

A Cost-Effectiveness Analysis of Diagnostic Strategies for Symptomatic Patients With Ileal Pouch–Anal Anastomosis

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OBJECTIVE: Pouchitis is often diagnosed based on symptoms and empirically treated with antibiotics (*treat-first* strategy). However, symptom assessment alone is not reliable for diagnosis, and an initial evaluation with pouch endoscopy (*test-first* strategy) has been shown to be more accurate. Cost-effectiveness of these strategies has not been compared. The aim of this study was to compare cost-effectiveness of different clinical approaches for patients with symptoms suggestive of pouchitis.

METHODS: Pouchitis was defined as pouchitis disease activity index scores ≥ 7 . The frequency of pouchitis in symptomatic patients with ileal pouch was estimated to be 51%; the efficacy for initial therapy with metronidazole (MTZ) and ciprofloxacin (CIP) was 75% and 85%, respectively. Cost estimates were obtained from Medicare reimbursement data.

RESULTS: Six competing strategies (MTZ trial, CIP trial, MTZ-then-CIP trial, CIP-then-MTZ trial, pouch endoscopy with biopsy, and pouch endoscopy without biopsy) were modeled in a decision tree. Costs per correct diagnosis with appropriate treatment were \$194 for MTZ trial, \$279 for CIP trial, \$208 for MTZ-then-CIP trial, \$261 for CIP-then-MTZ trial, \$352 for pouch endoscopy with biopsy, and \$243 for pouch endoscopy without biopsy. Of the two strategies with the lowest cost, the pouch endoscopy without biopsy strategy costs \$50 more per patient than the MTZ trial strategy but results in an additional 15 days for early diagnosis and thus initiation of appropriate treatment (incremental cost-effectiveness ratio \$3 per additional day gained). The results of base-case analysis were robust in sensitivity analyses.

CONCLUSIONS: Although the MTZ-trial strategy had the lowest cost, the pouch endoscopy without biopsy strategy was most cost-effective. Therefore, based on its relatively low cost and the avoidance of both diagnostic delay and

adverse effects associated with unnecessary antibiotics, pouch endoscopy without biopsy is the recommended strategy among those tested for the diagnosis of pouchitis. (Am J Gastroenterol 2003;98:2460–2467. © 2003 by Am. Coll. of Gastroenterology)

INTRODUCTION

Pouchitis is the most common complication after total proctocolectomy and ileal pouch–anal anastomosis (IPAA) in patients with ulcerative colitis (UC), with a 10-yr cumulative prevalence between 24% and 48% (1–4). Common symptoms of pouchitis are increased stool frequency, urgency, abdominal cramping, and pelvic discomfort. These symptoms, however, are not specific for pouchitis, and can be due to conditions such as inflammation of the rectal cuff (cuffitis) or irritable pouch syndrome (IPS), a condition resembling irritable bowel syndrome (1, 5–7). Symptoms do not necessarily correlate with endoscopic and histological findings (1, 5, 8–12).

The most common clinical scenarios in the outpatient setting are the following: 1) a patient has an initial episode of symptoms suggestive of pouchitis after total proctocolectomy and IPAA, 2) a patient has recurrent symptoms with or without prior treatment but has never had pouch endoscopy, and 3) a symptomatic patient carries a prior diagnosis of “pouchitis” based on symptom assessment alone and had previously failed therapy with a short course of metronidazole (MTZ). The most cost-effective approach to making an accurate diagnosis and initiating early, appropriate therapy is not known. In clinical practice, pouchitis is often diagnosed based on symptoms alone and empirically treated with antibiotics (the *treat-first* strategy). Patients who do not respond to initial therapy usually then undergo diagnostic testing (*i.e.*, pouch endoscopy). This strategy, however, has pitfalls. For example, patients who do not have pouchitis might be unnecessarily exposed to antibiotics, and some of those patients could experience adverse effects. Empiric

