

The cost-effectiveness and budget impact of competing therapies in hepatic encephalopathy – a decision analysis

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SUMMARY

Background

Treatment options for hepatic encephalopathy have disparate risks and benefits. Non-absorbable disaccharides and neomycin are limited by uncertain efficacy and common dose-limiting side effects. In contrast, rifaximin is safe and effective in hepatic encephalopathy, but is more expensive.

Methods

We conducted a decision analysis to calculate the cost-effectiveness of six strategies in hepatic encephalopathy: (i) no hepatic encephalopathy treatment, (ii) lactulose monotherapy, (iii) lactitol monotherapy, (iv) neomycin monotherapy, (v) rifaximin monotherapy and (vi) up-front lactulose with crossover to rifaximin if poor response or intolerance of lactulose ('rifaximin salvage'). The primary outcome was cost per quality-adjusted life-year gained.

Results

Under base-case conditions, 'do nothing' was least effective and rifaximin salvage was most effective. Lactulose monotherapy was least expensive, and rifaximin monotherapy was most expensive. When balancing cost and effectiveness, lactulose monotherapy and rifaximin salvage dominated alternative strategies. Compared to lactulose monotherapy, rifaximin salvage cost an incremental US\$2315 per quality-adjusted life-year-gained. The cost of rifaximin had to fall below US\$1.03/tab in order for rifaximin monotherapy to dominate lactulose monotherapy.

Conclusions

Rifaximin monotherapy is not cost-effective in the treatment of chronic hepatic encephalopathy at current average wholesale prices. However, a hybrid salvage strategy, reserving rifaximin for lactulose-refractory patients, may be highly cost-effective.

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INTRODUCTION

Chronic hepatic encephalopathy (HE) is a common and expensive complication of liver failure, requiring more than 55 000 hospitalizations annually, and costing over \$1.2 billion per year in the United States alone.¹ Once HE develops, mortality reaches 22–35% after 5 years.^{2, 3} Surviving patients suffer from diminished health-related quality of life, impaired daily functioning, and decreased work productivity.⁴ An additional 51–62% of cirrhotics have evidence of subclinical HE that interferes with cognition and behavior,^{5–7} and about 23–30% of these patients ultimately develop overt HE.^{6, 7} In addition, patients with HE have increased risks of motor vehicle accidents and other delirium-related injuries because of cognitive dysfunction.^{8–11}

Therapy of HE has been difficult and limited in long-term efficacy. In addition to identifying and treating precipitating factors of HE, clinicians traditionally rely on non-absorbable disaccharides, such as lactulose and lactitol, as the cornerstone of treatment. However, the primary disadvantage of these agents is their high incidence of poorly tolerated adverse events such as cramping, diarrhoea and flatulence. Moreover, although a recent Cochrane Systematic Review found that lactulose is more effective than placebo in resolving symptoms, the analysis found no statistically significant difference when limited to studies of high methodological quality.¹² The review concluded that there are insufficient data to support the use of lactulose in the management of HE given the existing data in the literature. Taken together, these data indicate that although lactulose may be effective for some patients, its effect is not robust, and compliance is often limited by side effects.

An alternative therapy to non-absorbable disaccharides is the poorly absorbed oral antibiotic neomycin. Although neomycin has been used in HE for over three decades, there are few data to support its efficacy. In fact, no controlled studies have found neomycin to be more effective than standard treatments, and data from one randomized trial found no difference between neomycin and placebo.¹³ Moreover, the long-term use of neomycin is limited by nephrotoxicity and ototoxicity of patients, and the incidence is even higher in patients with renal insufficiency – a common comorbidity in patients with advanced cirrhosis.

More recently, the non-absorbable oral antibiotic rifaximin has shown promise as an effective agent in

HE. Rifaximin demonstrates high antimicrobial activity against common gut flora *in vivo*,^{14, 15} achieves high gut concentrations,¹⁶ and is negligibly absorbed into the systemic circulation.^{15, 16} Several randomized-controlled trials have reported rifaximin to be equally or more efficacious than lactulose in the treatment of HE.^{17–21} In addition, rifaximin has lower risks of side effects and better oral tolerability among patients.^{20, 22} However, it is substantially more expensive than lactulose.²³ Therefore, there is a trade-off between the improved therapeutic benefits of rifaximin in HE and its increased cost compared to lactulose, lactitol and neomycin, which have more therapeutic disadvantages but are less expensive. In light of this trade-off, we performed a decision analysis to measure the cost-effectiveness and managed care budget impact of these competing therapies in HE.

METHODS

Decision model framework

Model overview

Using decision analysis software (DATA 4.0, TreeAge Software, Inc., Williamstown, MA, USA), we evaluated a hypothetical cohort of 50-year-old patients with cirrhosis and HE. Patients with hepatic coma, evidence of active gastrointestinal bleeding, tumours, renal insufficiency, respiratory distress, active infection, concomitant psychiatric diseases or electrolyte abnormalities were excluded from the analysis. To emulate the case-mix in clinical practice, we assumed that 50% of the cohort had subclinical HE, and the remainder had overt HE. We subsequently varied this estimate between 0% and 100% in sensitivity analysis. Patients entered the model without previous treatment for HE, and were then allocated among six treatment strategies: (i) no HE treatment ('do nothing'), (ii) lactulose monotherapy, (iii) lactitol monotherapy, (iv) neomycin monotherapy, (v) rifaximin monotherapy and (vi) up-front lactulose with crossover to rifaximin if poor response or intolerance of lactulose ('rifaximin salvage').

