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*Research Article*

# Cost-Effectiveness of Rifaximin-α versus Lactulose for the Treatment of Recurrent Episodes of Overt Hepatic Encephalopathy: A Meta-Analysis

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*Background*. Hepatic encephalopathy (HE) is a frequent and debilitating complication of liver disease. Treatments include lactulose and rifaximin-α. The objective of this literature review and meta-analysis was to assess the overall cost-effectiveness of rifaximin-α in HE treatment. *Methods*. Electronic database searches were conducted in November 2020 to identify cost-effectiveness studies comparing rifaximin-α with other interventions in HE, published in English. Incremental net benefit (INB) was calculated for each study using difference in effectiveness, difference in costs, and the willingness-to-pay threshold, or gross domestic product per capita for each country, and 95% confidence intervals (CI) were constructed. Costs were standardised to 2019 US$. An intervention was considered cost-effective if the INB was positive. Meta-analysis was used to pool calculated INB across studies, using a fixed-effects model if there was no heterogeneity or a random-effects model. *Results*. Eleven studies were included in the meta-analysis. For rifaximin-α plus lactulose in the second-line setting, the pooled INB was estimated at $20,156 (95% CI: $13,593-$29,887) versus lactulose monotherapy. For rifaximin-α monotherapy in the first-line setting, the pooled INB was $4834 (95% CI: $1601-$14,596) versus lactulose monotherapy. Due to lack of available data, meta-analyses were not possible for rifaximin-α added to lactulose therapy versus lactulose monotherapy in the first-line setting or for rifaximin-α as salvage therapy in the second-line setting. *Conclusions*. Rifaximin-α as an add-on treatment to lactulose in the second-line setting or as monotherapy in the first-line setting would be a cost-effective treatment for HE compared with lactulose monotherapy.

## 1. Introduction

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver disease, manifesting as a wide spectrum of neuropsychiatric abnormalities [1, 2]. It is a frequent and debilitating complication of liver disease, severely affecting the lives of patients and their caregivers [2]. Overt hepatic encephalopathy (OHE) symptoms include apathy, disorientation, personality change, inappropriate behaviour, somnolence, and coma. Minimal and covert HE (MHE and CHE) have more subtle effects and are not obvious on routine clinical examination [2].

The pathophysiology of HE is uncertain and likely to be multifactorial, with abnormalities in ammonia metabolism playing an important role [3, 4]. Ammonia is mainly derived from the gut, where gut bacteria produce it by metabolism of urea from proteins [4]. In patients with liver disease, impaired liver function reduces hepatic metabolism of ammonia, and

portal hypertension results in shunting of ammonia-containing blood into the systemic circulation without detoxification [4]. Ammonia crosses the blood-brain barrier into the brain, where astrocytes metabolise it into glutamine. Glutamine accumulation produces an osmotic gradient causing the astrocytes to swell, which in turn contributes to the cerebral dysfunction of HE [4]. Another possible pathophysiological mechanism is inflammation [5].

The nonabsorbable disaccharides, lactulose and lactitol, used as a first-line treatment for HE, reduce the production of ammonia from gut bacteria [3]. Oral antibiotics, such as rifaximin-$\alpha$, reduce the number of ammonia-producing bacteria in the gastrointestinal tract, thereby decreasing ammonia production and absorption, which can be used as a second-line treatment [3] or as salvage treatment in patients where lactulose is ineffective or is not tolerated.

Practice guidelines for the treatment of OHE have been published by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) [2]. These guidelines recommend lactulose as the first choice for treatment of OHE. In addition, rifaximin-$\alpha$ is an effective add-on therapy to lactulose for prevention of OHE recurrence [2]. Moreover, not all patients can tolerate lactulose, and for patients who develop gastrointestinal bloating or debilitating diarrhoea, a second-line agent can be considered [3]. In several randomised controlled trials, rifaximin-$\alpha$ was reported to effectively treat HE as compared to lactulose [6], showed similar results in MHE reversal [7], and improved health-related quality of life relative to placebo in patients with cirrhosis and recurrent HE [8]. Rifaximin-$\alpha$ has also been shown to be more effective than placebo in maintaining remission and reduces hospitalisation risk from HE [9] and has been associated with a notable reduction in blood ammonia [10]. Additionally, rifaximin-$\alpha$ has been demonstrated to increase clinical efficacy and decrease mortality in HE compared with lactulose alone [11]. In a 24-month open-label maintenance study, rifaximin-$\alpha$ appeared to provide a continued reduction in HE-related and all-cause hospitalisation without an increase in adverse events [12].

The cost-effectiveness of rifaximin-$\alpha$ has been evaluated in individual studies that cover a range of regimen treatments (first-line, second-line, and add-on); for example, one cost-effectiveness model found that rifaximin-$\alpha$ as an add-on to lactulose was within accepted thresholds for cost-effectiveness compared with lactulose monotherapy [13–15]. However, the results have not been consolidated using quantitative methods to provide an overall cost-effectiveness evaluation of rifaximin-$\alpha$ in HE. The objective of this literature review and meta-analysis was to assess the overall cost-effectiveness of rifaximin-$\alpha$ in HE using available published data.

## 2. Methods

*2.1. Literature Review.* A literature search was conducted in MEDLINE®, Embase®, MEDLINE® In-Process, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception up to November 2020. The National Health Service Economic Evaluation Database (NHS EED), the Health Technology Assessment Database (HTAD), and the Database of Abstracts of Reviews (DARE) were searched from the York Centre for Reviews and Dissemination (CRD) database. EconLit® was searched via the http://AEAweb.org/ interface. The full search strategy for Embase® and MEDLINE® is presented in Table S1. The reference lists of relevant systematic reviews were also searched. Relevant congress proceedings were searched in Embase® or via the congress website for 2018-2020.

Studies were eligible if they were published in English and met the criteria listed in Table 1. There was no restriction on countries in the search. Studies were selected for final data extraction if they were conducted in European and Middle Eastern countries, the United States, China, and Latin America (Mexico).

Studies identified in the search were initially screened based on the title and abstract; then, a second stage of screening was conducted using full-text papers. Two independent reviewers performed the screening, with a quality check conducted by a third independent reviewer.