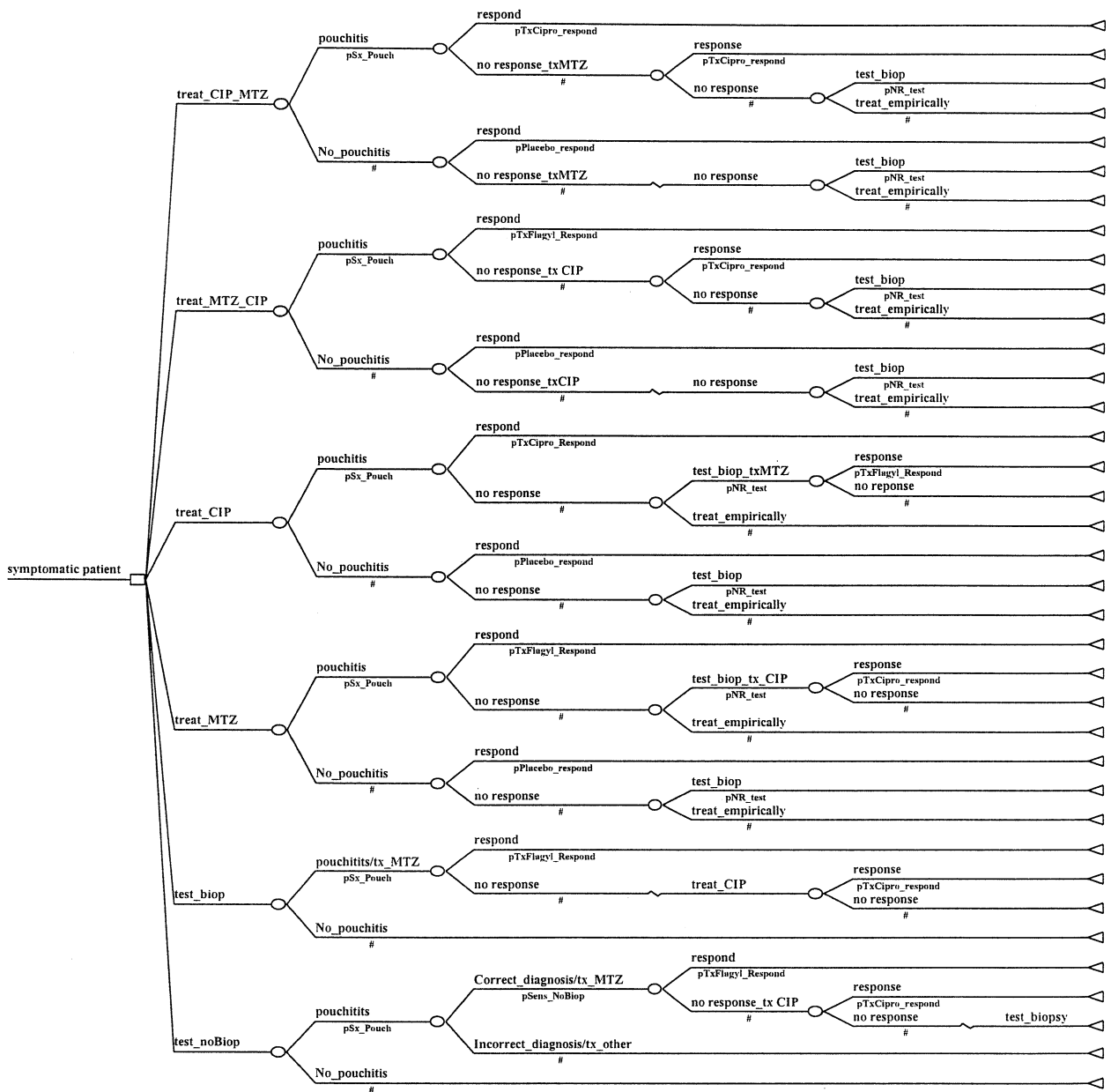


Figure 1. Decision tree.

treatment with antibiotics might delay more appropriate therapy for symptomatic patients who do not have pouchitis.