The model began with a decision node followed by six branches, each corresponding with one of the competing strategies. After being distributed between strategies, subjects in the model were exposed to Markov cycles governing the natural history of cirrhosis, including HE (Figure 1). Each treatment strategy

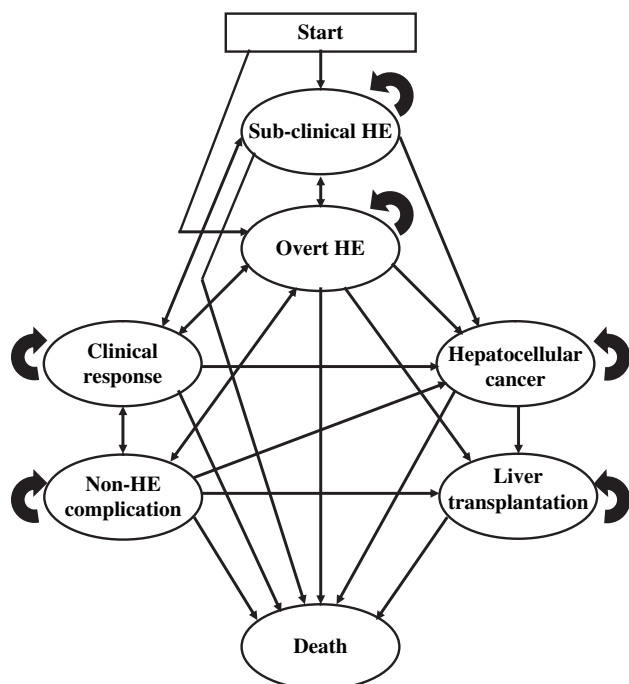


Figure 1. Markov State diagram. Patients start by entering the model with either subclinical or overt hepatic encephalopathy (HE). The clinician treats with one of six competing strategies: (i) 'do nothing', (ii) lactulose monotherapy, (iii) lactitol monotherapy, (iv) neomycin monotherapy, (v) rifaximin monotherapy and (vi) 'rifaximin salvage' (see text for details). Patients are followed up over a 10-year period. During each 1-year cycle, individual patients either remain in their assigned health state (recursive arrow), or progress to a new health state (straight arrow). Patients in all strategies may develop non-HE complications of cirrhosis (i.e. ascites, variceal bleeding), develop hepatocellular cancer, become eligible for liver transplantation, or remain in chronic HE state. Patients who receive therapy for hepatic HE may either achieve a clinical response in HE or fail treatment. We further assume patients on therapy may become non-compliant, lost to follow-up or fail ongoing therapy, in which case they re-enter Markov cycle of natural history of HE. Transition rates between health states were derived from a systematic review of the literature (Tables 1 and 2).

accounted for common challenges in caring for patients with HE, including medication non-compliance, follow-up non-compliance, treatment-related adverse events, efficacy failures, symptom relapse following successful therapy, need for liver transplantation, poor availability of donor organs for eligible patients and other consequences of poorly treated HE, including motor vehicle and other recognized acci-

idents (Tables 1 and 2). In addition, the model measured several resources, including doctor visits, hospital visits, laboratory tests, medications and hepatocellular cancer screening procedures, among others (Table 3). We adopted transition rates between health states based on a systematic review of the literature (see Data sources, below), and followed up subjects over a lifetime horizon based on life tables of patients with cirrhosis (mean = 10 years; refer to the Figure 1 and the Technical Appendix for a description of additional model assumptions).

Competing strategies

(1) **'Do nothing' strategy:** In this strategy, which served as the referent case for our analysis, we assumed that patients were followed up clinically but did not receive pharmacological therapy for HE. Patients underwent the natural history of cirrhosis and HE. We further assumed that all patients received regular ongoing care, including management of cirrhosis-related complications and hepatocellular carcinoma surveillance, as outlined by published management guidelines.²⁴⁻²⁹ We assumed that a proportion of patients with decompensated disease became eligible for liver transplantation, and further assumed that a subgroup of these patients subsequently received a liver transplantation at the rate reported by the United Network of Organ Sharing.³⁰

(2) **Lactulose monotherapy strategy:** Patients in this strategy began treatment with lactulose 30 cm³ twice daily, with subsequent doses titrated to ensure a minimum of two loose bowel movements daily. As in all active treatment arms, we accounted for non-compliance with therapy and adverse events as dictated by the results of our systematic literature review (see Technical Appendix). Patients achieving a clinical response continued on therapy, and those without a response or with non-compliance discontinued therapy and followed the natural course of HE. Patients developing recurrent symptoms or treatment resistance despite long-term therapy also discontinued active treatment in this strategy.

(3) **Lactitol monotherapy strategy:** Patients in this strategy began treatment with lactitol with doses titrated to achieve a minimum of two loose bowel movements daily. The strategy was otherwise similar to 'lactulose monotherapy'.

(4) **Neomycin monotherapy strategy:** Patients in this strategy received oral neomycin 1.5 g four times

| Table 1. Base-case treatment-related probability estimates | | | |
|--|------------------------|------------------|---------------------------------|
| Probability description | Base-case estimate (%) | Range tested (%) | References |
| Lactulose | | | |
| Probability of compliance in overt encephalopathy | 90 | 50–100 | 17–21, 55, 57, 66–70, 72, 74–78 |
| Probability of compliance in subclinical encephalopathy | 91 | 70–100 | 63–65, 67, 71, 79, 80 |
| Probability of improvement in overt encephalopathy | 55 | 30–95 | 12 |
| Probability of improvement in subclinical encephalopathy | 52 | 45–57 | 12 |
| Lactitol | | | |
| Probability of compliance in overt encephalopathy | 86 | 75–100 | 50, 67–70, 76, 81 |
| Probability of compliance in subclinical encephalopathy | 78 | 70–88 | 68, 71, 82 |
| Probability of improvement in overt encephalopathy | 69 | 15–100 | 50, 66–70 |
| Probability of improvement in subclinical encephalopathy | 79 | 50–95 | 71 |
| Neomycin | | | |
| Probability of compliance in overt encephalopathy | 83 | 50–100 | 20, 51, 52, 55, 57, 72 |
| Probability of compliance in subclinical encephalopathy | 84 | 75–100 | See Appendix |
| Probability of improvement in overt encephalopathy | 64 | 20–80 | 20, 51, 52, 55, 57, 72 |
| Probability of improvement in subclinical encephalopathy | 61 | 20–70 | See Appendix |
| Rifaximin | | | |
| Probability of compliance in overt encephalopathy | 96 | 50–100 | 17–22, 50–52, 72, 73, 83, 84 |
| Probability of compliance in subclinical encephalopathy | 97 | 70–100 | See Appendix |
| Probability of improvement in overt encephalopathy | 90 | 57–100 | 17–19, 50–52, 72, 84 |
| Probability of improvement in subclinical encephalopathy | 85 | 70–100 | See Appendix |

