Cost-effectiveness Analysis of Adjunct VSL#3 Therapy Versus Standard Medical Therapy in Pediatric Ulcerative Colitis

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See ''On the Cost-effectiveness of the Use of Probiotics in Inflammatory Bowel Disease'' by Samnaliev and Lightdale on page 473.

ABSTRACT

Background: Inflammatory bowel diseases (IBDs) are costly chronic gastrointestinal diseases, with pediatric IBD representing increased costs per patient compared to adult disease. Health care expenditures for ulcerative colitis (UC) are >$2 billion annually. It is not clear whether the addition of VSL#3 to standard medical therapy in UC induction and maintenance of remission is a cost-effective strategy.

Patients and Methods: We performed a systematic review of the literature and created a Markov model simulating a cohort of 10-year-old patients with severe UC, studying them until 100 years of age or death. We compared 2 strategies: standard medical therapy versus medical therapy + VSL#3. For both strategies, we assumed that patients progressed through escalating therapies—mesalamine, azathioprine, and infliximab—before receiving a colectomy + ileal pouch anal anastamosis (IPAA) if the 3 medical therapy options were exhausted. The primary outcome measure was the incremental cost-effectiveness ratio (ICER), defined as the difference of costs between strategies for each quality-adjusted life-year (QALY) gained. One-way sensitivity analyses were performed on variables to determine the key variables affecting cost-effectiveness.

Results: Standard medical care accrued a lifetime cost of $203,317 per patient, compared to $212,582 per patient for medical therapy + VSL#3. Lifetime QALYs gained was comparable for standard medical therapy and medical therapy + VSL#3 at 24.93 versus 25.05, respectively. Using the definition of ICER <50,000/QALY as a cost-effective intervention, medical therapy + VSL#3 produced an ICER of $79,910 per QALY gained, making this strategy cost-ineffective. Sensitivity analyses showed that 4 key parameters could affect the cost-effectiveness of the 2 strategies: cost of colectomy + IPAA, maintenance cost after surgery, probability of developing pouchitis after surgery, and the quality of life after a colectomy + IPAA. High surgical and postsurgical costs, a high probability of developing pouchitis, and a low quality of life after a colectomy + IPAA could make adjunct VSL#3 use a cost-effective strategy.

Conclusions: Given present data, adjunct VSL#3 use for pediatric UC induction and maintenance of remission is not cost-effective, although several key parameters could make this strategy cost-effective. The quality of life after an IPAA is the single most important variable predicting whether this procedure benefits patients over escalating standard medical therapy.

Key Words: colectomy, cost-effectiveness analysis, decision analysis, ileal pouch anal anastamosis, inflammatory bowel diseases, quality of life, VSL#3

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Inflammatory bowel disease (IBD) represents an increasingly prevalent chronic disease, requiring substantial health care resources in the United States (1–6). Approximately $2.1 billion annually are spent on chronic ulcerative colitis (UC) alone, and pediatric patients represent an increased health care burden (7). Recent investigations have used insurance claim data to summarize direct health care costs of IBD, but indirect and out-of-pocket expenses by patient families are difficult to assess. Increasingly popular among patients with IBD are nontraditional pharmacological therapies, including probiotics.

A recent investigation by Miele et al (8) suggests that a specific blend of high-dose probiotics, VSL#3, may be beneficial in acute pediatric UC exacerbation and maintenance of remission. VSL#3 is composed of 8 strains of bacteria (1 strain of streptococcus thermophilus, 3 strains of bifidobacterium, and 4 strains of lactobacillus) and contains 450 billion live probiotic bacteria per sachet. Adult studies have already shown the efficacy of VSL#3 in treatment of pouchitis after an ileal pouch anal anastamosis (IPAA) (9–11), but VSL#3 use as adjunct therapy in pediatric UC is a more novel concept that requires further investigation before recommending this added therapy as the standard of care. Furthermore, probiotics such as VSL#3 are rarely covered by insurance providers, and out-of-pocket expenses for patients and families may be costly (approximately $200/month for VSL#3 pediatric dosing).

The aims of this investigation were to perform a cost-effectiveness analysis comparing standard medical therapy to medical therapy + VSL#3 and to perform a sensitivity analysis to determine key parameters affecting the cost-effectiveness of these 2 strategies.

