complicated PUD was derived from a previously published cost model based in part on the OCCP database (40).

Because no local cost estimate for $^{13}$C-UBT was available, the average cost per test was determined from its fixed and variable cost components. Following convention, the capital cost of purchasing a mass spectrometer was converted to an equivalent annual capital outlay by amortizing over an expected life of 10 years using an interest rate of 5% (41). Annual fixed costs included technician salary and an institutional overhead cost proportionate to the square footage occupied by the laboratory, while variable costs included the purchase price of the test kits and the cost of collecting and shipping the samples to the central laboratory. An annual throughput of 5000 samples was assumed, and the mean cost per test was determined to be $66 (range $40 to $120).

Because serological testing for *H pylori* is performed outside the authors' centre at the regional public health laboratories, its cost is not captured by their administrative database. Therefore, a similar process was used to combine annual fixed costs, including facility overhead, technician salary, and washer/reader rental and calibration, with variable costs for test kits, specimen collection, transportation and processing. By this method, the mean cost per test was determined to be $20 (range $5 to $55) for an annual volume of 5000 samples.

All costs are reported in 1997 CDN$ (CDN$1 is approximately US$0.70).

**Cost effectiveness analysis:** Consistent with current guidance on economic evaluation (41), the expected costs per patient over one year for each strategy were estimated as the probability-weighted sum of costs outlined above. Similarly, the health outcomes per patient for each strategy were quantified as the expected number of *H pylori*-related ulcers cured with eradication of the organism.

The analytic strategy was twofold – to rule out any strategy 'dominated' by another, having both higher costs and worse outcomes, and to estimate between nondominated strategies the incremental cost effectiveness of the more costly alternative, the ratio of the difference in costs to the difference in outcome. One- and two-way sensitivity analyses were then performed to determine the effect of variation in key model parameters on each relevant incremental cost effectiveness ratio (ICER).

**TABLE 2**
**Cost inputs applied in the decision analysis model. (See text for explanation)**

| Item | Base case cost (CDN$) | Range for sensitivity analysis (CDN$) |
|---|---|---|
| First-line *Helicobacter pylori* eradication regimen (MOC, 7 days) | 88 | N/A |
| Second-line *H pylori* eradication regimen (AOC, seven days) | 94 | N/A |
| Third-line *H pylori* eradication regimen (R-BMT, 14 days) | 57 | N/A |
| Ranitidine (generic) for four weeks | 30 | N/A |
| Omeprazole (Losec*) for four weeks | 146 | N/A |
| Omeprazole (Losec*) for eight weeks | 289 | N/A |
| Outpatient endoscopy with biopsy and rapid urea test | 528 | 250–1250 |
| $^{13}$Carbon urea breath test | 66 | 40–120 |
| *H pylori* serology | 20 | 5–80 |
| Primary care visit | 25 | N/A |
| Specialist consultation | 105 | N/A |
| Specialist follow-up visit | 39 | N/A |

**AstraZeneca, Mississauga, Ontario. AOC Amoxicillin 1000 mg bid, omeprazole 20 mg bid, clarithromycin 500 mg bid; MOC Metronidazole 500 mg bid, omeprazole 20 mg bid, clarithromycin 500 mg bid; N/A Not assessed in sensitivity analysis; R-BMT Ranitidine 150 mg bid, bismuth subsalicylate 524 mg qid, metronidazole 250 mg qid, tetracycline 500 mg qid*

## RESULTS

**Base case scenario:** The number of endoscopies per 1000 patients was lowest with the $^{13}$C-UBT strategy (629.0), higher with serology (649.4) and highest with empirical ranitidine therapy (700.2) (Table 3). The number of *H pylori* eradication regimens prescribed per 1000 patients was lowest with empirical ranitidine (200.1), highest with serology (448.6) and intermediate with the $^{13}$C-UBT (433.8).