| Table 2. Base-case cirrhosis-related health state probability estimates | | | |
|---|--------------------|--------------|------------------------|
| Probability description | Base-case estimate | Range tested | References |
| Annual rate of progression from no HE to subclinical HE | 19% | 0–50% | 4–7, 86, 87 |
| Annual rate of progression from subclinical HE to overt HE | 23% | 0–50% | 6, 7, 87 |
| Annual rate of developing non-HE complication of cirrhosis in overt HE patients | 9% | 0–30% | 88–92 |
| Annual rate of developing non-HE complication of cirrhosis in subclinical HE patients | 7% | 0–30% | 88–92 |
| Probability of developing ascites in cirrhosis | 68% | 50–90% | 88, 91, 93, 94 |
| Probability of developing variceal bleeding in cirrhosis | 15% | 0–30% | 88, 90, 91, 95, 96 |
| Annual rate of mortality in decompensated cirrhosis | 19% | 6–25% | 88, 89, 91, 95, 97, 98 |
| Annual probability of receiving a liver transplant in decompensated cirrhosis | 25% | 0–40% | 30 |
| Annual rate of mortality after successful transplantation | 7% | 0–30% | 30 |
| Utility of compensated cirrhosis | 0.80 | 0.7–0.9 | 32 |
| Utility of overt HE (based on utility of complicated cirrhosis) | 0.60 | 0.5–0.7 | 32 |
| Utility of liver transplant | 0.86 | 0.7–0.9 | 32 |
| Utility of hepatocellular cancer | 0.73 | 0.5–0.8 | 32 |

HE, hepatic encephalopathy.

daily for 14 days. The strategy was otherwise similar to 'lactulose monotherapy'.

(5) **Rifaximin monotherapy strategy:** Patients in this strategy received oral rifaximin 400 mg three

times daily (1200 mg/day) for 14 days. The strategy was otherwise similar to 'lactulose monotherapy'.

(6) **'Rifaximin salvage' strategy:** As with the 'lactulose monotherapy' approach, patients in this strategy

Table 3. Base-case cost estimates

| Cost description | Estimate (\$) | Range tested (\$) | References |
|--|---------------|-------------------|------------|
| Medication costs | | | |
| Cost per day of rifaximin therapy (400 mg t.d.s; 200 mg tab = \$3.6) | 21.8 | 5–30 | 23 |
| Cost per day of lactitol therapy | 1.9 | 0.50–10 | 23 |
| Cost per day of lactulose therapy | 1.9 | 0.50–10 | 23 |
| Cost per month of neomycin therapy | 3.6 | 1–20 | 23 |
| Non-medication costs of treatment period | | | |
| Cost per doctor visit | 52 | 25–100 | 42 |
| Cost per set of laboratory tests | 80 | 50–150 | 42 |
| Cost per abdominal ultrasonography | 150 | 50–250 | 42 |
| Cirrhosis-related costs | | | |
| Cost per year for out-patient care of persistent encephalopathy | 3337 | 500–5000 | 43 |
| Cost of hospitalization for advanced encephalopathy | 23 192 | 10 000–30 000 | 43 |
| Cost of non-cirrhosis death (e.g. HE-related motor vehicle accident) | 5000 | 1000–10 000 | 43 |
| Cost of first year after variceal haemorrhage (assuming survival) | 22 444 | 10 000–30 000 | 43 |
| Cost per subsequent year after variceal haemorrhage | 4393 | 2000–10 000 | 43 |
| Cost per year of ascites | 4058 | 1000–10 000 | 43 |
| Cost of liver transplantation | 127 499 | 50 000–150 000 | 43 |
| Cost per year of follow-up care after liver transplantation | 22 266 | 10 000–50 000 | 43 |

began treatment with lactulose 30 cm³ twice daily, with subsequent doses titrated to ensure a minimum of two loose bowel movements daily. However, rather than discontinuing treatment upon failure (as in the 'lactulose monotherapy' strategy), patients with an inadequate clinical response or non-compliance were instead crossed-over to receive 'salvage' treatment with second-line rifaximin therapy. Patients were then managed as described in the 'rifaximin monotherapy' strategy.

Model assumptions and data sources

Refer to the Technical Appendix and Tables 1 and 2 for information regarding our key model assumptions, including base-case patient characteristics, survival assumptions, definitions of clinical response, treatment efficacy and compliance rates and impact of treatment-related adverse events. We derived our base-case point estimates from a systematic review of MEDLINE. When there were multiple studies supporting an individual point estimate, we calculated a mean weighted by study sample size. We relied on pre-existing meta-analyses when available.

Outcomes

Because the main objective of cost-effectiveness analysis was to permit comparisons between different interventions in medicine, and because quality-

adjusted life-years (QALYs) are the exchange currency to allow for these comparisons to be made, we adopted QALYs as our main outcome.³¹ This analysis incorporated a range of relevant health state utilities, or health-related quality of life estimates, employed in previous decision models in chronic liver disease (Table 2).^{32–34} Our analysis reports the incremental cost per QALY-gained between the competing strategies, along with the respective 2.5th and 97.5th percentiles around the point estimates as generated by a Monte Carlo analysis of 1000 trials. In addition, because utility estimates in encephalopathy may be unstable and unreliable, we also conducted a second analysis measuring incremental cost per unadjusted life year (LY)-gained.