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METHODS

Decision Analytic Model, Subjects, and Outcomes

We performed a cost-effectiveness analysis following the recommendations of the US Panel on Cost Effectiveness in Health and Medicine in the development of the model and in the analysis of results, including taking a societal perspective, considering costs and benefits over a lifetime horizon, and discounting at 3% annually (12). (A societal perspective includes direct health care costs paid by public and private payers, patients, and their families and caregivers.) Costs were converted to 2009 US dollars (USD) using the US gross domestic product deflator (13). Base case parameter values and ranges and distributions used in sensitivity analysis are presented in Table 1 (14–21). We implemented the model in TreeAge Pro 2009 Suite (TreeAge Software, Williamstown, MA) and Microsoft Excel 2007 (Microsoft, Redmond, WA).

We developed a Markov computer model to simulate a cohort of 10-year-old newly diagnosed patients with UC from diagnosis until death or 100 years of age using 3-month time steps. Figure 1 shows a simple schematic of our model. Markov models capture long-term effects of a chronic disease and allow movements between health states based on probabilities found in the literature, mimicking real-life clinical scenarios. Our simulated cohort consists of 10,000 patients with new moderate to severe UC confirmed by colonoscopic biopsies. We calculated the differences in costs and benefits (measured in life-years and quality-adjusted life-years [QALYs]) between 2 treatment strategies: standard medical therapy and medical therapy + VSL#3.

The primary outcome measure was the incremental cost-effectiveness ratio (ICER), which is defined as the difference in costs in USD divided by the difference in effectiveness in QALYs between 2 competing interventions. It is standard practice to use lifetime QALYs gained to compare health benefits in a formal decision analysis. Derived from published utility states, which measure patients' preference to certain disease states, values range from 0 (death) to 1 (perfect health). A Markov model adds patients' lifetime costs and utilities with certain health disabilities, allowing a comparison of health care strategies

TABLE 1. Model assumptions

Variables	Base case	1-way sensitivity range	References
Transition probabilities			
Initial UC flare responding to mesalamine/corticosteroid	0.344	0.25–0.75	(14)
Initial UC flare responding to mesalamine/corticosteroid + VSL#3	0.928	0.25–0.95	(14)
UC flare responding to azathioprine	0.550	0.25–0.90	(15)
UC flare responding to infliximab	0.447	0.25–0.90	(16)
UC flare after remission on mesalamine	0.031	0.016–0.062	(14)
UC flare after remission on mesalamine + VSL#3	0.020	0.01–0.04	(14)
UC flare after remission on azathioprine	0.064	0.032–0.128	(15)
UC flare after remission on infliximab	0.064	0.032–0.128	(15)
Pouchitis after colectomy + IPAA	0.043	0.021–0.20	(17)
Stabilizing pouchitis after colectomy + IPAA	0.820	0.20–0.90	(17)
CRC/dysplasia on any medical therapy	0.0001	—	(18)
Perioperative death after colectomy + IPAA	0.01	—	
Costs			
UC severe UC flare with initial hospitalization (1 time)	$4017	$2009–$8034	LPCH, OSHPD, CMS
Mesalamine after initial flare (per mo)	$995	$497–$1991	Online pharmacies
Mesalamine + VSL#3 after initial flare (per mo)	$1169	$584–$2337	Online pharmacies
Initial azathioprine (per mo)	$599	$299–$1197	Online pharmacies
Maintenance azathioprine (per mo)	$348	$174–$696	Online pharmacies
Initial infliximab (per mo)	$28947	$14,474–$57,894	Online pharmacies
Maintenance infliximab (per mo)	$4825	$2412–$9649	Online pharmacies
Colectomy + IPAA (1 time)	$68500	$34,250–$137,000	LPCH, OSHPD, CMS
Stable health after colectomy + IPAA (per mo)	$177	$89–$400	LPCH, OSHPD, CMS
Pouchitis (per mo)	$1126	$563–$2252	LPCH, online pharmacies
Diagnosing CRC/dysplasia (1 time)	$1189	$595–$2378	LPCH, OSHPD, CMS
Utilities			
UC flare	0.48	0.40–0.60	(19)
UC remission	0.91	0.80–0.95	(20)
Pouchitis	0.57	0.40–0.80	(19)
Initially after receiving colectomy + IPAA	0.80	0.40–0.90	(20)
Stable health after receiving colectomy + IPAA (6 mo postoperatively)	0.89	0.40–0.98	(19,20)
After diagnosis of CRC/dysplasia	0.74	0.60–0.80	(21)
Death	0.00	—	
Discount rate			
Annual discount rate	0.03	0.0–0.05	

CMS = Centers for Medicare and Medicaid Services; CRC = colorectal cancer; IPAA = ileal pouch anal anastamosis; LPCH = Lucile Packard Children's Hospital; OSHPD = Office of Statewide Health Planning and Development; UC = ulcerative colitis.

based on the lifetime QALYs gained for each competing intervention.