In the base case scenario, the direct medical cost per patient over 12 months was $598 in the ranitidine strategy, $635 in the $^{13}$C-UBT strategy and $603 in the serology strat-

**TABLE 3**
**Expected one-year outcomes, costs and incremental cost effectiveness ratios (ICER). Reported results are rounded to the nearest whole value, while calculations have been performed on unrounded values**

| Strategy | Endoscopies per 1000 patients | *H pylori* treatments per 1000 patients | Cost per patient (CDN$) | Cost increment, CDN$ ($\delta$C) | Ulcer cures per 1000 patients | Increment in ulcer cures ($\delta$E) | ICER ($\delta$C/$\delta$E×1000) |
|---|---|---|---|---|---|---|---|
| Ranitidine | 700 | 200 | 598 | – | 53 | – | – |
| *H pylori* serology | 649 | 449 | 603 | 5 | 92 | 39 | $118/cure |
| $^{13}$C-UBT | 629 | 433 | 635 | 32 | 128 | 36 | $885/cure |

*UBT Urea breath test*

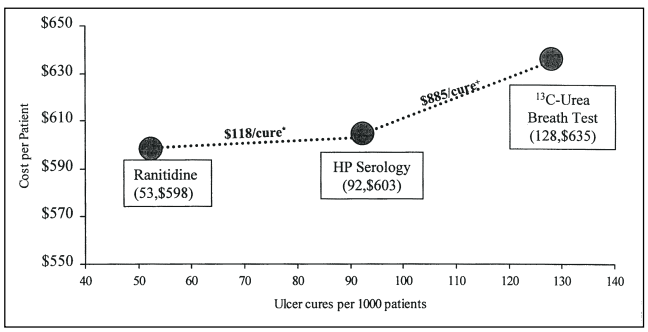


**Figure 2)** *Base case scenario estimates of costs and outcomes (ulcer cures per 1000 patients) for three alternative strategies. Dashed lines represent the incremental cost effectiveness ratios of successive strategies. *($603-$598)/(92-53) × 1000 (values rounded); +($635-$603)/(128-92) × 1000 (values rounded). HP* Helicobacter pylori

egy (Table 3). The number of *H pylori*-positive peptic ulcers cured was 53/1000 patients with the ranitidine strategy, 128/1000 patients with the $^{13}$C-UBT and 92/1000 patients with serology. No strategy demonstrated dominance over any other because none was both more effective and less costly (Figure 2). The ratio of total cost to total number of ulcers cured was highest with ranitidine ($11,300/cure), intermediate with the serology strategy ($6,543/cure) and lowest with the $^{13}$C-UBT test and treat strategy ($4,945/cure).

The incremental change in cost and ulcer cures was determined by advancing from the least costly and least effective strategy (ranitidine) to the most costly and most effective option ($^{13}$C-UBT). The ICER of serology compared with ranitidine was $118 per additional ulcer cure, while that of the $^{13}$C-UBT relative to serology was $885/cure.

**One-way sensitivity analysis:** Each path probability and cost estimate were varied over their plausible range to determine their impact on the ICERs of $^{13}$C-UBT versus serology and of serology versus ranitidine. In several instances, an ICER fell below zero, implying a dominant relationship between the two alternatives. In such cases, a 'dominance threshold' value for that model parameter was identified as the point where the ICER numerator (cost increment) or denominator (effect increment) approached zero.

The ICER of serology versus ranitidine ranged from $0/cure to $1400/cure in sensitivity analysis (Table 4). In no circumstance did ranitidine become dominant over serology. However, serology dominated ranitidine when any of the following conditions were satisfied: prevalence of *H pylori* greater than 35%; prevalence of PUD greater than 39% if *H pylori*-positive; specificity of serology greater than 94%; proportion of ulcers with symptoms greater than 83%; annual relapse rate of *H pylori*-positive patients with prior PUD greater than 88%; cost of serology less than $16; or (7) cost of endoscopy greater than $610.

The ICER of $^{13}$C-UBT versus serology ranged from $57/cure to over $32270/cure in sensitivity analysis and exceeded $2000/cure only with variation in $^{13}$C-UBT cost and serology specificity (Table 5). In no case did $^{13}$C-UBT dominate serology. However, serology became dominant over $^{13}$C-UBT when the specificity of $^{13}$C-UBT fell below 81%.