Extracted data included study details, country, study design, setting, treatments, and study outcomes; data were screened by two independent reviewers, and any discrepancies were adjudicated by a third independent reviewer based on the consensus view. Where incremental cost-effectiveness ratio (ICER) data were available, ICERs with 95% confidence interval (CI) data were extracted. Where ICER data were not available, incremental cost and incremental outcome data for rifaximin-$\alpha$ versus comparators were extracted. Included studies were assessed for quality using published checklists [16, 17].

*2.2. Meta-Analysis.* Comparative efficiency research (COMER) is a method for combining cost-effectiveness study data, proposed by Crespo et al. [18]. In order to pool estimates across multiple studies, a measure of variance is needed for all studies included. However, not all studies consistently present 95% CIs around reported ICER values, and because the ICER is a ratio and follows a nonsymmetric distribution, it is not advisable to construct a CI around ICER data. However, incremental net benefit (INB) is distributed normally and therefore CIs can be constructed. Therefore, we calculated the INB for each study (see Supplementary Materials). An intervention is considered cost-effective if the INB is positive.

Costs were standardised by converting to US$ for the corresponding year and then adjusted to 2019 values using consumer price index data from the World Bank [19]. The heterogeneity of INB between studies was assessed using the Cochran $Q$ test and the $I^2$ statistic. A meta-analysis [18] was performed to pool calculated INB across studies, using a fixed-effects model (if there was no heterogeneity) or a random-effects model.

In the absence of data on variance of difference in effectiveness (incremental quality-adjusted life-years, QALYs), these data were simulated using a Monte Carlo simulation (MC), and MC standard error (MCSE) was calculated for each study using univariate normal distribution with

Table 1: PICOS criteria for inclusion of studies.

| | Inclusion |
|---|---|
| Population | HE (types A, B, or C) |
| Intervention | Rifaximin-$\alpha$, antibiotics such as neomycin, metronidazole, vancomycin, and lactulose (+ rifaximin-$\alpha$), LOLA, and lactitol |
| Control | Lactulose monotherapy |
| Outcomes of interest | ICER or incremental cost and outcomes data |
| Study design | Cost-effectiveness, cost-utility, cost-benefit, or cost-minimisation analyses; budget impact models; cost surveys; cost/economic burden of illness studies; database studies collecting cost data; or studies providing resource use data |
| Language | English |

Abbreviations: HE: hepatic encephalopathy; ICER: incremental cost-effectiveness ratio; LOLA: L-ornithine L-aspartate; PICOS: population, intervention, control, outcomes of interest, study design, language.

population mean = 0 and standard deviation (SD) = 1. In line with standard practice, incremental costs were simulated using a gamma distribution with 10% sigma and respective shape. Scale parameter MC error was estimated using the MCSE function in MCMCSE packages in R (https://www.R-project.org/).

Willingness-to-pay thresholds were extracted from the published studies with relevant data. Where willingness-to-pay thresholds were not reported, gross domestic product (GDP) per capita was used as an alternative. GDP per capita for each country for the corresponding year and for 2019 was obtained from the World Bank website [20].

When feasible, subgroup analyses were also performed based on treatment type (add-on or monotherapy), line of treatment (first or second line), and time horizon.

## 3. Results

*3.1. Search Results and Studies Included.* Fifteen studies identified in the search met the inclusion criteria for this literature review (Figure 1) [13–15, 21–32].

The characteristics of the studies are summarised in Table 2. Most studies reported cost-utility analyses with cost/QALY as the outcome measure. The time horizon ranged from 10 days to a lifetime, with 5 years most reported. Most studies (11/15) conducted sensitivity analysis, but only three reported the results: Kabeshova et al., [15], Berni et al., [13], and Jesudian et al., [14] (Table 2).

Of the 15 studies identified, 11 were included in the meta-analysis, and four were excluded; Alhawwashi et al., [21] was a budget impact analysis, Bajaj et al., [22] assessed diagnosis as well as treatment and reported an outcome measure of reduction in motor vehicle accidents, Paul et al., [28] did not report ICER data with incremental costs or sufficient cost or QALY data to back-calculate ICER data; moreover, the population assessed—adults (> 50 years of age) with overt HE—was different from the rifaximin-$\alpha$-labelled population, and Koh et al., [27] did not report sufficient data.

The calculated INB for each study is shown in Table S2.

*3.2. Rifaximin-α as an Add-on Therapy to Lactulose Compared with Lactulose Monotherapy.* Table 3 summarises the studies reporting data on the cost-effectiveness of rifaximin-$\alpha$ added to lactulose therapy versus lactulose monotherapy. One study [25] was conducted in the first-line setting; all the others were second line. The single first-line study reported that rifaximin-$\alpha$ added to lactulose therapy was not cost-effective compared with lactulose monotherapy, as the ICER was $94,680 and the mean INB calculated was −$11,909 (Table 3, Figure S1, Table S3). As only one study was identified, a meta-analysis in the first-line setting was not feasible.

Rifaximin-$\alpha$ added to lactulose therapy was cost-effective compared with lactulose monotherapy in the second-line studies, as the ICER was less than the reported willingness-to-pay threshold or GDP per capita (Table 3). The results of the meta-analysis in the second-line studies are shown in Figure 2. The pooled INB was estimated at $20,156 (95% CI: $13,593-$29,887) (random-effects model) for rifaximin-$\alpha$ plus lactulose versus lactulose monotherapy irrespective of time horizons. As the INB exceeded zero, this indicates that rifaximin-$\alpha$ plus lactulose was cost-effective compared with lactulose monotherapy in the second-line setting. High heterogeneity was observed ($I^2 = 100\%$), and results from the random-effects model at the 2-year time horizon had a wide confidence band (Figure 3), indicating high uncertainty.