Ideally, diagnosis of pouchitis should be made by a combined assessment of symptoms, endoscopy, and histology, with the use of a diagnostic instrument, such as the pouchitis disease activity index (PDAI) (5, 13). Using the PDAI criteria, we found that 43% of symptomatic patients with IPAA had no endoscopic or histological evidence of pouch inflammation (7). Instead, pouch endoscopy and histology revealed either cuffitis or normal pouch and rectal cuff (7). These findings suggest that symptom assessment alone is not reliable for the diagnosis of pouchitis. We believe that initial evaluation with pouch endoscopy (the *test-first* strategy) is needed to make an accurate diagnosis in symptom-

atic patients with IPAA (5). Whether the *test-first* strategy is cost-effective is unknown. In the current cost-effectiveness analysis, we compared the *test-first* strategies with the *treat-first* strategies to determine the best approach to diagnosing and managing patients with suspected pouchitis.

MATERIALS AND METHODS

A decision analytic model was developed to evaluate the cost-effectiveness of the six competing diagnostic strategies from the payers' perspective (Fig. 1). The *treat-first* strategies consisted of the MTZ trial, ciprofloxacin (CIP) trial, MTZ-then-CIP trial, and the CIP-then-MTZ trial. All MTZ regimens consisted of 500 mg *p.o. t.i.d.* × 14 days. All CIP

Table 1. Variables, Baseline Values, and Sensitivity Ranges

Description	Baseline Value	Low	High	References
Cost of a ciprofloxacin 500-mg tablet	\$4.51	\$2.25	\$9	Redbook
Cost of a metronidazole 500-mg tablet	\$0.22	\$0.1	\$3.5	Redbook
Cost of endoscopy with biopsy	\$342	\$250	\$800	Medicare
Cost of endoscopy without biopsy	\$210	\$100	\$420	Medicare
Cost of histology	\$84.69	\$42	\$170	Medicare
Duration of ciprofloxacin trial	14 days	7 days	28 days	15–17
Duration of metronidazole trial	14 days	7 days	28 days	2, 14–16
Dosage of ciprofloxacin trial	1000 mg/day	500 mg/day	1500 mg/day	15–17
Dosage of metronidazole trial	1500 mg/day*	750 mg/day	2250 mg/day	2, 14, 16, 17
Probability of pouchitis if symptomatic	0.52	0.37	0.80	7
Probability of response to ciprofloxacin	0.85	0.60	.99	15–17
Probability of response to metronidazole	0.75	0.50	0.90	2, 14–16
Probability of endoscopy with biopsy for patients who fail empiric regimens	1.00	0.25	1.00	Expert opinion
Diagnostic sensitivity of pouch endoscopic without biopsy	0.97	0.90	1.00	20
Diagnostic delay with biopsy and histology	3 days	1 day	5 days	Expert opinion
Rate of placebo response to empiric antibiotics in symptomatic patients without pouchitis	20%	0%	30%	25, and expert opinion
Rate of adverse effects on drug therapy that require a return clinic visit	0%	10%	90%	Expert opinion

* 20 mg/kg/day for a 75-kg patient.

regimens consisted of 500 mg *p.o. b.i.d.* \times 14 days. For the MTZ trial and CIP trial strategies, patients who did not respond to empiric therapy subsequently underwent pouch endoscopy with biopsy. In the MTZ-then-CIP trial strategy, patients who did not respond to MTZ were treated with CIP before pouch endoscopy with biopsy. In the CIP-then-MTZ trial strategy, patients who did not respond to CIP were treated with MTZ before pouch endoscopy with biopsy. The *test-first* strategies consisted of pouch endoscopy with biopsy and pouch endoscopy without biopsy approaches. Only patients who met diagnostic criteria for pouchitis were treated with MTZ, then CIP if needed.

The target population for this study was adult UC patients with symptoms suggestive of pouchitis. All patients underwent clinical evaluation and pouch endoscopy with biopsy. Patients with Crohn's disease or chronic refractory pouchitis who were taking chronic maintenance therapy were excluded.