In each cycle of our model, patients in any health state could die at a rate based on average age-specific mortality as estimated by the Centers for Disease Control and Prevention (22). Patients who survive may continue on their present treatment regimen or they may stop responding to that line of treatment and may move to the next line of treatment. All of the patients eventually receive a subtotal colectomy with IPAA once medical management alternatives have been exhausted.

Once a patient receives a colectomy with IPAA after failing medical therapy options, they move into a "cured" health state initially but are at risk for developing pouchitis. Pouchitis is treated with metronidazole and ciprofloxacin and undergoes the probability of reestablishing a cured health state according to rates found in the literature (Table 1).

Medical Therapies

Patients in either therapy arm progressed through treatment options as recommended by guidelines for management of moderate to severe UC according to the American College of Gastroenterology (23). For induction therapy of the initial UC flare, patients in the standard medical therapy arm received mesalamine and intravenous/oral steroids and then were maintained on mesalamine $50\,mg \cdot kg^{-1} \cdot day^{-1}$ (up to 2.4 g/day) after the initial exacerbation. The patients in the medical therapy + VSL#3 arm received VSL#3 (weight-based dose range of 450–1800 billion bacteria/day) as adjunct therapy to mesalamine and steroids, then progressed to mesalamine with VSL#3 as the initial maintenance regimen.

If patients failed mesalamine or mesalamine with VSL#3, either because they did not respond to initial induction or they relapsed after successfully achieving remission, they were started on azathioprine $2\,mg \cdot kg^{-1} \cdot day^{-1}$. A nonresponse to azathioprine therapy or failure to remain in remission escalated medical treatment to infliximab. Infliximab 5 mg/kg per dose at week 0, 2, and 6 was used for induction, and subsequent maintenance infusions were given every 8 weeks.

Health State Transition Probabilities

A summary of model assumptions for health state probabilities is shown in Table 1. The model used health state transition probabilities, which estimate rates of moving from 1 health state to another, published in the literature. Pertinent studies were selected by performing a thorough review of the literature on MEDLINE, Google Scholar, and the Cochrane controlled trials registry. Additional studies were identified by referring to the bibliographies of the selected manuscripts. Manuscripts selected for our model were based on 2 main criteria: the quality of the investigation (randomized controlled trials or large observational studies were given priority), and the clinical applicability of the findings to a pediatric UC cohort. The base case value was derived from means or medians from the published literature.

The probabilities of patients responding or flaring while receiving 5-aminosalicylic acid ± corticosteroids come directly from a randomized placebo-controlled clinical trial for adjunct VSL#3 use in pediatric UC (14). The probability of a UC flare responding to infliximab comes from the ACT I and II trials (16), which are the largest randomized placebo-controlled clinical trials to date for infliximab use in UC. A separate cross-reference was made to a study on infliximab use in pediatric UC by Fanjiang et al for comparison, although it was not used in the model because of the retrospective design and small sample size (24). The probabilities of UC patients' clinical response to azathioprine come from Chebli et al (15); this recent prospective observational study was conducted for a 3-year period and had as its outcome measure steroid-free UC remission. Probabilities of pouchitis after IPAA come from Ståhlberg et al (17), who reported the epidemiology of pouchitis after IPAA during a 13-year span using a substantial sample size (n = 113). The risks of colon cancer are included in the model based a landmark population-based study by Söderlund et al (18).