Figure 3(a) shows the cost-effectiveness acceptability curve at the 2-year time horizon. The results indicate that there was a 70% probability that the second-line treatment with rifaximin-$\alpha$ plus lactulose would be cost-effective at a willingness-to-pay threshold of $20,000 per QALY gained. Figure 3(b) shows the cost-effectiveness plane at the 2-year time horizon, plotting incremental costs versus incremental QALYs. The confidence ellipses indicate the area within which 95% CI, 75% CI, and 50% CI of the estimates fall. Figures 3(c) and 3(d) show the cost-effectiveness acceptability curve and the cost-effectiveness plane at the 5-year time horizon. Using a 10-year time horizon, there was a 100% probability that the second-line treatment with rifaximin-$\alpha$ plus lactulose would be cost-effective at all willingness-to-pay thresholds. Figures S2(a) and S2(b) show the cost-effectiveness acceptability curve and the cost-effectiveness plane at the 10-year time horizon, and Figures S3(a) and S3(b) show the cost-effectiveness acceptability curve and

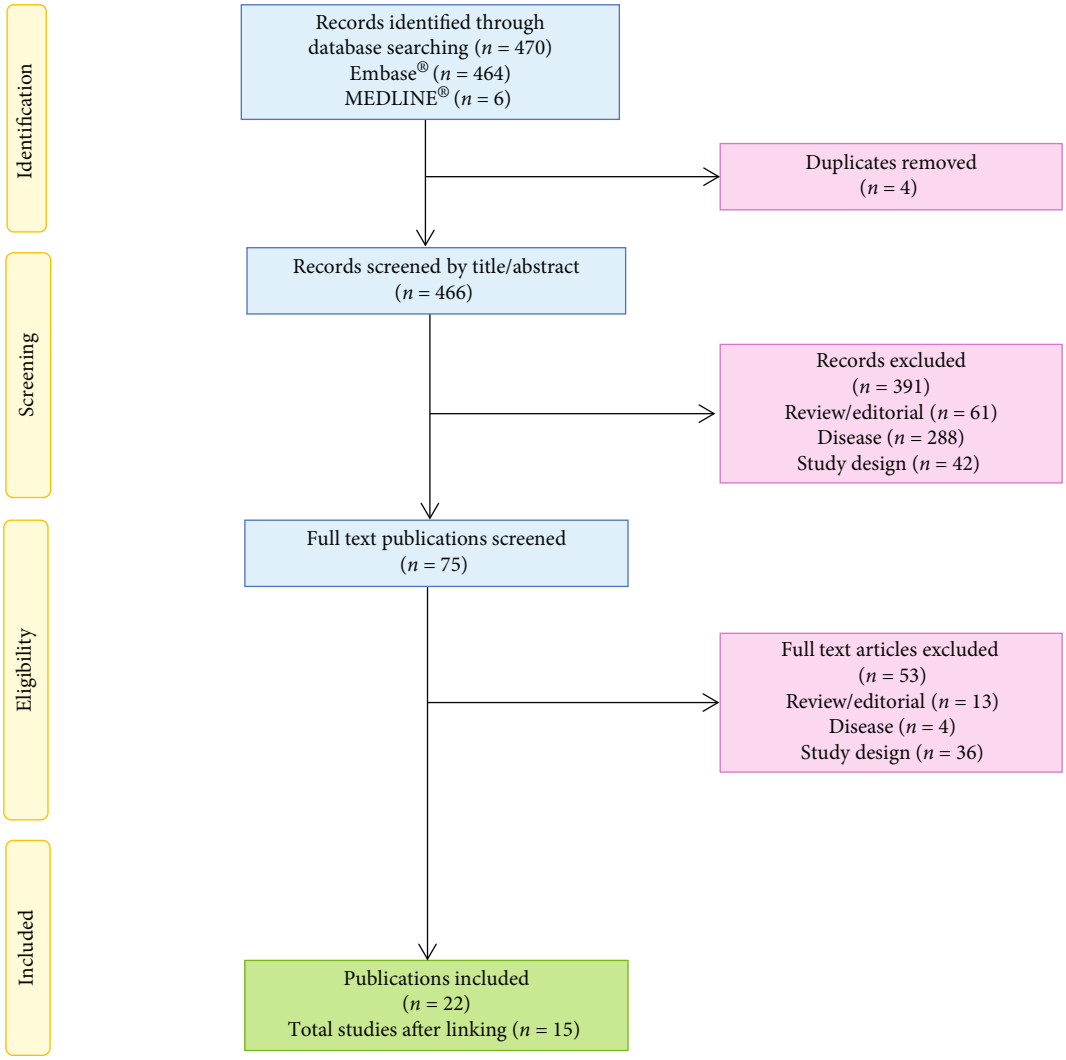


Figure 1: Prisma flow diagram for study search and selection. Abbreviations: Embase®: Excerpta Medica Database; MEDLINE®: Medical Literature Analysis and Retrieval System Online; *n*: number; Prisma: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

the cost-effectiveness plane at the lifetime horizon. There is a 100% probability that the second-line treatment with rifaximin-$\alpha$ plus lactulose would be cost-effective at all willingness-to-pay thresholds above $20,000 per QALY gained.

*3.3. Rifaximin-α Monotherapy Compared with Lactulose Monotherapy in the First-Line Setting.* Four studies evaluated rifaximin-$\alpha$ monotherapy versus lactulose monotherapy in the first-line setting (Table S4) [24, 26, 29, 31]. The results of the meta-analysis of rifaximin-$\alpha$ monotherapy versus lactulose monotherapy in the first-line setting are shown in Figure S4. As the pooled INB exceeded zero, the results indicated that rifaximin-$\alpha$ monotherapy was cost-effective compared with lactulose monotherapy in the first-line setting. There was no heterogeneity between these four studies ($I^2 = 0\%$). The pooled INB for rifaximin-$\alpha$ monotherapy versus lactulose monotherapy in the first-line setting was $4834 (95% CI: $1601-$14,596) (Figure S4).

Figures 4(a) and 4(b) show the cost-effectiveness acceptability curve and the cost-effectiveness plane for rifaximin-$\alpha$ monotherapy versus lactulose monotherapy in the first-line setting at a time horizon of 10-14 days. At these short time horizons, rifaximin-$\alpha$ monotherapy was highly cost-effective compared with lactulose monotherapy. At a time horizon of 5 years, represented by a single UK study, rifaximin-$\alpha$ monotherapy was also cost-effective compared with lactulose monotherapy (Figures 4(c) and 4(d)).

*3.4. Rifaximin-α as Salvage Therapy Compared with Lactulose Monotherapy.* Table 4 summarizes the studies reporting data on the cost-effectiveness of rifaximin-$\alpha$ salvage therapy versus lactulose monotherapy. Salvage therapy is defined as lactulose followed by rifaximin-$\alpha$ in patients in whom lactulose is ineffective or initiation with lactulose and crossover to rifaximin-$\alpha$ in case of inadequate response or intolerance to lactulose.