Budget-impact model

In the current era of increasingly managed care, it is important to distinguish 'cost-effectiveness' from 'budget impact'. In contrast to cost-effectiveness analysis, which measures both cost and clinical outcomes without regards to underlying disease prevalence, budget-impact models focus exclusively on cost and adjust for the underlying prevalence of disease. Adjusting for disease prevalence is critical, because a medical therapy that is 'cost-effective' might apply to a large subset of patients, and therefore have a prohibitive budget impact. For example, proton pump inhibitors are 'cost-

effective' for acid-peptic disorders,³⁵⁻³⁷ but 10-20% of patient have an acid-peptic disorder. Therefore, the budget impact of proton pump inhibitors is large in spite of their cost-effectiveness.³⁸ In contrast, a therapy might be 'cost-ineffective' by usual standards, yet apply only to a very small subset of patients. In this instance, an expensive therapy can be subsidized at an acceptable cost if only a small minority of patients require the therapy, since the cost is spread over the entire paying population (e.g. liver transplantation). Therefore, budget-impact models are more closely grounded in clinical reality, not only because they acknowledge that disease prevalence is a critical determinant of health economic outcomes, but also because they provide readily actionable budgetary data for policy decisions in lieu of theoretical outcomes such as cost per QALY. These differences have slowly persuaded managed care administrators to consider carefully the results of budget-impact models, in addition to cost-effectiveness analyses, when making formulary and policy decisions.^{39, 40}

We therefore performed a budget-impact model, and adopted the per-member per-month (PMPM) cost as our primary outcome for this analysis. We specifically focus on the incremental PMPM cost of employing each therapeutic strategy in a hypothetical managed care organization (MCO) with 1 000 000 covered lives. On the basis of published incidence data, we assumed a baseline cirrhosis incidence of 360 per 100 000 patients per year, and assumed that 50% had either subclinical or overt HE.^{5-7, 41} We used the following simple algebraic expression to calculate the incremental PMPM of competing strategies (in this instance, 'strategy A' vs. 'strategy B'):

$$\frac{(\text{Average cost/Patient in strategy A}) \times (\text{Number of patients with cirrhosis})}{\text{Total members in MCO}} - \frac{(\text{Average cost/Patient in strategy B}) \times (\text{Number of patients with cirrhosis})}{\text{Total members in MCO}}$$

Cost estimates

We conducted our analysis from the perspective of a US third-party payer and incorporated the direct healthcare costs for a range of therapies, doctor visits, hospital visits, diagnostic tests and complications of cirrhosis and HE (Table 3). We obtained costs for doctor services and procedures from the 2006 American Medical Association Current Procedural Terminology code-

book and the 2006 Medicare Fee Schedule, and derived our base-case pharmaceutical costs from the average wholesale prices listed in the 2006 Red Book.^{23, 42} We obtained cost estimates for cirrhosis and related health states from a published study of detailed itemized in-patient and out-patient direct costs incurred by patients with cirrhosis.⁴³ As these costs were originally generated in 1997, we updated all the cost estimates to 2006 US dollars using the medical care component of the US consumer price index.⁴⁴ We discounted all costs and effects at a rate of 3% per year.³¹

Sensitivity analyses

Tables 1 and 2 list our base-case probability estimates with respective ranges. We performed a multivariable sensitivity analysis ('tornado analysis')⁴⁵ to test the influence of all variables on the model results, and rank-ordered the most influential variables. We then performed one-way sensitivity analyses on the most influential variables. We conducted a Monte Carlo simulation assuming triangular probability distributions, and plotted the results on cost-effectiveness acceptability curves stratified by willingness-to-pay thresholds.⁴⁶

Role of funding source

We did not receive funding for this study. Dr Spiegel's research is supported by a Veteran's Affairs Health Services Research and Development (HSR&D) Career Development Award (RCD 03-179-2), and the CURE Digestive Disease Research Center (NIH 2P30 DK 041301-17). Drs Huang and Esrailian do not currently receive funding for research support.

RESULTS

Base-case results

Figure 2 displays the results of the base-case analysis. The 'do nothing' strategy was the least effective (affording 2.8 QALY and 3.9 LY), and lactulose monotherapy was the least expensive (US\$56 967 total lifetime combined cost of care) of the six competing

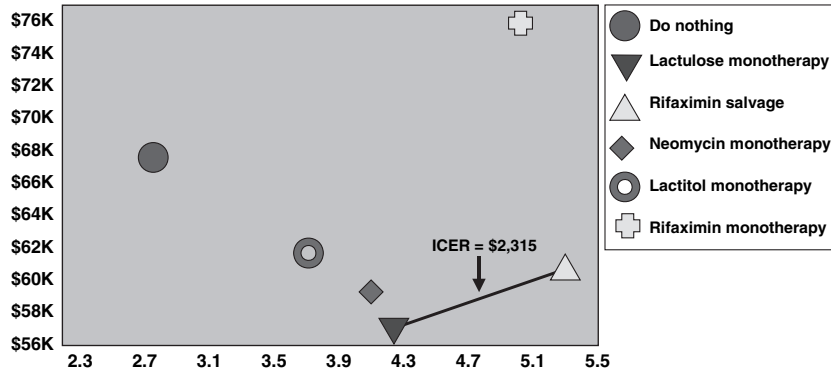


Figure 2. Base-case cost-utility results. The base-case analysis assumes that 50% of patients have subclinical hepatic encephalopathy (HE), and 50% have overt HE. The vertical axis below displays the lifetime cumulative US cost, and the horizontal axis displays the quality-adjusted life-years (QALYs) gained. Thus, the most 'cost effective' point on the plane is the bottom right corner. The diagonal line represents the incremental cost-effectiveness ratio (ICER) between the two 'non-dominated' strategies, including lactulose monotherapy and rifaximin salvage. The ICER between strategies represents the additional cost that must be expended to gain one additional QALY when adopting the more expensive of the two compared strategies. In this instance, using 'rifaximin salvage' instead of lactulose monotherapy cost an additional \$2315 to gain one additional QALY. The 'do nothing', lactitol monotherapy, neomycin monotherapy and rifaximin monotherapy strategies are 'dominated' (i.e. more expensive yet less effective than alternatives) because they fall above and to the left of the diagonal line composing the 'cost-effectiveness frontier'.