Diagnostic Criteria

Patients with a total PDAI score \geq 7 were classified as having pouchitis (13). Cuffitis was defined as inflammation of the rectal cuff and absence of inflammation of the pouch. Symptomatic patients without endoscopic and histological evidence of pouchitis or cuffitis were defined as having IPS.

Treatment

Patients diagnosed with pouchitis were treated with MTZ (2, 14–16) or CIP (15–17) with the dosages mentioned above. A reduction in the PDAI score by more than 3 points was considered as response to therapy (16, 17). In the decision model, only patients with suspected pouchitis who initially received empiric antibiotic therapy but failed to respond

would undergo confirmatory pouch endoscopy and biopsy, as a second cycle of evaluation.

Frequency of Pouchitis Among Symptomatic Patients

Cumulative frequencies of clinical pouchitis from two large series have been reported: 24% of 1005 patients from the Cleveland Clinic (18) and 48% of 1310 patients from the Mayo Clinic (4). Hurst *et al.* from University of Chicago (15) reported a prevalence of pouchitis of 50%. The diagnosis of pouchitis in the majority of patients in those studies, however, was based on clinical symptoms alone. The prevalence of those studies does not reflect the proportion of endoscopically confirmed pouchitis among patients presenting with symptoms. Our recent study showed that only 31 of 61 symptomatic patients (51%) were diagnosed with pouchitis (7). The rest of the patients with symptoms suggestive of pouchitis were diagnosed with cuffitis (7%) or IPS (43%) (7). The frequency of pouchitis in symptomatic patients was estimated to be 51% in the base-case analysis, with a wide range assigned to the variable in the sensitivity analysis (Table 1).

Efficacy of Antibiotic Therapy

A randomized clinical trial of 16 patients compared MTZ (n = 9) (20 mg/kg/day \times 14 days) to CIP (n = 7) (1000 mg/day \times 14 days) therapy. In the MTZ group, 67% of patients responded to therapy, and 33% of patients experienced adverse effects (16). In another placebo-controlled trial, MTZ was effective in 73% of patients with active pouchitis (14). In noncontrolled trials, the reported efficacy of MTZ was 78% (2) and 79% (15). For the base-case analysis, MTZ efficacy was estimated to be 75%.

Our previous study showed that all patients with acute pouchitis (7/7, 100%) responded to CIP and that none of the patients experienced adverse effects (16). The efficacy of combination therapy of CIP and rifaximin for 15 days was 89% in the treatment of 18 patients with chronic pouchitis (17). Because of the small number of cases treated with CIP reported in the literature, CIP efficacy was conservatively estimated to be 85% for the base-case analysis.

The usual dosages for MTZ ranged from 750 mg/day to 1500 mg/day (1, 14, 15); the usual dosage for CIP was 1000 mg/day (15, 17, 18). In the randomized clinical trials, courses of antibiotics, including MTZ and CIP, ranged from 7 to 28 days (14, 15, 17, 19, 20).

Despite the potentially greater efficacy of CIP, MTZ is generally considered as the first-line therapy because of its lower cost. In a small study, eight of 11 patients (94%) with acute pouchitis who failed to respond to or could not tolerate MTZ responded to a 7-day course of CIP (15). In the base-case analysis for the MTZ-then-CIP trial strategy, we assumed that efficacy of MTZ was 75% and efficacy of subsequent CIP in MTZ-resistant pouchitis was 75%, with a 14-day course for each medicine. The efficacy of using rescue MTZ in patients who failed to respond to a conventional dose of CIP has not been reported in the literature. In the CIP-then-MTZ strategy, we assumed that efficacy of MTZ was 75%.