Two studies evaluated salvage therapy in the second-line setting (Table 4) [25, 26]. As the time horizons differed, and

Table 2: Characteristics of studies identified in the literature review.

| Study | Country | Modelling approach | Time horizon | Discounting (C/B) | Perspective | Sensitivity analysis | Population |
|---|---|---|---|---|---|---|---|
| Kabeshova et al., [15] | France | Markov model | 2 years and 5 years | NR | French national health insurance | 1-way and PSA | Age ≥ 18 years and in remission from previous episodes of OHE, associated with hepatic cirrhosis (equivalent to conn score ≥ 2) |
| Bajaj et al., [22] | United States | Markov model | 5 years | 3.0% | Societal perspective | Univariate | A simulated cohort of 1000 cirrhotic patients with compensated liver disease and without OHE, from entry into treatment |
| Congly et al., [25] | United States | Markov model | 5 years | NR | Third-party payer's perspective | 1 way | Patients in remission from previous OHE |
| Jesudian et al., [14] | United States | Markov model | Lifetime | 3.0% | Third-party US payer perspective | Univariate, PSA | Patients in remission of recurrent HE |
| Huang et al., [26] | United States | Markov model | Lifetime | 3.0% | Third-party US payer perspective | 1 way | Patients entered the model without previous treatment for HE and were then allocated among 6 treatment strategies |
| Rivas et al., [31] | Mexico | Decision tree model | 14 days | 5.0% | Mexican Institute of Social Security perspective | Univariate | Patients with acute HE |
| Berni et al., [13] | United Kingdom | Markov model | 2 years, 5 years, 10 years, and lifetime | 3.5% | UK National Health Service | Deterministic and PSA | Adult cirrhotic patients in remission (conn score 0-1) from recurrent OHE episodes (≥ 2 prior episodes) |
| Cardona et al., [24] | Mexico | Decision tree model | 10 days | NR | Mexican Institute of Social Security (IMSS) perspective | Univariate | Patients with HE |
| Whitehouse et al., [32] | Netherlands | Markov model | 5 years | 4.0%/1.5% | NR | NR | Patients with liver cirrhosis |
| Paul et al., [28] | NR | Markov model | 6 months, 1 year, and lifetime | NR | Third-party payer's perspective | Unspecified | Adult patients (age ≥ 50 years) with OHE |
| Poole et al., [30] | United Kingdom | Markov model | 5 years and 10 years | 3.5%/3.5% | UK National Health Service payer perspective | Unspecified | Cirrhotic patients with OHE |
| Poole et al., [29] | Sweden | Markov model | 5 years, 10 years, and lifetime | 3.5%/3.5% | Payer perspective of the Swedish healthcare system | Unspecified | Cirrhotic patients with OHE |
| Berni et al., [23] | Belgium | Markov model | 5 years, 10 years, and lifetime | 3.5%/1.5% | Payer perspective of the Belgian healthcare system | NR | Cirrhotic patients with recurrent OHE |
| Alhawwashi et al., [21] | Saudi Arabia | NR | NR | NR | Healthcare payer perspective: Tertiary hospital in Riyadh, Saudi Arabia | NR | Patients with HE |
| Koh et al., [27] | Singapore | Markov model | NR | NR | NR | NR | Patients with HE |

Abbreviations: B: benefit; C: cost; HE: hepatic encephalopathy; NR: not reported; OHE: overt hepatic encephalopathy, PSA: probabilistic sensitivity analysis.

Table 3: Cost-effectiveness of rifaximin-$\alpha$ plus lactulose compared with lactulose monotherapy.

| Study | LOT | Time horizon | Country | ICER | WTP per QALY reported across studies | Sensitivity analysis results | GDP per capita (US$, 2019) |
|---|---|---|---|---|---|---|---|
| Kabeshova et al., [15] | Second | 2 years | France | €19,187.00 | €27,000.00 | €13,507.00 (95% Cl €8887.00-21,733.00) | 40,493.30 |
| Kabeshova et al., [15] | Second | 5 years | France | €18,517.00 | €27,000.00 | €13,507.00 (95% CI €8887.00-21,733.00) | 40,493.30 |
| Congly et al., [25] | First | 5 years | United States | $94,680.00 | NR | NR | 65,297.52 |
| Jesudian et al., [14] | Second | Lifetime | United States | $29,161.00 | $50,000.00 | NR | 65,297.52 |
| Berni et al., [13] | Second | 2 years | United Kingdom | −£15,916.00 | £30,000.00 | −£17,014.00-17,168.00 | 42,330.12 |
| Berni et al., [13] | Second | 5 years | United Kingdom | −£1087.00 | £30,000.00 | −£17,014.00-17,168.00 | 42,330.12 |
| Berni et al., [13] | Second | 10 years | United Kingdom | £4470.00 | £30,000.00 | −£17,014.00-17,168.00 | 42,330.12 |
| Berni et al., [13] | Second | Lifetime | United Kingdom | £7215.00 | £30,000.00 | −£17,014.00-17,168.00 | 42,330.12 |
| Whitehouse et al., [32] | Second | 5 years | Netherlands | €9576.00 | NR | NR | 52,331.32 |
| Poole et al., [29] | Second | 5 years | Sweden | €17,916.36 | NR | NR | 51,615.02 |
| Poole et al., [29] | Second | Lifetime | Sweden | €639.00 | NR | NR | 51,615.02 |
| Berni et al., [23] | Second | 5 years | Belgium | €28,467.86 | NR | NR | 46,420.66 |

Abbreviations: CI: confidence interval; GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; LOT: line of therapy; NR: not reported; QALY: quality-adjusted life-year; WTP: willingness-to-pay.