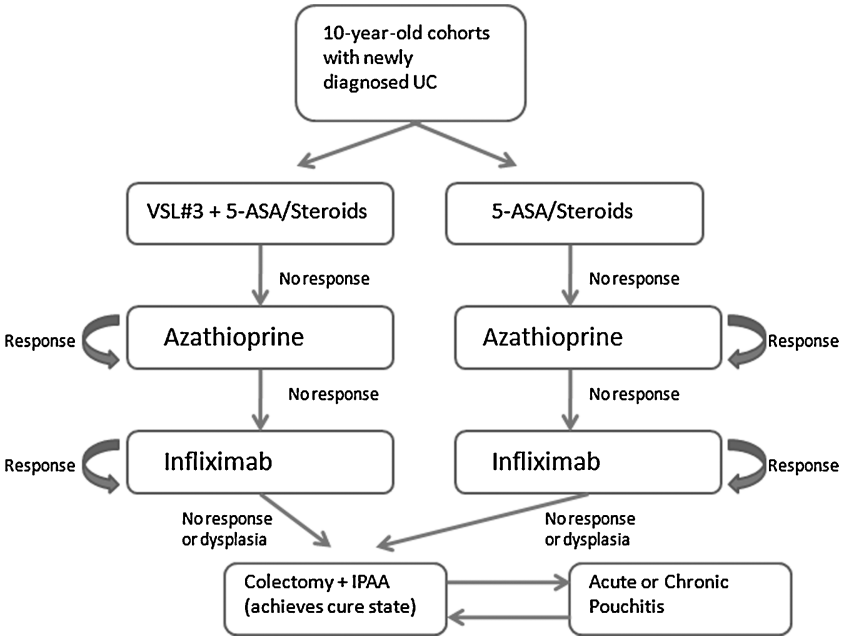

FIGURE 1. Simple model schematic. 5-ASA = 5-aminosalicylic acid; IPAA = ileal pouch anal anastamosis.

Costs

A summary of model assumptions for costs is shown in Table 1. Direct costs of hospitalizations, outpatient visits, procedures, and laboratory costs were estimated using national reimbursements from the Centers for Medicare and Medicaid Services (CMS) for 2009 and average reimbursement rates from all available deidentified patient billing records in 2009 at Lucile Packard Children's Hospital (LPCH)/Stanford University Medical Center. To ensure generalizability of the cost data, tables from the Office of Statewide Health Planning and Development (OSHPD) were used to validate institutional rates to best reflect the national average of costs. Wholesale costs of medical therapies (prednisone, mesalamine, azathioprine, and infliximab) were estimated by prices from 2 online pharmacies (drugstore.com and americarx.com) and validated with the drug costs at the LPCH pharmacy.

Utilities

Utilities estimate patients' quality of life, ranging from 0 (death) to 1 (perfect health). Health benefits in this model are estimated by adding all of the utilities associated with each intervention in the model throughout the lifetime perspective. The sum of the utilities for each strategy arrives at a lifetime QALY. The model assumptions for utilities are shown in Table 1. Established studies measuring utilities were performed using time tradeoff (TTO) or standard gamble (SG) methods (18,19). Patients in severe UC flare and remission had a utility of 0.48 and 0.91, respectively. Tengs and Wallace (19) reported the largest compilation of utility states using methods estimating quality of life, including TTO and SG methods, which found that patients who had a stable colectomy and an ileal pouch had a utility of 0.91 (same as a patient in UC remission). Muir et al conducted a separate study on patients with UC who had an IPAA and found a perioperative (<6 months) utility of 0.8 and a stable cure state (>6 months postsurgery) utility of 0.87. For the purposes of our analysis, we used a utility of 0.8 for patients within the 0- to 6-month perioperative period, and averaged the 2 estimates from Tengs and Wallace and Muir et al to arrive at a post–6-month utility of 0.89 for patients with a stable IPAA. The model assumes a utility of 0.74 and 0.57 for CRC or dysplasia and pouchitis, respectively, as reported by Tengs and Wallace (19).

Sensitivity Analysis

We performed a deterministic sensitivity analysis on all health state probabilities, costs, and utilities in the model (Table 1). One-way deterministic sensitivity analyses were performed over the specified range of values derived from the literature and clinical judgment.

RESULTS

Standard Medical Therapy Versus Medical Therapy + VSL#3

A summary of the cost-effectiveness of the 2 strategies is shown in Table 2. The standard medical therapy strategy accrued a total discounted lifetime cost of $203,317. The medical therapy + VSL#3 strategy accrued a total discounted lifetime cost of $212,582. This represents an incremental lifetime cost of $9264 if VSL#3 were standard adjunct therapy with steroids and mesalamine at the time of diagnosis. The total lifetime QALYs for standard medical therapy and medical therapy + VSL#3 are 24.93 and 25.05, respectively. This represents a small incremental QALY difference of 0.12 between the 2 strategies. More important, the ICER (Δcosts/ΔQALY) was $79,910 per QALY gained. Typically, ICERs <$50,000 per QALY gained is considered cost-effective (12). The cost-effectiveness plane is shown in Figure 2, which plots the medical therapy + VSL#3 strategy at a slightly higher lifetime QALY and higher total lifetime costs compared with the standard medical therapy strategy. A separate microsimulation analysis was performed, which ran the model 1000 independent times to estimate the 95% confidence intervals for costs, QALYs, and the incremental costs and QALYs.