Pouch Endoscopy With and Without Histology

We used the PDAI as a gold standard for diagnosing patients with pouchitis. Significant diagnostic costs for pouchitis can be attributed to endoscopy, endoscopic biopsy, and histopathologic evaluation. Based on our recent study (21) as well as another study (22), a combination of symptoms and endoscopic evidence of mucosal inflammation without histology is adequate to diagnose pouchitis. Specifically, our previous study has shown that symptom assessment and endoscopic evaluation without histology (named *modified PDAI*) yields a sensitivity of 97% and specificity of 100%, compared with the standard PDAI, and the area under the receiver-operating characteristic curve was 0.995 (21). On the other hand, pouch endoscopy without biopsy was estimated to save an average of 2–3 days in making a diagnosis, by avoiding delay in histological evaluation and calculation of a full PDAI score.

Cost-Effectiveness Analysis

Costs considered in the model were the costs of medications, pouch endoscopy, biopsy, and histological evaluation (Table 1). Medication costs for the model were based on the average wholesale price from the 2001 *Drug Topic Red Book* (Medical Economics Company, Montvale, NJ). Costs of pouch endoscopy, biopsy, and histology were estimated from allowed Medicare reimbursement for office-based procedures. To assess these strategies on a clinically meaningful base, the incremental effectiveness measured for the analysis was the difference in the length of time to correct

diagnosis and appropriate treatment. This measure of effectiveness is appropriate, given the differences in time to a correct diagnosis and initiation of appropriate treatment between the strategies and the significant discomfort that patients suffer until they are appropriately treated.

An incremental cost-effectiveness analysis was performed (23–25). The strategies were ranked according to their effectiveness. The costs of the strategies were compared; the incremental cost and the extra cost compared with the next-cheapest alternative were calculated for each strategy. In like manner, the effectiveness (in days) and incremental effectiveness of the strategies were calculated. The incremental cost-effectiveness ratio (ICER) of each strategy was calculated by dividing the incremental cost by the incremental effectiveness. The ICER is interpreted as the additional cost per additional unit of effectiveness compared with the next-cheapest alternative.

If patients responded to antibiotic therapy in the *treat-first* strategies, the regimen was considered to be effective at the end of treatment course. All patients who did not respond to the *treat-first* regimens were assessed with pouch endoscopy with biopsy. For these patients who did not respond, the time to endoscopy with biopsy was used as the measure of effectiveness. We assumed that symptoms in patients without inflammation on endoscopy and histology were due to IPS (7). Estimation of the frequency of placebo effects of antibiotic therapy is difficult in patients with cuffitis or IPS, because there have been no published trials. We did not directly extrapolate data from trials in irritable bowel syndrome, in which the placebo effect rates were extremely variable (26). Therefore, in the base-case analysis, we assigned a rate of 20% placebo response to antibiotics for patients who did not have pouchitis, with a range of 0% to 30% the sensitivity analysis, based on our expert opinion (Table 1).

The *test-first* strategies were considered effective when the correct diagnosis was made and appropriate treatment was started. For the *test-first* strategies in the current study, we assumed that all pouchitis could be diagnosed by pouch endoscopy with biopsy and that 97% of patients with pouchitis could be accurately diagnosed by pouch endoscopy without biopsy (21). For the pouch endoscopy with biopsy strategy, a period of 2–3 days was required for results of the biopsy to become available and to be introduced into the calculation of PDAI, thus delaying correct diagnosis. If a patient was diagnosed with pouchitis, he received appropriate treatment with a 14-day course of MTZ, with an estimated efficacy of 75%. If the patient did not respond to this treatment, a 2-wk course of CIP was given, with an estimated efficacy of 85% (Fig. 1).

We conducted sensitivity analyses to determine the impact of important model uncertainties. One-way sensitivity analysis was performed for all variables, and the model was reanalyzed for a range of values for each parameter. Cost estimates were at least halved and doubled. Other probability estimates and model parameters were varied over gen-

Table 2. Cost-Effectiveness of Diagnostic Strategies

Strategy	Cost	Incremental Cost	Effectiveness (Days)	Incremental Effectiveness (Days Saved)	C/E	Incremental Cost-Effectiveness*
Treat-MTZ	\$193.7		12.2		\$15.9	
Test-no biopsy	\$243.4	\$ 49.7	27.6	15.4	\$ 8.8	\$3.24
MTZ-then-CIP	\$208.1	\$ 14.4	6.7	-5.5	\$30.9	(Dominated)
CIP-then-MTZ	\$261.4	\$ 18.0	7.4	-20.1	\$35.1	(Dominated)
Treat-CIP	\$278.8	\$ 35.4	12.9	-14.6	\$21.6	(Dominated)
Test-biopsy	\$352.3	\$108.9	25.0	-2.6	\$14.1	(Dominated)

C/E = cost-effectiveness ratio.