**Two-way sensitivity analysis:** Because the use of serology to diagnose *H pylori* in low prevalence populations has been criticized for its low positive predictive value (26), the initial two-way sensitivity analysis assessed the influence of simultaneous variation in *H pylori* prevalence and serology specificity on the ICER of serology versus empirical ranitidine and $^{13}$C-UBT versus serology (Figure 3).

The ICER of the $^{13}$C-UBT versus serology fell to $352/cure, with a serology specificity of 70% and an *H pylori* prevalence of 10%. However, high serology specificity (95%) with *H pylori* prevalence greater than 30% caused the serology strategy to become dominant over $^{13}$C-UBT.

The ICER of serology versus ranitidine rose as high as $1872/cure with low *H pylori* prevalence (10%) and low serology specificity (70%). The ICER of serology versus ranitidine revealed dominance of serology when the prevalence of *H pylori* exceeded 29%, with a specificity of 95%, or exceeded 38% with a specificity of 70%.

A second two-way sensitivity analysis assessed the influence of simultaneous variation in serology specificity and serology cost (Figure 4). The ICER of $^{13}$C-UBT versus serology fell to zero, implying dominance of $^{13}$C-UBT over serology, in conditions of low serology specificity and high cost ($46 for a sensitivity of 70% or $49 for a sensitivity of 75%). The ICER of serology versus ranitidine reached a maximum of $953/cure with a specificity of 70% and cost of $50. This ICER also became negative, implying dominance of serology, when the cost fell below $21 with a specificity of 95% or $13 with a specificity of 70%.

A third two-way sensitivity analysis was performed to test the impact of variation in both serology and $^{13}$C-UBT costs on the ICER of $^{13}$C-UBT versus serology (Figure 4). When serology cost $50 (baseline $20), this ICER fell to zero and $^{13}$C-UBT became dominant when its cost fell below $64 (baseline $66). The threshold cost for dominance of $^{13}$C-

**TABLE 4**
**One-way sensitivity analysis examining the incremental cost effectiveness ratio (ICER) of the serology strategy versus empirical ranitidine**

| Model parameter | Range | ICER range ($/cure) | Serology dominant (threshold) | ICER >$1000/cure (threshold) |
|---|---|---|---|---|
| Serology sensitivity | 0.70–0.95 | 47–262 | N/A | N/A |
| Serology specificity | 0.70–0.95 | 0–187 | Over 0.94 | N/A |
| *Helicobacter pylori* prevalence in dyspepsia | 0.10–0.50 | 0–1400 | Over 0.35 | Below 0.14 |
| PUD prevalence if *H pylori*-positive | 0.20–0.50 | 0–752 | Over 0.39 | N/A |
| PUD recurrence if *H pylori*-positive | 0.50–1.00 | 0–282 | Over 0.88 | N/A |
| PUD recurrence if *H pylori*-negative | 0.00–0.20 | 65–336 | N/A | N/A |
| *H pylori* eradication effectiveness | 0.60–1.00 | 3–492 | N/A | N/A |
| Relapse rate of NUD | 0.00–1.00 | 45–253 | N/A | N/A |
| Proportion of PUD patients with symptoms | 0.00–1.00 | 0–550 | Over 0.83 | N/A |
| Cost of endoscopy | $250–$1250 | 0–442 | Over $610 | N/A |
| Cost of serology | $5–$50 | 0–883 | Below $16 | N/A |

*The dominance threshold reflects the value of the model parameter above or below which serology is dominant over ranitidine. A second threshold is calculated where the ICER exceeds $1000/cure (see discussion). N/A Not assessed in sensitivity analysis; NUD Nonulcer dyspepsia; PUD Peptic ulcer disease*