Deterministic Sensitivity Analysis

We tested the robustness of our model by varying individual variable inputs over a range of low to high values as listed in Table 1. A deterministic sensitivity analysis tests each variable to identify key variables in the model that may affect the cost-effectiveness of the competing strategies. In our investigation, we determined sensitive 4 variables of interest, which could influence the cost-effectiveness of the competing strategies. These 4 key parameters were the cost of colectomy + IPAA, the cost of stable health after colectomy + IPAA, the probability of pouchitis after colectomy + IPAA, and the utility (quality of life) of stable health after colectomy + IPAA.

Cost of Colectomy + IPAA

The estimated one-time cost of receiving a colectomy + IPAA was the least-sensitive parameter, but we included this variable for discussion because extremely high costs could influence the cost-effectiveness of adjunct VSL#3 use. The base cost for this variable was $68,000, varying between $34,250 and $137,000. As Figure 3 shows, increasing the cost of the surgery made the medical therapy + VSL#3 more cost-effective (smaller ICER). If the procedure cost more than $116,000, then the ICER was less than the cost-effective threshold of $50,000/QALY.

TABLE 2. Cost-effectiveness of standard medical therapy vs medical therapy with VSL#3

Strategy	Cost	QALY	Incremental cost	Incremental QALYs	ICER
Standard medical therapy	$ 203,317 ($146,716–$354,662)	24.93 (13.26–27.48)	—	—	—
Medical therapy with VSL#3	$212,582 ($159,571–$334,218)	25.05 (13.34–27.87)	$9264 ($−136,102–$107,412)	0.12 (0–0.37)	$79,910

Average lifetime discounted costs and quality-adjusted life-years (QALYs) and incremental cost-effectiveness ratios (ICERs) of the 2 competing interventions (per patient) with empirically estimated 95% confidence intervals from 1000 microsimulations.

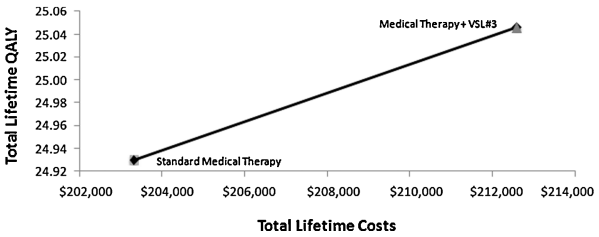

FIGURE 2. Cost-effectiveness plane. Although the addition of VSL#3 adds incremental lifetime costs to standard medical therapy, the lifetime benefits (measured in quality-adjusted life-years [QALYs] gained) are minimal (a difference of 0.12 QALYs gained).

Cost of Stable Health After Colectomy + IPAA (Per Month)

The cost of maintaining stable health after colectomy + IPAA was a sensitive key parameter. We assumed that a stable patient after colectomy + IPAA would cost on average $177 per month from biannual outpatient follow-up visits with basic laboratory tests ($1376/year) and an annual surveillance colonoscopy ($753). The base cost of $177/month was varied between $89 and $400/month. As Figure 4 shows, increasing the cost of maintaining postsurgical patients increases the cost-effectiveness of medical therapy + VSL#3. If the monthly maintenance cost was >$302, the ICER was less than the cost-effective threshold of $50,000/QALY.

Probability of Pouchitis After Colectomy + IPAA

The monthly probability of developing pouchitis after colectomy + IPAA was another key parameter affecting cost-effectiveness. Our literature search showed that approximately 0.043 of the patients developed pouchitis per month after receiving a colectomy + IPAA. We varied this probability from 0.021 to 0.2. As Figure 5 shows, increasing the likelihood of pouchitis in postsurgical patients increased the cost-effectiveness of medical therapy + VSL#3. If the monthly probability of pouchitis after colectomy + IPAA was >0.093, then the ICER was less than the cost-effective threshold of $50,000/QALY.

Utility of Stable Health After Colectomy + IPAA

The utility of stable health after colectomy + IPAA was the final parameter potentially affecting cost-effectiveness of adjunct VSL#3 use. Assuming a base case utility for this variable of 0.89 (19,20), the parameter varied from 0.4 to 0.98. Figure 6 shows that increasing the utility from 0.4 increases the ICER until a peak ICER of $221,447/QALY at a utility of 0.92. Threshold analysis on this variable indicates that a baseline utility <0.86 would make adjunct VSL#3 use a cost-effective strategy. If the actual utility of the stable health state after a colectomy + IPAA is comparable or exceeds the utility of UC remission state of 0.91, then adjunct VSL#3 use is cost-ineffective.