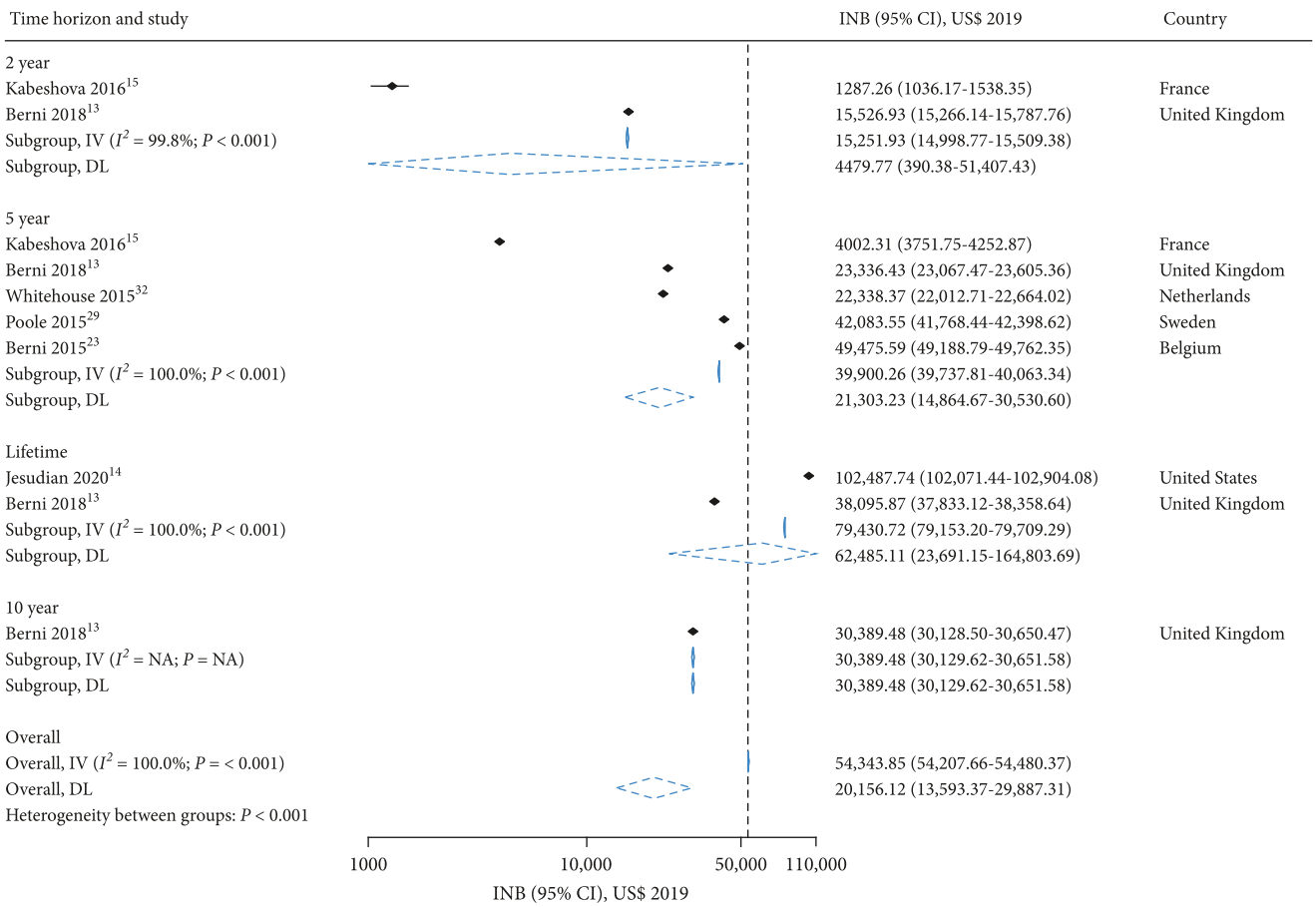


Figure 2: Meta-analysis of the cost-effectiveness of rifaximin-$\alpha$ plus lactulose compared with lactulose monotherapy in the second-line setting. A minimum of two studies are required to generate heterogeneity statistics (i.e. $I^2$ value or $P$ value); therefore, where only one study was available, these values could not be determined and were marked as not applicable (NA). Abbreviations: CI: confidence interval; DL: DerSimonian and Laird (random-effects model); $I^2$: heterogeneity statistics; INB: incremental net benefit; IV: inverse variance; Lact: lactulose; $P$: probability; Rif: rifaximin; US$: United States dollars.

Huang et al., [26] reported insufficient detail on clinical benefits and did not match the label population for rifaximin-$\alpha$, a meta-analysis was not feasible. The INB exceeded zero for both studies (Table S5), indicating that the second-line rifaximin-$\alpha$ salvage therapy was cost-effective compared with lactulose monotherapy.

Two studies evaluated therapy in the first-line setting in Mexico with time horizons of 10-14 days (Table 4) [24, 31]. Although the studies listed in Table 4 could in theory be combined in a meta-analysis, this was not done because of the overall heterogeneity of the studies in terms of time horizon and country of origin. Poole et al., [30] reported data at 5- and 10-year time horizons. The results of each study are discussed along with the overall pooled estimate across these studies. The reported ICER was less than GDP/capita in all three studies (Table 4), indicating that the first-line rifaximin-$\alpha$ salvage therapy was cost-effective compared with lactulose monotherapy.

## 4. Discussion

Clinical guidelines recommend lactulose for the first-line treatment for overt HE [2, 33]. In addition, the antibiotic rifaximin-$\alpha$ is an effective add-on therapy to lactulose for the prevention of overt HE recurrence [2] and for the treatment of patients with HE who are intolerant to lactulose due to its gastrointestinal side effects [2, 3]. Furthermore, for some patients who are lactulose intolerant, rifaximin-$\alpha$ can potentially be given in the first-line setting instead of lactulose or as the second-line monotherapy after lactulose [2].

This study was a meta-analysis of published cost-effectiveness studies of rifaximin-$\alpha$ in HE, at different lines of treatment and over a range of time horizons. The results indicated that add-on rifaximin-$\alpha$ was cost-effective compared with lactulose monotherapy in the second-line setting at 2-year, 5-year, 10-year, and lifetime time horizons. High heterogeneity was observed ($I^2$ = 100%), which may reflect differences in the time horizons and country settings.