strategies. In contrast, rifaximin salvage was the most effective (5.3 QALY and 6.9 LY), and rifaximin monotherapy was the most expensive (\$75 671) of the competing strategies. When balancing cost and effectiveness, lactulose monotherapy and rifaximin salvage strategies were less expensive yet more effective than comparators, and therefore 'dominated' the alternative strategies. Compared to using lactulose monotherapy, using rifaximin salvage cost an incremental \$2315 per QALY-gained (2.5th and 97.5th percentile, \$995, \$4816) and \$1894 per LY gained (2.5th and 97.5th percentile, \$1111, \$2614). In contrast, rifaximin monotherapy cost an incremental \$26 720 per QALY-gained and \$20 553 per LY-gained compared to lactulose monotherapy. These data converted to an incremental PMPM of \$0.49 for rifaximin salvage vs. lactulose monotherapy, and an incremental PMPM of \$3.40 for rifaximin monotherapy vs. lactulose monotherapy. In other words, it would cost each member of a MCO an additional \$3.40 per month to subsidize a policy decision to switch from lactulose to rifaximin monotherapy, but only \$0.49 to switch from lactulose monotherapy to rifaximin salvage.

Base-case sensitivity analyses

Tornado analysis revealed that the model was sensitive to seven variables. Table 4 displays the results of one-

way sensitivity analyses for these variables in decreasing order of influence, and lists the thresholds where the cost-effectiveness order between the strategies changed. The remaining estimates did not impact the model when varied over a wide range.

Monte Carlo analyses

Taken together, the above results indicate that of the five active therapy strategies, the lactulose monotherapy and 'rifaximin salvage' strategies were potentially cost-effective. To determine which of these comparators to employ under different budgetary restraints, we performed three Monte Carlo analyses to compare lactulose and rifaximin salvage across a range of willingness to pay thresholds. Figures 3 and 4 display cost-effectiveness and budget-impact acceptability curves reflecting 1000 hypothetical patients. The curves reveal that the use of rifaximin salvage in lieu of lactulose monotherapy falls within most healthcare budgets. For example, if a MCO were willing to pay \$20 000 per QALY or \$0.10 PMPM for rifaximin salvage therapy, then 100% of patients would fall within the budget.

DISCUSSION

The most cost-effective approach to managing HE is uncertain. Recent clinical trials suggest that rifaximin

Table 4. Results of one-way sensitivity analyses

| Variable | Base-case estimate | Threshold | Comment |
|---|--------------------|-----------|--|
| Cost per dose of lactulose | \$0.98 | \$1.80 | If above, then neomycin dominates lactulose monotherapy |
| | \$0.98 | \$13.00 | If above, then rifaximin monotherapy dominates lactulose monotherapy |
| Cost per tablet of rifaximin | \$3.60 | \$3.00 | If below, then rifaximin salvage dominates lactulose monotherapy |
| | \$3.60 | \$1.30 | If below, then rifaximin monotherapy dominates lactulose monotherapy |
| Cost of liver transplantation | \$127 000 | \$185 000 | If above, then rifaximin salvage dominates lactulose monotherapy |
| Probability of compliance with lactulose in overt encephalopathy | 0.90 | 0.76 | If below, then neomycin dominates lactulose monotherapy |
| Probability of compliance with neomycin in overt encephalopathy | 83% | 65% | If below, then neomycin dominated by lactulose monotherapy and rifaximin salvage |
| Probability of improvement with lactulose in overt encephalopathy | 55% | 46% | If below, then neomycin dominates lactulose monotherapy |
| Probability of improvement with neomycin in overt encephalopathy | 64% | 75% | If above, then neomycin dominates lactulose monotherapy |

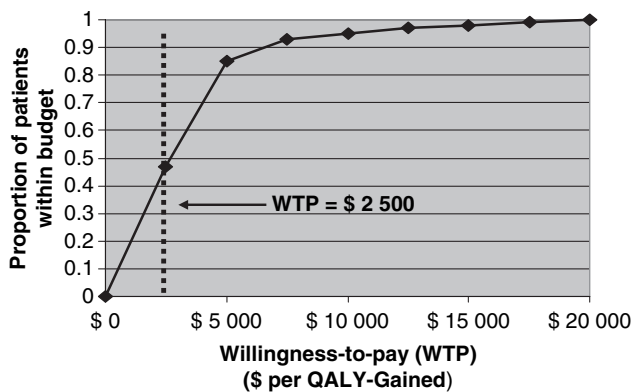


Figure 3. Cost-effectiveness acceptability curves of 'rifaximin salvage' vs. lactulose monotherapy. The horizontal axis displays the willingness-to-pay budgetary thresholds to gain one additional quality-adjusted life-year (QALY) when using rifaximin salvage in lieu of lactulose, and the vertical axis displays the percentage of 1000 patients that fall within the available budget. For example, if a third-party payer had a budget of US\$2500 per QALY-gained to substitute rifaximin salvage vs. lactulose monotherapy (vertical broken line), then only 47% of the cohort would fall within the budget. In contrast, rifaximin salvage becomes cost-effective for over 100% of patients in healthcare systems willing to pay at least \$20 000 per QALY-gained.