DISCUSSION

We chose to investigate the cost-effectiveness of VSL#3 in particular because the use of probiotics has been increasing in the treatment of IBDs. There is increased demand for probiotics and other ''natural'' therapy options among patients and families, forcing gastroenterologists to address the issue of efficacy, adherence to historically accepted medical therapy regimens, and the incremental cost–benefit of these adjunct therapies. To our knowledge, VSL#3 represents mainly out-of-pocket expenses for patients' families. Most private and government-subsidized insurance plans do not reimburse for VSL#3 or other probiotics. Expensive medical therapy options should be proven to be not only clinically efficacious but also cost-effective, especially when it adds

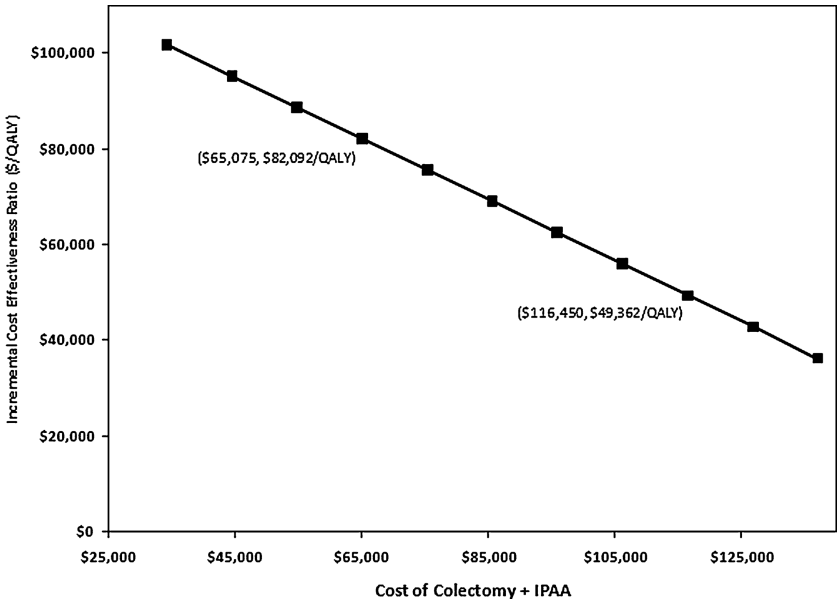

FIGURE 3. Sensitivity analysis on the cost of colectomy + IPAA (ileal pouch anal anastamosis). The base cost is $68,000. Varying this estimate from $34,250 to $137,000 produced a cost-effective incremental cost-effectiveness ratio of <$50,000 per quality-adjusted life-year (QALY) at a high cost of surgery (>$116,000).

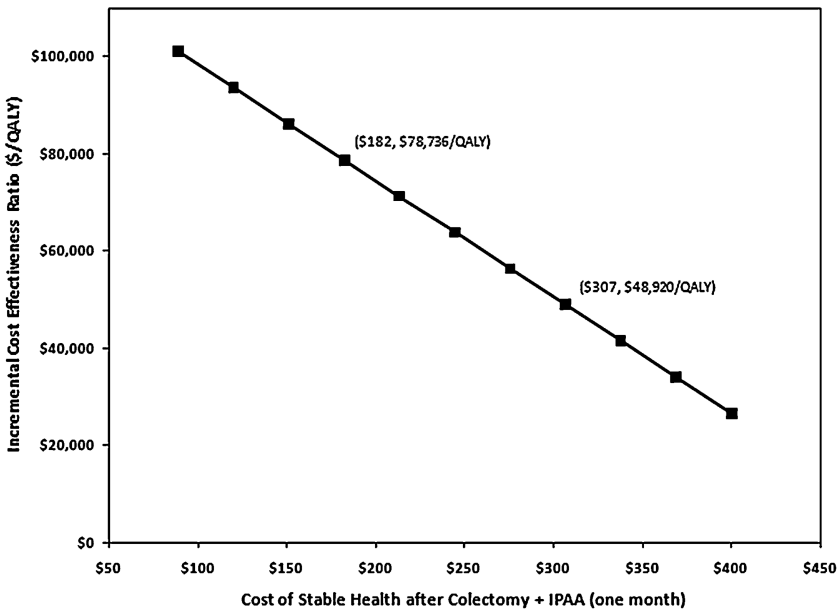

FIGURE 4. Sensitivity analysis on the cost of stable health after colectomy + IPAA (ileal pouch anal anastamosis; per month). The base cost is $177. This estimate varied from $84 to $400. If the cost of maintaining stable health after a colectomy + IPAA is more (>$302 per month), then adding VSL#3 to medical therapy is cost-effective. ICER = incremental cost-effectiveness ratio.

another layer to standard medical therapy. As pediatric subspecialists, we have generally not focused our investigative efforts on showing the economic impact of clinical decisions. Our simple Markov model showcases the utility of applying decision analyses to different clinical strategies and provides a more global insight into the economics of our practice in pediatric gastroenterology.