The implications of these findings are very important in the management of cirrhotic patients with HE. A potential advantage of rifaximin-$\alpha$ treatment is that patients could take the drug after the initial period of HE without waiting for a recurrence under lactulose treatment, which could decrease the recurrence of HE and hospital readmission. As each episode of HE is associated with high morbidity

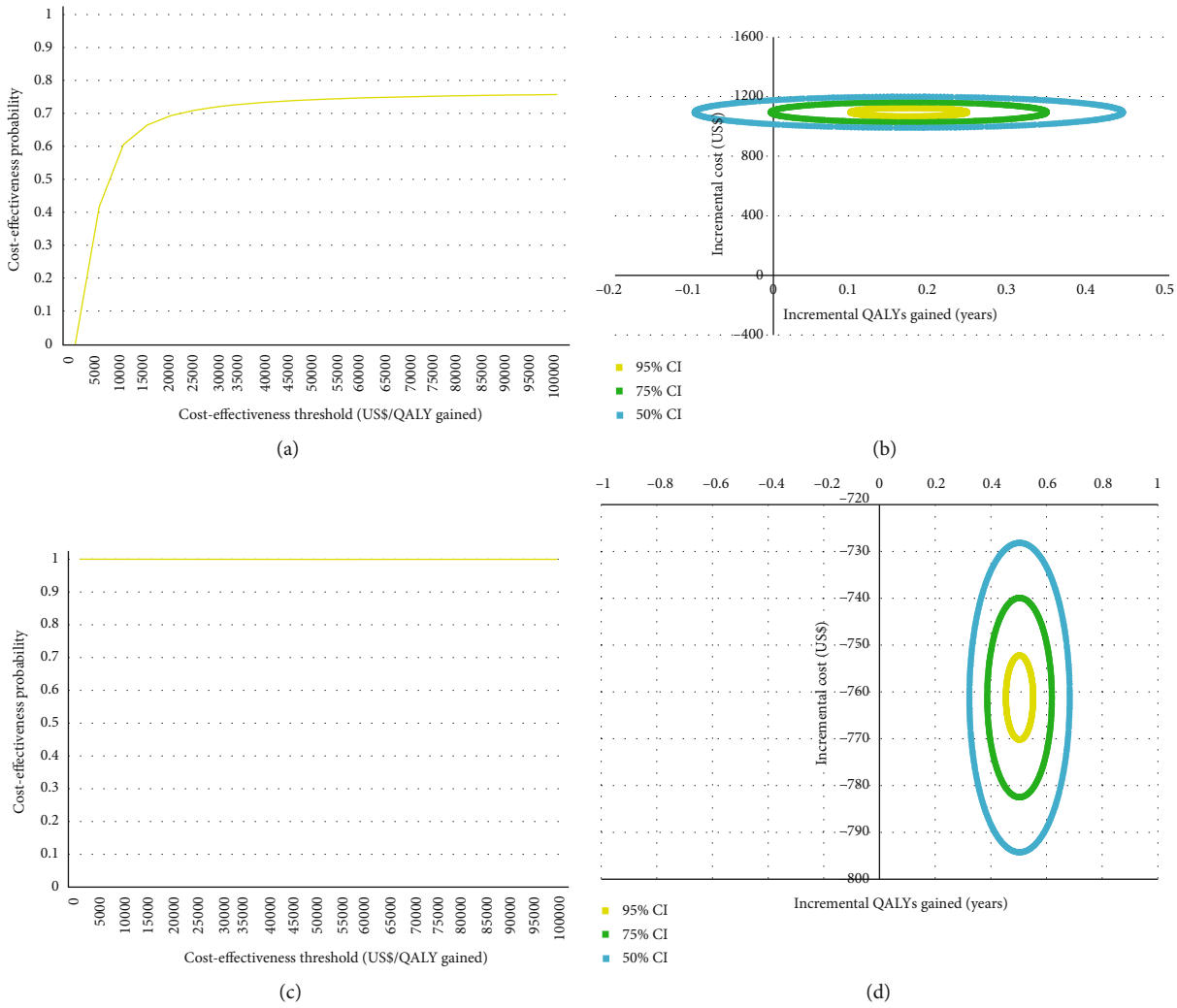


Figure 3: Cost-effectiveness of rifaximin-$\alpha$ plus lactulose compared with lactulose monotherapy in the second-line setting: (a) cost-effectiveness acceptability curve at a 2-year time horizon; (b) cost-effectiveness plane at a 2-year time horizon; (c) cost-effectiveness acceptability curve at a 5-year time horizon; and (d) cost-effectiveness plane at a 5-year time horizon. In panel (a) and (c), the horizontal axis (cost-effectiveness threshold) displays willingness-to-pay budgetary thresholds to gain one additional QALY when using rifaximin-$\alpha$ plus lactulose in lieu of lactulose. The vertical axis (probability cost-effective) displays the proportion of patients that fall within the budget. In panel (b) and (d) the confidence intervals (CI) define the regions that contain 95% CI (yellow), 75% CI (green), and 50% CI (blue) of the samples that can be drawn from the underlying Gaussian distribution. Abbreviations: CI: confidence interval; QALY: quality-adjusted life-year; US$: United States dollars.

and risk of death, avoiding recurrence and readmission is a strong endpoint in this setting.

Rifaximin-$\alpha$ has been reported to have higher patient adherence than lactulose [34], and if so, this may be an important contributor to the favourable cost-effectiveness of rifaximin-$\alpha$ observed in our meta-analysis. In a retrospective study of patients discharged after an HE-related hospitalisation or emergency room visit, lactulose was the most commonly used medication (68% of those receiving medication) and had the lowest adherence, measured as proportion of days covered (mean 0.56 days), while lactulose combined with neomycin or rifaximin-$\alpha$ had the highest adherence (mean 0.82 days) [35]. Lactulose nonadherence may therefore have serious consequences, as nonadherence was identified as a precipitating factor in about 50% of patients hospitalised for OHE [36]. Consequently, many patients have no prophylaxis when taking lactulose alone. Finally, lactulose therapy can induce dehydration itself, favouring metabolic disorders, hyponatremia, and renal failure, which precipitates HE [37].

Compared with lactulose, rifaximin-$\alpha$ has few side effects. However, treatment cost contributes to the reluctancy to prescribe this medication. In certain countries, such as France, price is still not available. This study provides an important contribution in demonstrating the necessity of rifaximin-$\alpha$ treatment after the initial period of HE.