* Incremental costs and effectiveness are not calculated for dominated strategies.

erous ranges (Table 1). A sensitivity analysis was conducted by simultaneously increasing and decreasing the duration of treatment with MTZ and CIP. A sensitivity analysis was conducted whereby the effectiveness of *treat-first* regimens was based on the beginning of regimens to which patients responded. Sensitivity analyses were also performed to account for second clinic visits in patients who did not respond to empiric antibiotic therapy and who experienced adverse effects from the drug therapy.

RESULTS

Cost per correct diagnosis and initiation of appropriate treatment was lowest for MTZ trial (\$194) and MTZ-then-CIP trial (\$208), followed by pouch endoscopy without biopsy (\$243), CIP-then-MTZ trial (\$261), CIP trial (\$279), and pouch endoscopy with biopsy (\$352) (Table 2, Fig. 2). CIP trial, MTZ-then-CIP trial, CIP-then-MTZ trial, and pouch endoscopy with biopsy strategies were associated with higher costs and lower effectiveness than other strategies

(i.e., were “dominated”) (Table 2). The pouch endoscopy without biopsy strategy costs \$50 more per patient than the MTZ trial strategy but also resulted in an additional 15 days of diagnosis and appropriate treatment per patient. Therefore, the pouch endoscopy without biopsy strategy costs \$3 per additional day of being diagnosed and initiated for appropriate treatment.

In the sensitivity analysis, if the cost of pouch endoscopy without biopsy exceeded \$375 (baseline \$210), pouch endoscopy with biopsy is no longer dominated, although it still remains less effective than pouch endoscopy without biopsy. Calculating the effectiveness of *treat-first* regimens based on beginning of regimens to which patients responded did not change the relationship between the strategies.

We assumed that pouch endoscopy and histology along with symptom assessment could accurately diagnose all patients with pouchitis on a single clinic visit. However, some patients, especially symptomatic patients without pouchitis who had empirically been treated with antibiotics and did not respond to the therapy might require a second clinic