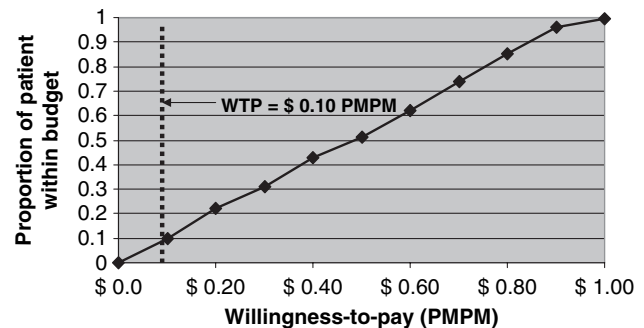


Figure 4. Per-member per-month (PMPM) cost acceptability curve of 'rifaximin salvage' vs. lactulose monotherapy. The horizontal axis displays the willingness-to-pay budgetary PMPM thresholds, and the vertical axis displays the percentage chance that introducing 'rifaximin salvage' to a managed care organization will fall within the PMPM threshold. For example, if a managed care organization is willing to increase its PMPM costs by only US\$0.10 to subsidize rifaximin salvage (vs. lactulose monotherapy), then there is only a 10% chance that rifaximin salvage will fall within the budget. However, if a managed care organization is willing to increase its PMPM costs by \$1.0, then there is a 100% chance that rifaximin salvage will fall within the budget.

may be safer and more effective than non-absorbable disaccharides in HE, yet rifaximin is over four times more expensive than traditional therapy such as lactulose. In light of this health economic trade-off, we performed a comprehensive decision analysis to identify the most cost-effective therapeutic approach under varying clinical and budgetary conditions.

Our analysis has three key findings. First, the use of rifaximin as up-front therapy for HE is unlikely to be highly cost-effective under most circumstances. We found that rifaximin monotherapy has an incremental cost of more than \$26 000 per QALY-gained when compared with lactulose monotherapy – a value that exceeds the cost of many commonly accepted medical interventions. In addition, we estimated that using rifaximin monotherapy instead of lactulose monotherapy would cost each member of a MCO an incremental \$3.40 per month to subsidize. This PMPM cost exceeds the managed care cost of common medication both within gastroenterology (e.g. intravenous proton pump inhibitors for gastrointestinal bleeding = \$2.90 PMPM;⁴⁷ H₂RA for GERD = \$0.23 PMPM⁴⁸) and in other fields of medicine (e.g. sildenafil for erectile dysfunction = \$0.18 PMPM;⁴⁹ triptan therapy for migraine headache = \$0.44 PMPM;⁴⁸ oral contraceptives = \$0.74 PMPM⁴⁸). We estimated that rifaximin monotherapy would save overall costs vs. lactulose monotherapy only if the cost of rifaximin falls to one-third its current price. Secondly, despite our finding that rifaximin is not cost-effective as first-line therapy in HE, our analysis reveals that rifaximin may be highly cost-effective if provided as second-line therapy to patients failing an initial trial of a less expensive agent (e.g. lactulose, neomycin). This 'rifaximin salvage' approach appears highly cost-effective across a range of healthcare budgets from the most liberal to the most conservative (Figure 3). Thirdly, although neomycin monotherapy was dominated in our base-case analysis, our data indicate that this agent may yet be a reasonable strategy in some patients with low compliance on lactulose (Table 4), even after accounting for the side-effect profile of neomycin, including nephrotoxicity. However, any use of neomycin must be strongly tempered by its relative lack of high-quality supporting data in the literature.

Our analysis reveals that medication cost – not drug effectiveness – is the single most important factor driving cost-effectiveness in HE. This conclusion arises because absolute differences in effectiveness between

HE therapies are small, as evidenced by our projection that rifaximin provides only an additional 0.7 of a QALY over a 10-year period vs. lactulose, even after accounting for adverse events and compliance rates. This finding, in turn, arises from the published randomized clinical trials. The overall efficacy difference between rifaximin and other therapies is not statistically significant.^{18–21, 50–52} This has also been documented in a recent meta-analysis, which revealed that antibiotics, including rifaximin, provide minimal overall benefits and no mortality benefit vs. lactulose.¹² It is a health economic principle that cost concerns become magnified when effectiveness between therapies is small, as is the case in HE. Therefore, as rifaximin is four times more expensive than lactulose, but appears only marginally more effective on average, the incremental cost of rifaximin monotherapy is substantial when compared to other benchmarks in medicine. Further head-to-head research studies are warranted to measure cost-effectiveness more precisely in this field.

It is not coincidental that our analysis identified a hybrid strategy (i.e. 'rifaximin salvage') as the preferred approach under most clinical and economic circumstances. This trend is evident in other areas of medicine as well. For example, in the primary care management of uninvestigated dyspepsia, the combination of *Helicobacter pylori* 'test and treat' and empiric proton pump inhibitor therapy dominates the use of either therapy alone, so long as patients failing 'test and treat' are crossed-over to proton pump inhibitor therapy.³⁶ In the management of chronic arthritis, the combination of naproxen and a COX-2 selective inhibitor is more cost-effective than either therapy alone, so long as patients failing naproxen are crossed-over to a COX-2 inhibitor.⁵³ In screening for oesophageal varices in cirrhosis, endoscopy is more cost-effective than empiric beta-blockers, so long as patients intolerant of initial beta-blocker therapy are crossed-over to receive endoscopic screening.⁵⁴ In the management of chronic hepatitis B infection, adefovir is more cost-effective than lamivudine, so long as patients developing viral resistance on lamivudine are crossed-over to adefovir.³⁴ All of these examples reserve the use of expensive yet effective therapies for the subset of patients failing first-line therapies that are less effective yet less expensive. The net result is to maximize cost-effectiveness by targeting the use of resource intensive therapies only to patients most in need, and therefore

most likely to benefit from these therapies. This approach is not only economically prudent, but is also effective, as multiplying sequential therapies in a rational order often provides more benefit than relying on any single therapy alone. In the current analysis, we find that reserving the use of rifaximin for patients with poor response or non-compliance with up-front lactulose is more cost-effective than using either lactulose or rifaximin monotherapy alone. This hybrid strategy represents a potentially high-yield therapeutic niche for rifaximin in the management of patients with chronic HE.