**TABLE 5**
**One-way sensitivity analysis examining the incremental cost effectiveness ratio (ICER) of $^{13}$carbon urea breath test ($^{13}$C-UBT) strategy versus serology strategy**

| Model parameter | Parameter range | ICER range ($/cure) | $^{13}$C-UBT dominant (threshold) | ICER >$1000/cure (threshold) |
|---|---|---|---|---|
| $^{13}$C-UBT sensitivity | 0.70–1.00 | 871–1065 | N/A | Below 0.89 |
| $^{13}$C-UBT specificity | 0.70–1.00 | 712–infinity* | N/A* | Below 0.97 |
| Serology sensitivity | 0.70–0.95 | 806–1052 | N/A | Below 0.74 |
| Serology specificity | 0.70–0.95 | 465–32270 | N/A | Above 0.80 |
| *H pylori* prevalence in dyspepsia | 0.10–0.50 | 672–1654 | N/A | Above 0.34 |
| PUD prevalence if *H pylori*-positive | 0.20–0.50 | 497–1855 | N/A | Below 0.33 |
| PUD recurrence if *H pylori*-positive | 0.50–1.00 | 880–889 | N/A | N/A |
| PUD recurrence if *H pylori*-negative | 0.00–0.20 | 855–1004 | N/A | Above 0.19 |
| *H pylori* eradication effectiveness | 0.60–1.00 | 795–1315 | N/A | Below 0.80 |
| Relapse rate of NUD | 0.00–1.00 | 677–1270 | N/A | Below 0.46 |
| Proportion of PUD patients who are symptomatic | 0.00–1.00 | 843–901 | N/A | N/A |
| Cost of endoscopy | $250–$1250 | 465–1026 | N/A | Below $300 |
| Cost of $^{13}$C-UBT | $40–$120 | 167–2375 | N/A | Above $70 |
| Cost of serology | $5–$50 | 57–1298 | N/A | Below $16 |

*The dominance threshold reflects the parameter value above or below which $^{13}$C-UBT is dominant over serology. A second threshold is calculated where the ICER exceeds $1000/cure (see discussion). *Serology dominates $^{13}$C-urea breath test (UBT) when the specificity of $^{13}$C-UBT is less than 81%. N/A Not assessed in sensitivity analysis; NUD Nonulcer dyspepsia; PUD Peptic ulcer disease*

UBT fell to $39 if serology cost $25 and $17 if serology cost only $5. The ICER of the $^{13}$C-UBT relative to serology reached a maximum value of $2788/cure when the costs of serology fell to $5 and that of $^{13}$C-UBT increased to $120.

## DISCUSSION

Current guideline statements from medical societies in North America and Europe have endorsed noninvasive testing for *H pylori* infection as an appropriate initial intervention for young patients with uninvestigated dyspepsia. It is argued that a 'test and treat' approach is safe, efficient and cost effective. Indeed, a number of economic evaluations have supported the cost effectiveness of serological testing for *H pylori* in this low risk subset of patients (42-46). Ours is the first published decision model to assess the relative cost effectiveness of a test and treat strategy using $^{13}$C-UBT. Because the $^{13}$C-UBT is more accurate than serology and is becoming widely available at a reasonable cost, it is an important option to consider when developing cost effective management protocols for dyspepsia.

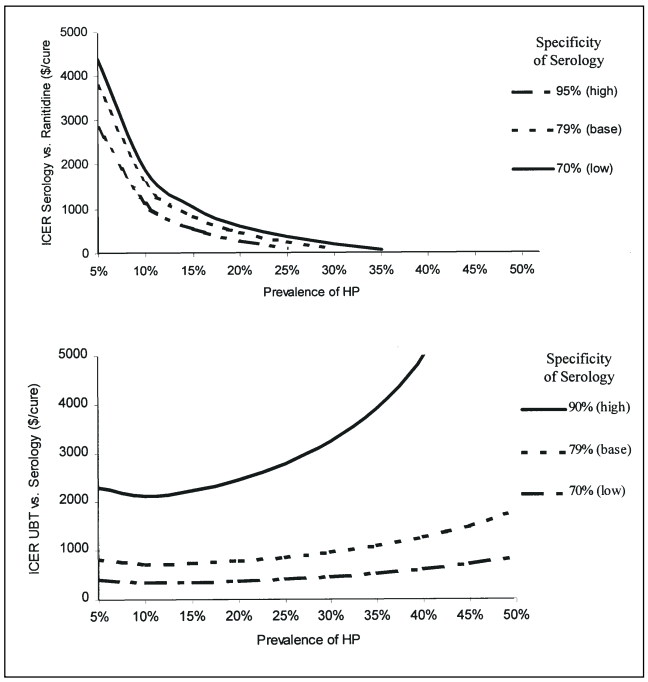


**Figure 3)** *Two-way sensitivity analysis testing the influence of* Helicobacter pylori *(HP) prevalence and serology specificity on the incremental cost effectiveness ratio (ICER) of serology versus ranitidine (upper panel) and the* $^{13}$*carbon urea breath test (UBT) versus serology (lower panel)*