Studies identified in our literature review also indicated that rifaximin-$\alpha$ is cost-effective as salvage therapy (defined as lactulose followed by rifaximin-$\alpha$ in patients in whom lactulose is ineffective or initiation with lactulose and crossover

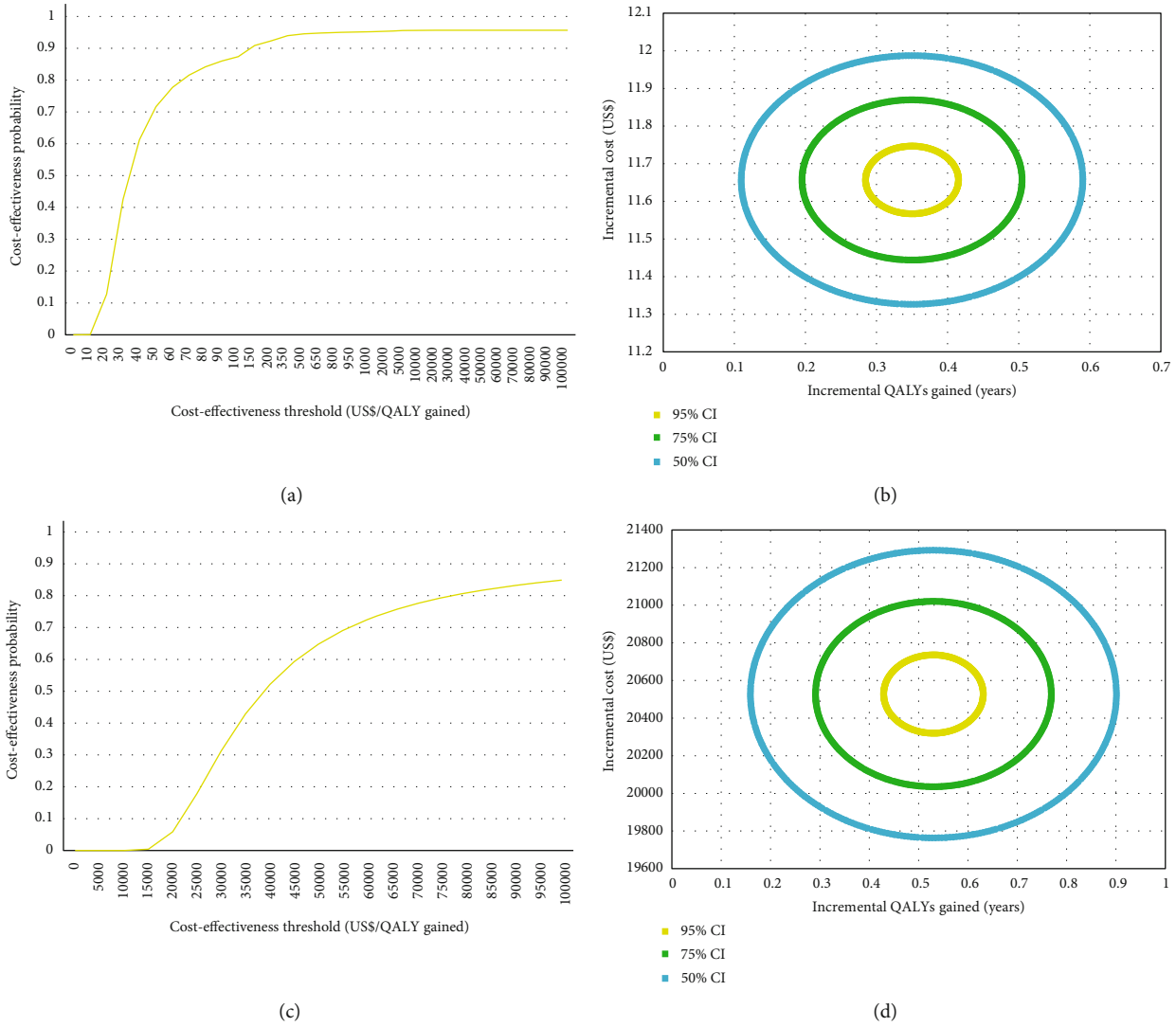


Figure 4: Cost-effectiveness of rifaximin-$\alpha$ monotherapy compared with lactulose monotherapy in the first-line setting: (a) cost-effectiveness acceptability curve at a 10- to 14-day time horizon; (b) cost-effectiveness plane at a 10- to 14-day time horizon; (c) cost-effectiveness acceptability curve at a 5-year time horizon; and (d) cost-effectiveness plane at a 5-year time horizon. In panel (a) and (c), the horizontal axis displays willingness-to-pay budgetary thresholds to gain one additional QALY when using rifaximin-$\alpha$ plus lactulose in lieu of lactulose. In panel (b) and (d) the confidence intervals (CI) define the regions that contain 95% CI (yellow), 75% CI (green), and 50% CI (blue) of the samples that can be drawn from the underlying Gaussian distribution. Abbreviation: CI: confidence interval; QALY: quality-adjusted life-year.

to rifaximin-$\alpha$ in case of inadequate response or intolerance to lactulose) in the first- and second-line settings, although a meta-analysis in the first-line setting was not possible due to a lack of data. However, the single study available indicated that add-on rifaximin-$\alpha$ would incur higher costs and provide higher benefits compared with lactulose monotherapy. The results indicated that rifaximin-$\alpha$ monotherapy was also highly cost-effective compared with lactulose monotherapy in the first-line setting at short time horizons of 10-14 days. A meta-analysis of rifaximin-$\alpha$ salvage therapy compared with lactulose monotherapy was not feasible due to the differences in the populations studied.

Ammonia is believed to be an important mechanism in the pathophysiology of HE [4] and a previously published network meta-analysis found that rifaximin-$\alpha$ was associated with the greatest reduction in blood ammonia among the five interventions compared [10]. It is possible that our results, indicating favourable cost-effectiveness for rifaximin-$\alpha$, may reflect its effects on ammonia metabolism. Unfortunately, ammonia levels were not available in the analysed studies, as is almost always the case in HE therapeutic studies. However, as with lactulose, rifaximin-$\alpha$ treatment has been shown to lower ammonia levels. In a recent large retrospective study ($n = 498$), ammonia levels appeared to play a prognostic role in patients with acute-on-chronic liver failure (ACLF) and was an independent risk factor associated with mortality in patients with cirrhosis [38]. Interestingly, this was true in patients with HE and in patients with ACLF without HE, meaning that lowering

Table 4: Cost-effectiveness of rifaximin-$\alpha$ salvage compared with lactulose monotherapy.

| Study | LOT | Time horizon | Country | ICER | WTP per QALY reported across studies | GDP per capita (US$, 2019) | Sensitivity analysis results |
|---|---|---|---|---|---|---|---|
| Congly et al., [25] | Second | 5 years | United States | US$38,833.00 | NR | 65,297.52 | 1-way |
| Huang et al., [26] | Second | Lifetime | United States | US$2315.00 | US$20,000.00 | 65,297.52 | 1-way |
| Rivas et al., [31] | First | 14 days | Mexico | NR | NR | 9946.03 | NR |
| Cardona et al., [24] | First | 10 days | Mexico | US$19.52 (cost-effective based on signs and symptoms) | NR | 9946.03 | 19.50-136.70 (CER variation with varying effectiveness) |
| Poole et al., [30] | First | 5 years | United Kingdom | £20,852.00 | NR | 42,330.12 | £13,919.00-21,425.00 |
| Poole et al., [30] | First | 10 years | United Kingdom | £19,122.00 | NR | 42,330.12 | NR |
| Huang et al., [26] | First | Lifetime | United States | US$26,720.00 (not cost-effective) | US$20,000.00 | 65,297.52 | NR |

Abbreviations: CER: comparative effective research; GDP: gross domestic product; ICER: incremental cost-effectiveness ratio; LOT: line of therapy; NR: not reported; QALY: quality-adjusted life-year; WTP: willingness-to-pay; US$: United States dollar.

ammonia levels could be beneficial outside of HE for lowering mortality rates.