This analysis has several strengths and unique features. First, to our knowledge, this is the first decision analysis to measure the cost-effectiveness of competing agents in HE and, in particular, to consider the health economic implications of rifaximin. This is relevant because the publication and dissemination of rifaximin data has led many providers to begin using this agent in HE, and third-party payers are now faced with deciding whether and when to support use of rifaximin in HE. Secondly, our model attempts to capture the everyday challenges facing clinicians and patients in HE, including medical non-compliance, doctor visit non-compliance, recurrent symptoms despite initial effectiveness, side-effect profiles, cirrhosis-related complications other than HE, liver transplantation and organ availability and delirium-related accidents, among other considerations. By acknowledging these practical issues, our analysis attempts to reflect the health economic consequences of everyday practice and improve the generalizability of our findings. Thirdly, rather than conducting one base-case analysis, we conducted several analyses to gauge health economic outcomes across several domains, including cost-effectiveness, cost-utility and budget impact. Whereas it is often difficult to decide how best to make policy decision on the basis of cost-effectiveness analyses alone (which do not adjust for underlying disease prevalence), the results of budget-impact models allow healthcare decision makers to make explicit and direct comparisons between competing strategies within and between areas of medicine, and thus complement findings of cost-effectiveness models.^{39, 40} We therefore believe our data are relevant, practical and actionable.

Our study also has several limitations. First, our base-estimates are derived from studies of varying design, patient population, follow-up and quality. However, we have attempted to guard against

inaccurate base-case results by systematically reviewing the literature, calculating weighted means to account for study sample size and relying on pre-existing meta-analyses when available. In addition, we varied our base-case estimates over a wide range in multiple forms of sensitivity analysis. Secondly, our cost-utility analysis employed utility estimates that may be unreliable. Clearly, it is difficult to expect truly encephalopathic patients to complete accurately quality of life questionnaires or utility assessments. Therefore, the existing utility estimates in cirrhosis and HE may not be fully reliable. For this reason, we conducted a second analysis to measure cost per unadjusted LY – an analysis that did not rely on any utility estimates. In addition, we varied our utility estimates over a wide range in sensitivity analysis to acknowledge the high likelihood that existing estimates are unstable. Thirdly, we did not explore other potential strategies, such as lactulose and rifaximin co-therapy, or rifaximin salvage after initial neomycin. Although these treatment approaches would be relevant variants of our model analysis, our systematic review could not identify any study on the use of combination therapy, in particular lactulose and rifaximin. In addition, the strategy of stacking antibiotics with initial neomycin followed by rifaximin salvage is not widely used, and is therefore less relevant to this analysis. Fourthly, our study does not include patients with hepatic coma, evidence of active gastrointestinal bleeding, renal insufficiency, severe electrolyte abnormalities, active infection, tumours, psychiatric disorders and respiratory distress. This clearly limits the generalizability of our findings. However, our model is largely based on data derived from studies that excluded these patient groups, thus we are limited by the inherent shortcomings of the source data. Thus, although our study is limited by lack of generalizability, it is also true that most of the existing data supporting treatments for HE are similarly limited. Finally, our analysis applies only to a narrow patient population. Specifically, our hypothetical cohort has chronic HE without evidence of renal failure, electrolyte abnormalities and active infection or gastrointestinal bleeding. Therefore, our results would not be applicable to alternative populations, including patients with acute HE, hepatorenal syndrome, hyponatremia, spontaneous bacterial peritonitis, variceal bleeding or liver transplant. However, we used the most common and clinically relevant presentation of chronic HE in our base-case estimates (consistent with

published clinical trials), and therefore aimed to generalize our findings to most community-based practice settings.

In conclusion, this analysis reveals that rifaximin monotherapy is not cost-effective in the management of HE at current average wholesale prices. Based on the current prices, only lactulose monotherapy and 'rifaximin salvage' are potentially cost-effective. Our model indicates that the apparent clinical benefits of rifaximin are undermined by its high cost compared to lactulose or neomycin. However, rifaximin monotherapy becomes significantly more cost-effective if the cost of rifaximin falls to one-third of its current price. In addition, our data suggest that neomycin may still be a reasonable choice for some patients who cannot tolerate lactulose therapy, although it may be less effective than rifaximin-based strategies and remains limited by scant supporting data. Finally, our data indicate that a hybrid salvage strategy using rifaximin for lactulose-refractory patients may be highly cost-effective and have an acceptable managed care budget impact. Future research should aim to measure prospectively the cost-effectiveness of these competing management strategies in representative samples of community-based patients with HE, and should also examine the effects of combination therapy in refractory HE.

TECHNICAL APPENDIX

Definitions of clinical efficacy

The clinical trials in HE employ a wide range of disparate outcome measures. These include biochemical tests such as serum ammonia and stool pH, neuropsychiatric measures such as electroencephalography (EEG), number connection tests and the West Haven mental status criteria, and physical signs such as asterixis. Conn *et al.* developed a multicomponent Portal-Systemic Encephalopathy (PSE) Index, which combines mental status, number connection test, EEG, asterixis and serum ammonia to score the global severity of HE.⁵⁵ For studies reporting multiple outcomes in HE, we abstracted data from the most clinically relevant and/or validated outcome measure, such as the PSE sum/index or West Haven criteria if available. For studies reporting multiple outcomes in subclinical HE, we included those with reported data pertaining to improvements in EEG and psychometric testing.