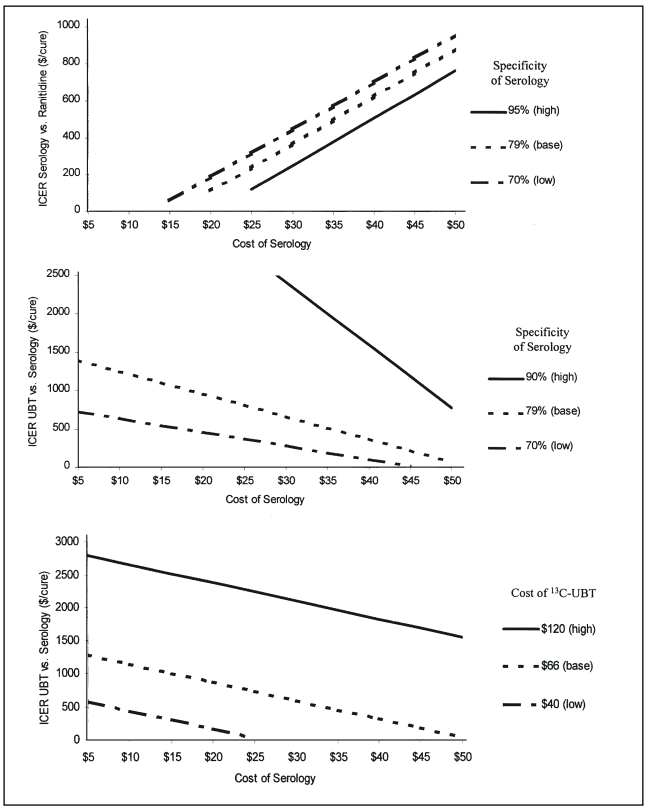


**Figure 4)** *Two-way sensitivity analysis testing the influence of serology cost and serology specificity on incremental cost effectiveness ratio (ICER) of serology versus ranitidine (upper panel) and* $^{13}$*carbon urea breath test (UBT) versus serology (middle panel). Two-way sensitivity analysis demonstrating the effect of simultaneous variation in serology and* $^{13}$*C-UBT costs on the ICER of* $^{13}$*C-UBT versus serology (lower panel)*

In our base case scenario, we did not find any of the three strategies to be dominant; that is, none was both more effective and less costly than another. The least effective and least expensive strategy was treatment with empirical ranitidine, while $^{13}$C-UBT was the most expensive and most effective, and serology was intermediate with respect to both effectiveness and cost. Having found no dominance, we examined the ICER of serology versus ranitidine and of $^{13}$C-UBT versus serology to identify the relationships between increments in effectiveness and increments in cost. The base case ICER of serology versus ranitidine was $118/cure, while that for $^{13}$C-UBT versus serology was $885/cure. The outcome of the model was highly sensitive to change in the costs of $^{13}$C-UBT and serology themselves. The serology strategy became dominant over empirical ranitidine when the cost of serology fell below $16. Furthermore, $^{13}$C-UBT became dominant over serology when its cost fell to $39 and serology cost $25. Thus, if test costs fall in the future, as is likely to happen, clear dominance of one over the other may emerge.

Calculation of an ICER makes tradeoffs between cost and effect explicit but does not inform decision makers whether the increment in effect warrants the associated increment in cost. Such a judgment requires some knowledge of the value assigned to cure *H pylori*-positive PUD. Other authors have approached this issue by estimating the present value of the future medical costs avoided by cure of ulcer disease (44). The recurrence rate of PUD without eradication of *H pylori* or antacid prophylaxis may approach 95% within the first year (47). If the management strategy of our model is extended, each symptomatic ulcer recurrence would incur costs of nearly $1000 for primary care assessment ($50), specialist consultation and follow-up ($200), diagnostic endoscopy and biopsy ($530), *H pylori* eradication therapy ($100) and confirmatory $^{13}$C-UBT ($65); each recurrence complicated by hemorrhage would incur costs of $3000 for hospital care. Thus, a cost of $1000 for cure of PUD may be justified. In our model, the baseline ICER of $^{13}$C-UBT versus serology and of serology versus ranitidine are each less than $1000/cure. Hence, a shift from empirical ranitidine to the most effective but most expensive strategy ($^{13}$C-UBT) may be an acceptable value for the money and a cost effective treatment option.