In this investigation, we aimed to determine the cost-effectiveness of adding VSL#3 to standard medical therapy (medical therapy + VSL#3). We found that adding VSL#3 to mesalamine and corticosteroids at the time of UC diagnosis produced an incremental cost of $9264 over a lifetime. The difference in quality of life (incremental QALY of 0.12) was only marginally increased for medical therapy + VSL#3. An ICER of $79,910/QALY gained is technically considered not cost-effective because this is above the $50,000/QALY gained threshold for cost-effective interventions.

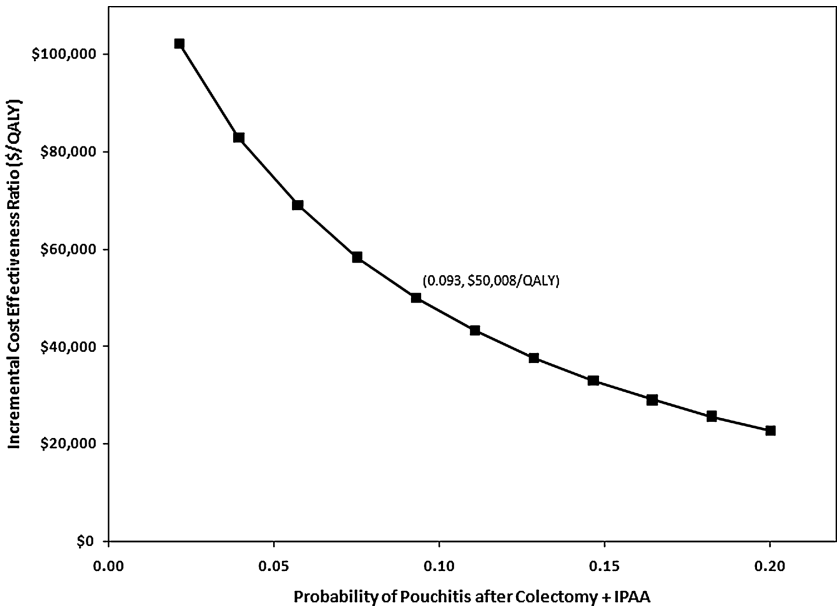

FIGURE 5. Sensitivity analysis of the probability of pouchitis after colectomy + IPAA (ileal pouch anal anastamosis). The base case probability is 0.043. This estimate varied from a low probability of 0.021 to a high probability of 0.2. The analysis indicates that a high probability of developing pouchitis (≥0.093) will make adding VSL#3 to medical therapy cost-effective. ICER = incremental cost-effectiveness ratio.