Indeed, ammonia toxicity is not restricted to the central nervous system and has been shown to be involved in liver injury and fibrosis, impairment of neutrophil phagocytic function, increase in immune dysfunction, hyperammonemia associated with sarcopenia, myosteatosis, and hepatocyte apoptosis [39–43]. Finally, the interplay between ammonia and sepsis is well known [44], with a reduction in serum ammonia levels being a predictor of improved prognosis [45]. The beneficial effects of rifaximin-$\alpha$ could therefore act via this mechanism. Further, rifaximin-$\alpha$ is more widely applicable than lactulose, as adherence to this treatment is often poor. However, this was not considered in the present analysis and could be a subject for future research.

Another interesting aspect is that rifaximin-$\alpha$ efficacy and safety is strictly related to its unique mechanism of action. This nonabsorbable antibiotic has been shown to act as a eubiotic drug, promoting the growth of beneficial bacterial such as Lactobacilli, in cirrhotic patients with HE, even persisting in the short term after treatment interruption [46, 47]. Furthermore, rifaximin-$\alpha$ treatment downregulates the inflammatory response by reducing the expression of proinflammatory cytokines tumour necrosis factor-alpha and interleukin-1, inhibiting the activation of nuclear-factor kappa B [47, 48] and reducing bacterial translocation and virulence without significantly changing the overall composition of the gut microbiota [46, 47, 49, 50]. In addition, low systemic absorption (0.4% of the orally administered dose), low incidence of drug-related adverse events, and minimal risk of inducing bacterial resistance support the use of rifaximin-$\alpha$ for the treatment patients with advanced liver disease [47, 51–54].

The recommended dose for rifaximin-$\alpha$ for prevention of recurrences of HE is 550 mg twice daily; however, a lower dose of 200 mg is available for HE and for the treatment of hyperammonemia in some countries. As is common practice in meta-analysis, we pooled data across all doses. A comprehensive meta-analysis comparing the efficacy of rifaximin-$\alpha$ for the management of HE showed that rifaximin-$\alpha$ is at least equivalent to conventional antibiotic therapies (neomycin and paromomycin) or nonabsorbable disaccharides (lactulose and lactitol), with the advantage of a more favourable safety profile [52].

To our knowledge, no other meta-analyses of cost-effectiveness studies of rifaximin-$\alpha$ in HE have been published. As such, the present analysis builds on the individual cost-effectiveness studies already published by synthesising the data available using quantitative methods to provide an overall cost-effectiveness evaluation of rifaximin-$\alpha$ in HE. This study followed an established method of meta-analysis, with data transformed to INB as suggested by Crespo et al. [18]. However, the results should be interpreted with caution given the differences in parameters included in the cost assessment across studies, as well as country-specific variations in practice.

In conclusion, the results of this meta-analysis indicate that rifaximin-$\alpha$ as an add-on treatment to lactulose in the second-line setting or as monotherapy in the first-line setting would be a cost-effective treatment for HE compared with lactulose monotherapy.

## Data Availability

Data sharing not applicable as all data from the published studies are duly cited with the manuscript.

## Disclosure

An earlier version of this work was presented as a poster at the International Liver Congress, 2021. Medical writing support for this manuscript was provided by Sue Neville, MSc, and Stacey Human, PhD, of Parexel International.

## Conflicts of Interest

MKS, SA, MO, FL, and VM have no competing interests to declare. DDT serves on the Alfasigma advisory board and has received payment from Alfasigma for educational lectures.

## Authors' Contributions

MKS, SA, MO, FL, and VM designed the research study. MKS and SA performed the research. MKS, SA, MO, FL, VM, and DT analysed and interpreted the data. MKS, SA, MO, FL, VM, and DT contributed to all drafts of the manuscript and approved the final version for submission. M. K. Siddiqui is the guarantor of this article.

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## Supplementary Materials

Table S1: search strategy for Embase® and MEDLINE®, searched through http://Embase.com/ on 11 December 2020. Table S2: calculated INB for addition of rifaximin-$\alpha$ with or without lactulose compared with lactulose monotherapy, or rifaximin-$\alpha$ salvage treatment in reducing episodes of overt HE. Table S3: meta-analysis in the first-line setting was not feasible for rifaximin-$\alpha$ plus lactulose compared with lactulose monotherapy. Table S4: meta-analysis of rifaximin-$\alpha$ monotherapy compared with lactulose monotherapy in the first-line setting. Table S4: meta-analysis of rifaximin-$\alpha$ monotherapy compared with lactulose monotherapy in the first-line setting. Figure S1: cost-effectiveness of rifaximin-$\alpha$ plus lactulose compared with lactulose monotherapy in the first-line setting at a 5-year time horizon: (a) cost-effectiveness acceptability curve; (b) cost-effectiveness plane. Figure S2: cost-effectiveness of rifaximin-$\alpha$ plus lactulose compared with lactulose monotherapy in the second-line setting at a 10-year time horizon: (a) cost-effectiveness acceptability curve; (b) cost-effectiveness plane. Figure S3:

cost-effectiveness of rifaximin-$\alpha$ plus lactulose compared with lactulose monotherapy in the second-line setting at a lifetime time horizon: (a) cost-effectiveness acceptability curve; (b) cost-effectiveness plane. Figure S4: meta-analysis of the cost-effectiveness of rifaximin-$\alpha$ monotherapy compared with lactulose monotherapy in the first-line setting. *(Supplementary Materials)*

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