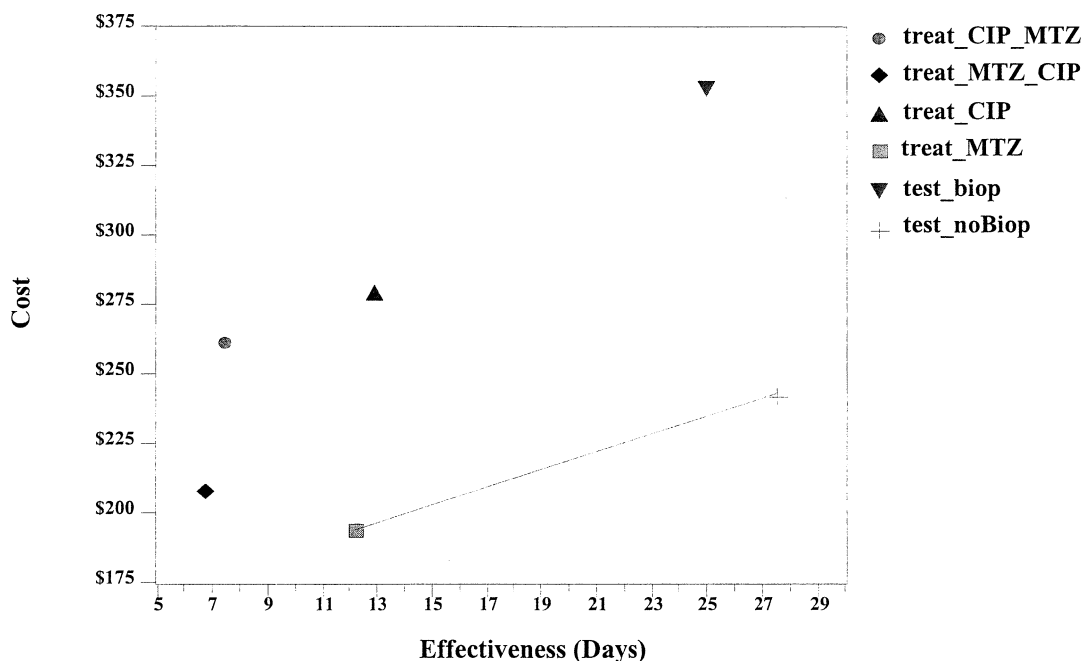


Figure 2. Costs vs effectiveness of diagnostic strategies.

visit to have an accurate diagnosis by pouch endoscopy and biopsy. Therefore, we performed a sensitivity analysis to account for the patients who would require a second clinic visit. Inclusion of the cost of a second clinic visit did not appreciably change the results of the base-case analysis.

We anticipated that some patients undergoing the treat-first strategies would develop adverse effects, such as nausea, dysgeusia, or oral or vaginal thrush. Although some of those patients would choose to simply discontinue taking the medicine, others (10–100% in the sensitivity analysis) could return for an additional clinic visit and/or receive medical therapy for the adverse effects, which would incur additional costs for the treat-first strategies. We estimated that a single level III established clinic visit for an established patient would cost \$39.07 (Current Procedural Terminology code 99213). Assuming 10% of patients who received drug therapy experienced adverse effects, the ICER for the pouch endoscopy without biopsy decreased from \$2.98 in the base-case analysis to \$2.76. If we assumed 90% of patients who received drug therapy developed adverse effects, the ICER for the pouch endoscopy without biopsy strategy would further decrease to \$1.72.

DISCUSSION

There are no symptoms specific for the diagnosis of pouchitis. Our previous study showed that up to 49% of symptomatic patients did not have pouchitis, based on the PDAI criteria. These patients, with either cuffitis or IPS, would have been unnecessarily exposed to antibiotic treatment and would have had their diagnosis delayed if they had been treated empirically with antibiotics (7). Other problems of the *treat-first* strategies include cost (especially CIP), adverse effects (peripheral neuropathy, dysgeusia, nausea, and vomiting caused by MTZ), concerns regarding microbial resistance with overuse of antibiotics, and morbidity from delay of appropriate treatment for the patients with symptoms due to causes other than pouchitis.

Currently there is no consensus regarding the best way to approach a symptomatic patient with IPAA. Our previous study suggests that symptom assessment alone is not reliable to accurately diagnose pouchitis and that endoscopic and histological evaluation is needed along with symptom assessment (5). Cost-effectiveness for the *test-first* strategies has not been previously compared with the commonly used *treat-first* strategies. The current study showed that pouch endoscopy with biopsy bore the highest cost (\$352) among all six competing diagnostic strategies. The high costs together with the inherent delay in calculating PDAI scores, especially because of the histological component, limit the initial pouch endoscopy with biopsy strategy to refractory patients with such conditions as chronic pouchitis or Crohn's disease of the pouch.

From a clinical standpoint, pouch endoscopy without biopsy and histology could simplify the evaluation of symptomatic patients with IPAA. Our recent study showed that a