Treatment efficacy estimates

Non-absorbable disaccharide efficacy

Non-absorbable disaccharides include lactulose and lactitol. Als-Nielsen *et al.* conducted a meta-analysis of clinical trials employing these agents in HE. The authors found that 55% of patients receiving lactulose achieved clinically significant improvements in overt HE, while 52% improved in subclinical HE.¹² Our systematic review identified 16 randomized-controlled studies reporting data meeting our criteria for efficacy on both partial and complete response to lactulose in HE, and the weighted mean response was 68% in overt HE,^{17-21, 55-62} and 52% in subclinical HE.⁶³⁻⁶⁵ However, to bias our model explicitly in favour of rifaximin, and against lactulose, we adopted the lower efficacy rate as our base-case estimate (i.e. 55% response in meta-analysis instead of 68% response). We varied this estimate over a wide range in sensitivity analysis. Our review found that 69% of overt HE patients on lactitol achieved a clinical response,^{50, 66-70} and 79% of subclinical HE patients responded to this agent.⁷¹

Neomycin efficacy

Our literature review identified six randomized-controlled studies that met our criteria for efficacy of neomycin in overt HE.^{20, 51, 52, 55, 57, 72} The weighted mean response to neomycin was 64%. We did not find literature pertaining to neomycin in the treatment of subclinical HE. We assumed a neomycin response rate of 61% in subclinical HE, which is proportional to the corresponding lactulose response rate between patients with subclinical and overt HE.

Rifaximin efficacy

Our review identified eight randomized-controlled studies meeting our criteria for efficacy of rifaximin in HE.^{17-19, 50-52, 72, 84} The weighted mean response to rifaximin in these studies was 90% in patients with overt HE. One study measured efficacy in subclinical HE, and reported a complete 100% response to rifaximin (as measured by NH₃ levels and number connection tests).⁷³ However, the patients in this study were first treated with lactulose without a washout period, suggesting that rifaximin monotherapy (i.e. without initial lactulose) would likely have a

lower response rate than the 100% documented in this study. We therefore assumed a lower base-case response rate to rifaximin monotherapy in subclinical HE. Specifically, we assumed a rate of 85% (instead of 100%), which is proportional to the corresponding lactulose response rate between patients with overt and subclinical HE. We did not find data pertaining to the incremental benefit of rifaximin in overt (in contrast to subclinical) HE patients failing initial lactulose. We therefore assumed that patients receiving 'rifaximin salvage' following lactulose failure had the same response rates as patients receiving rifaximin monotherapy. However, because 'rifaximin salvage' could lead to diminishing returns with sequential therapies, we varied this estimate over a wide range in sensitivity analysis.

Compliance rates

We based our compliance estimates on the principles of intention-to-treat analysis. Our model incorporated patient dropout, non-compliance with therapy, and the likelihood of reporting non-compliance to the doctor. To calculate the compliance rate, we reviewed the adverse event profiles and dropout rates from the published clinical trials regardless if they were randomized and/or controlled.

Non-absorbable disaccharide compliance

The most common adverse events from lactulose and lactitol are diarrhoea, abdominal cramping, nausea and flatulence. Although these side-effects are prevalent, they rarely lead to discontinuations in the context of the published clinical trials, where nearly all patients were able to continue participation despite the adverse events. In addition, several studies report gradual resolution of these common adverse events as treatment progresses,^{18–20} suggesting that the long-term quality of life with lactulose might not be as severe as some recent reviews otherwise suggest. Our analysis revealed a weighted mean compliance rate of 90% in overt HE,^{17–21, 55, 57, 66–70, 72, 74–78} and 91% in subclinical HE.^{63–65, 67, 71, 79, 80} In addition, we calculated a weighted mean lactitol compliance 86% in overt HE,^{50, 67–70, 76, 81} and 78% in subclinical HE.^{68, 71, 82} Nonetheless, because clinical experience with these agents may not entirely comply with published trials, we varied these estimates over a wide range in sensitivity analysis.

Neomycin compliance

The most concerning side-effects of neomycin are ototoxicity and renal toxicity. However, there were no instances of these complications in the published studies of neomycin in HE.^{20, 55, 57, 72, 81} The most commonly reported side effects were nausea, abdominal discomfort and diarrhea.^{55, 57, 72, 81} After accounting for dropouts from adverse events, the weighted mean compliance with neomycin in overt HE was 83%.^{20, 51, 52, 55, 57, 72} We did not find any studies that reported data on neomycin compliance rates in patients with subclinical HE. In the absence of data, we assumed a compliance rate of 84% in subclinical HE, which is proportional to the corresponding lactulose compliance rate between patients with overt and subclinical HE.

Rifaximin compliance

The major clinical benefit of rifaximin is its low rate of adverse events and corresponding high rate of compliance. Our review of the literature found that 96% of patients with overt HE are compliant with rifaximin.^{17–22, 50–52, 72, 73, 83, 84} We did not find any studies that reported data on rifaximin compliance rates in patients with subclinical HE. In the absence of data, we assumed a compliance rate of 97% in subclinical HE, which is proportional to the corresponding lactulose compliance rate between patients with overt and subclinical HE.

Antibiotic-related complications

Both rifaximin and neomycin are associated with nausea, abdominal discomfort and diarrhoea in the treatment of HE.^{20–22, 52, 72, 85} We assumed that no additional costs were incurred unless the side effects resulted in discontinuation of therapy. Although there are no reports of serious complications with use of rifaximin or neomycin in HE, we conservatively assumed a 0.05% risk of developing pseudomembranous colitis requiring out-patient treatment. Finally, we assumed that 0.001% of patients developed a 'worst-case' scenario of pseudomembranous colitis requiring in-patient hospitalization.

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