The primary outcomes of interest to our model were the direct medical costs incurred and the number of *H pylori*-positive peptic ulcers cured by each management strategy. While we believe these measures to be important, other relevant outcomes are not captured by reporting a cost effectiveness ratio with a third-party payer perspective and must be emphasized. For example, the $^{13}$C-UBT strategy imposed fewer endoscopies and required fewer specialist referrals than either serological testing or empirical ranitidine. This may affect indirect costs and reduce the 'intangible' costs of discomfort and inconvenience, but many patients and physicians may be reluctant to accept the reassurance

provided by a negative noninvasive test for *H pylori*. Endoscopy can provide definitive diagnosis and/or reassurance, and such information may have intrinsic value (48). In our model, the ranitidine and $^{13}$C-UBT strategies also required substantially fewer courses of antibiotics than serology, which would reduce adverse effects such as pseudomembranous colitis and avoid the inconvenience of multidrug dosing.

This model makes the explicit assumption that eradication of *H pylori* offers no specific benefit in NUD. Although this issue remains highly controversial, some authors have reported improvement in dyspeptic symptoms (35,36). If this were true, modification of our model would likely show test and treat strategies to be even more appealing. Patients with NUD and *H pylori* who are detected through serology or $^{13}$C-UBT and cured of their symptoms would avoid referral for endoscopy, thus reducing costs and improving outcome.

Our model followed costs and health outcomes up to a one-year time horizon. Although we have not tested a longer horizon, we suspect that an extended model would continue to favour the noninvasive *H pylori* testing strategies. In the ranitidine arm of our model, there remains at one year a large pool of patients who presented with a peptic ulcer but whose *H pylori* infection persists. Given the relapsing natural history of *H pylori*-related PUD, most of this group would eventually suffer a recurrence (with or without complications), which would prompt definitive investigation and treatment, including endoscopy and/or barium radiography. Thus, while an extended time horizon might see a gradual equalization of 'effectiveness' rates among the three strategies, the costs accrued by a ranitidine strategy could rise dramatically and cause that strategy to become dominated by the noninvasive approaches.

The portability of cost effectiveness models across health care jurisdictions is limited, and individual practitioners must examine the costs and probabilities used in our model closely to determine whether its conclusions are at all relevant to their own practice (49). If several parameters must be substantially altered in order to 'adjust' the model to another local practice, more complex two- or three-way sensitivity analysis would be required and might generate very different results. All diagnostic tests, including both serology and $^{13}$C-UBT, must be validated locally to verify their performance (10,11).

Decision analytic modelling is only one of many approaches to answering complex questions raised by clinical management protocols. As with health care guidelines, models can only address 'typical' patients, and clinical judgment is needed to determine whether their conclusions should be applied to a given individual in a specific clinical setting. It must be emphasized that, while decision models attempt to simulate true clinical scenarios, real life is substantially more complex than any algorithm can anticipate. Prospective studies that use an 'effectiveness' format are needed to confirm our conclusions in day to day practice.

## CONCLUSIONS

Our decision model did not demonstrate one strategy to be dominant over another. However, the ICER of serological versus empirical ranitidine therapy was low and frequently demonstrated dominance of serology in sensitivity analysis. The $^{13}$C-UBT appeared to be a cost effective alternative to serology in our base case scenario, but the ICER of the $^{13}$C-UBT over serology varied substantially in sensitivity analysis and was highly sensitive to variation in the cost of the tests themselves. While the $^{13}$C-UBT warrants consideration in the evaluation of patients with uninvestigated dyspepsia, close attention must be paid to local variation in costs and outcomes if it is to be accepted as a cost effective first-line test in test and treat strategies.

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