diagnostic instrument consisting of symptom assessment and endoscopy evaluation without biopsy and histology, with a cut-off point of 5 on a 12-point scale, had a sensitivity of 97% and specificity of 100%, when compared with the standard PDAI with a cut-off point of 7 on a scale of 18 (19). The current study demonstrated that this strategy bore a low cost (\$243), comparable to the lowest-cost approach, the MTZ trial strategy (\$194). Although this strategy costs \$50 more than MTZ trial strategy, it was offset by a faster time to correct diagnosis and initiation of appropriate treatment (15 days). The incremental cost per additional day of being accurately diagnosed and thus being initiated appropriate treatment was \$3 for the pouch endoscopy without biopsy strategy. In other words, quicker diagnosis and treatment occur in the pouch endoscopy without biopsy strategy when compared with the MTZ trial strategy. We consider this extra cost to be trivial compared with 15 days of suffering and anxiety borne by patients in the MTZ trial group. Therefore, we consider the pouch endoscopy without biopsy strategy to be the most cost-effective among all six competing strategies. Despite the favorable lower cost of the MTZ trial strategy, the test-first strategy of pouch endoscopy without biopsy is recommended because of its comparable cost, reduced morbidity from diagnostic delay for pouchitis, and avoidance of unnecessary antibiotics in patients without pouchitis.

A combination therapy of MTZ and CIP was occasionally used in the treatment of chronic pouchitis. In a recent, open-label, nonrandomized trial, 82% of patients (36/44) with relapsing pouchitis or chronic pouchitis who received a combination therapy of CIP (500 mg *b.i.d.*) and MTZ (500 mg *b.i.d.*) for 4 wks were able to achieve remission (20). However, our decision model did not integrate this recent study because the target population of the current study was patients with acute symptoms suggestive of pouchitis who underwent initial evaluation. In routine clinical practice, combination therapy with MTZ and CIP is hardly used as an initial therapy in patients with pouchitis.

The six diagnostic strategies theoretically work regardless of whether a patient has previously tried therapy. A patient who previously did not respond to MTZ essentially has the MTZ-first, the CIP-then-MTZ, and the MTZ-then-CIP strategies eliminated. In such patients, the remaining three diagnostic options can be compared. The preferred strategy in this situation is the pouch endoscopy without biopsy. That strategy dominates the CIP-first and the pouch endoscopy with biopsy strategies (*i.e.*, has lower costs and higher effectiveness).

From a societal perspective, a lack of timely treatment due to delayed diagnosis, and adverse effects from inappropriate therapy would incur indirect costs, such as loss of productivity or leisure time; this also tips the balance to favor the pouch endoscopy without biopsy strategy. On the other hand, some symptomatic patients with IPAA would prefer the *treat-first* alternative, so as to avoid the inconvenience and discomfort of an endoscopic procedure; this

would tip the balance to favor the *treat-first* strategies. Given that calculation of costs from the societal perspective is difficult, and the societal perspectives favoring the *treat-first* or *test-first* strategies were viewed with balance, our study did not further analyze from this perspective.

Although we recommend the pouch endoscopy without biopsy strategy as an initial approach to patients with symptoms suggestive of acute or acute relapsing pouchitis, the pouch endoscopy with biopsy and histology would be appropriate for patients suspected of having Crohn's disease of the pouch, chronic pouchitis, or cytomegalovirus related pouchitis, despite its higher cost. Fortunately Crohn's disease of the pouch (27–29) and cytomegalovirus pouchitis (30–32) are rare.

The majority of studies on the diagnosis and treatment of pouchitis on which our decision analytic model was based have limited sample sizes. It is not clear whether the studied population is a true representation of symptomatic patients with UC and IPAA, and whether changes of the size of study populations would alter cost-effectiveness ratios and ICERs. Based on the limited information available, we generously assigned wide ranges for the value of variables in the sensitivity analysis. Conclusions drawn from the base-case analysis have not been affected significantly by the results of the sensitivity analysis.

Although the MTZ-trial first bore the lowest cost, we believe that making a timely and accurate diagnosis and instituting appropriate therapy in a cost-effective manner is the best way to provide our patients with high quality care without wasting limited health care resources. In the future, there might be new noninvasive and cost-effective ways to diagnose pouchitis, such as with the identification of biomarkers. Until then, the pouch endoscopy without biopsy strategy is the most cost-effective and is therefore recommended, to avoid diagnostic delay and unnecessary antibiotic use and to enable timely administration of appropriate therapy.

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