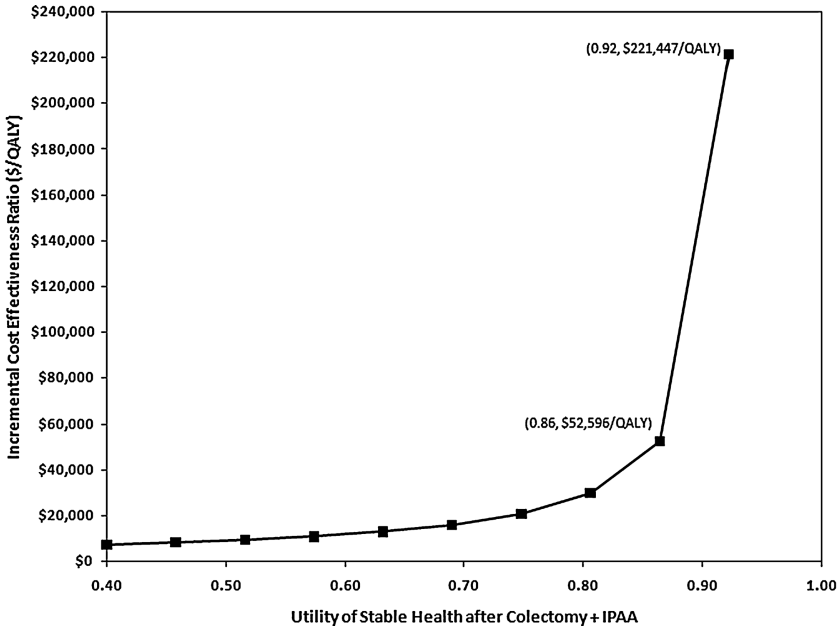

FIGURE 6. Sensitivity analysis of the utility of stable health after colectomy + IPAA (ileal pouch anal anastamosis). The base case utility (a measurement of quality of life) was 0.89. The estimate varied between a poor quality of life estimate of 0.4 and a near-perfect estimate of 0.98. This analysis indicates that poorer quality of life after surgery (0.4–0.85) would make adding VSL#3 cost-effective, but a quality of life that is comparable to or better than the remission state (≥0.86) would make adding VSL#3 cost-ineffective. ICER = incremental cost-effectiveness ratio.

Our sensitivity analysis revealed 4 sensitive variables affecting the cost-effectiveness of adjunct VSL#3 use: the cost of colectomy + IPAA, the cost of stable health after colectomy + IPAA, the probability of pouchitis after colectomy + IPAA, and the utility (quality of life) of stable health after colectomy + IPAA. Using wide variations in 1-way sensitivity ranges for all of these variables, we showed that an extremely high cost of a colectomy + IPAA (>$116,000) (Fig. 3), a high monthly maintenance cost after surgery (>$302) (Fig. 4), a high monthly probability of developing pouchitis (>0.093) (Fig. 5) after an IPAA, and a low baseline quality of life after surgery (<0.86) (Fig. 6) could make adjunct VSL#3 use a cost-effective strategy.

Interestingly, most important for our discussion, our sensitivity analysis also showed that patients' quality of life after an IPAA was the most sensitive variable. When the colectomy + IPAA produces a quality of life that is comparable (utility >0.86) to UC remission, the incentive for any medical therapy is offset by the potentially good outcome of choosing surgery. A separate investigation needs to be done to analyze this scenario further because our model only raises the hypothesis of recommending this procedure more readily to pediatric patients with UC, perhaps especially to those individuals with severe pancolitis. Specifically, future health services research is needed to delineate the clinical scope, efficacy, and cost-effectiveness of choosing colectomy + IPAA in pediatric UC over conventional medical therapy options.

The major limitation to our study was the lack of data about VSL#3 except from 1 small randomized controlled trial for pediatric UC by Miele et al (8). Although the investigators in this randomized controlled trial showed a statistically significant benefit of adding VSL#3 to induction and maintenance of remission using mesalamine + VSL#3, it is unknown how VSL#3 can alter the clinical course of UC on patients escalating through immunomodulators and biological therapies. It is conceivable, however, that the difference in treatment effects will be even smaller in patients taking either immunomodulators and/or biologics such as azathioprine or infliximab, because the disease activity has progressed beyond what is manageable without substantial immunosuppression. Nevertheless, our Markov model would be more exhaustive if data existed measuring clinical differences if VSL#3 were added to all of the medical therapies.

Another limitation of our investigation was that the majority of the transition probabilities were derived from randomized clinical trials of adult patients with UC. Large randomized controlled trials are often lacking in pediatrics. We do not believe this to be a significant limitation because there is evidence to suggest a high correlation between adult and pediatric severity of IBDs (25). Finally, we used single-center reimbursement rates for some costs, which may not represent national averages. We attempted to standardize the cost data by comparing all of the cost data to national rates from CMS and state rates from OSHPD whenever possible.

In conclusion, we have shown that adjunct VSL#3 therapy, as it is presently proposed by the available evidence, is not cost-effective, although there were multiple variables that could make adjunct VSL#3 use a cost-effective strategy. Our investigation highlights the need to objectively evaluate clinical interventions in pediatric gastroenterology, especially in chronic digestive diseases such as IBDs, in which layers of multiple medical therapy options can obscure the underlying optimal strategy. Perhaps the most important discussion from our analysis is the question of whether pediatric patients with UC would benefit from electively undergoing a colectomy + IPAA. Small changes in this variable produced large changes in the ICER near the utility of UC remission state, making this the most important variable. Further analysis is needed to assess the quality of life in pediatric patients with IBD to produce a robust analysis that distinguishes surgical versus exhaustive medical therapy options in pediatric UC.

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