Safety, efficacy, and patient acceptability of rifaximin for hepatic encephalopathy

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Abstract: Hepatic encephalopathy is a complex disease entity ranging from mild cognitive dysfunction to deep coma. Traditionally, treatment has focused on a reduction of ammonia through a reduced production, absorption, or clearance. Rifaximin is a nonabsorbable antibiotic, which reduces the production of ammonia by gut bacteria and, to some extent, other toxic derivatives from the gut. Clinical trials show that these effects improve episodes of hepatic encephalopathy. A large randomized trial found that rifaximin prevents recurrent episodes of hepatic encephalopathy. Most patients were treated concurrently with lactulose. Trials have varied greatly in design, outcomes, and duration of treatment regimes. Although a number of retrospective studies have indicated that long-term treatment with rifaximin is safe and possibly beneficial, high quality trials are needed to further clarify efficacy and safety of long-term treatment with rifaximin and evaluate effects of combination therapy with lactulose and branched-chain amino acids for patients with liver cirrhosis and hepatic encephalopathy.

Keywords: prevention, lactulose, liver cirrhosis

Introduction

Hepatic encephalopathy (HE) is a neuropsychiatric complication to liver failure, ranging from mild confusion to severe coma. Patients with cirrhosis and ascites have a 15% risk of developing HE within 1 year. Once HE is developed, the 1-year mortality exceeds 60%.¹ Hospitalizations are common and present a considerable challenge to the patient, the concerned family, and the health care system.²,³ The high morbidity and mortality combined with the costs underline the importance of effective treatment and prevention of HE.

HE is a complex disease that may be associated with acute liver failure, portal-systemic bypass, or cirrhosis and portal hypertension.⁴ Based on the clinical characteristics, HE can be classed as minimal, recurrent, or overt HE. Minimal HE presents with minor neurological and cognitive deficits that require advanced neuropsychological testing to diagnose. Overt HE presents with confusion and loss of consciousness, which can be episodic or persistent.⁵ A number of scoring systems are developed to grade the severity of overt HE. The West Haven criteria are often used and class HE on a scale from 0 to 4. A more recent guideline, which underlines the difficulty of diagnosing minimal signs of HE, recommends the term covert HE, which covers both minimal HE and HE with minor clinically discernible signs (corresponding to West Haven grade 1).⁶

The presumed pathology of HE includes a derangement in ammonium metabolism due to increased bacterial ammonia production in the gut and possibly a decreased ammonia clearance from the kidneys.⁷ Hyperammonemias induce encephalopathy...
by promoting cerebral edema, modulating the blood–brain barrier, decreasing blood flow, or modulating neurotransmission. A number of treatments therefore aim at eliminating the ammonia producing bacteria from the gut.5–10 The recommended treatments include the nonabsorbable disaccharides lactulose and lactitol, which have several potential mechanisms of action. The beneficial effects include reduced generation of ammonia from gut bacteria and an increased intestinal transit time. Branched-chain amino acids are also recommended for the treatment of HE. These amino acids include leucine, isoleucine, and valine, which are believed to correct the ratio between aromatic and branched-chain amino acids, resulting in a decreased formation of false neurotransmitters. Branched-chain amino acids also improve nitrogen metabolism and reduce malnutrition.

Rifaximin is a nonabsorbable antibiotic with antimicrobial effects on a broad spectrum of gut bacteria.11,12 Rifaximin has little effect on the normal gut flora, and resistance is infrequent.13

In the last three decades, several trials have investigated the efficacy of rifaximin in comparison with placebo, or no intervention, or to other active treatments such as disaccharides and other antibiotics.14–19 Trials are diverse in size, outcome measures, and patient inclusion criteria, which makes a thorough evaluation of the drug efficacy difficult. In 2010, the US Food and Drug Administration (FDA) approved the use of rifaximin as prophylaxis for episodic or recurrent HE following the publication of a large randomized trial stating a significant decrease in hospitalization rates among patients treated with rifaximin for 6 months or more.15 Rifaximin is also used with the same indication in several European countries. Unfortunately, rifaximin remains expensive, with an average wholesale price of US$1,586 for 1 month of treatment. The average wholesale price for lactulose is about US$79 per month depending on the necessary dose.20 Previous studies have suggested a cost-effective benefit of rifaximin compared with disaccharides,21 but patient acceptability and adherence to treatment remains unclear. In this review, we will assess the safety, efficacy, and patient acceptability of maintenance therapy of HE.

Assessment of the available literature

We conducted a systematic search of the potentially relevant available literature identified through searches in MEDLINE®, Web of Science™, and Embase®. The search terms “rifaximin AND hepatic encephalopathy,” “rifaximin AND hepatic encephalopathy AND cost,” and “long-term rifaximin AND hepatic encephalopathy” revealed 15 randomized trials (reported in 16 records), two prospective clinical trials, eight retrospective trials and decision analyses, and 25 relevant reviews and meta-analyses. Manual searches of bibliographies and abstracts from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver within the last 5 years (2008–2013) identified another eight randomized trials, three prospective studies, and two retrospective analyses (Table 1).

The 23 randomized trials were published between 1984 and 2013. Outcomes were diverse, and patient cohorts highly heterogeneous. Seven randomized trials reported no clinical outcomes or evaluated rifaximin administered for less than 7 days.17,22–28 The remaining trials evaluated long-term treatment or prevention of HE with rifaximin. Twelve randomized trials assessed the effect of rifaximin on overt HE.16,18,19,29–37 Two trials assessed the effect of rifaximin on minimal HE,14,38 and one trial (described in two records) assessed the prophylactic effect of rifaximin on recurrent HE.15,39

Five prospective cohort studies (described in three full-paper articles10–12 and three abstracts43–45) assessed complications and recurrence of HE in patients receiving rifaximin for 6 months up to 5 years.

Six retrospective studies evaluated the effects of rifaximin on the number of hospitalizations, rates of infections, and treatment patterns in patients with overt HE.24–26,40–42 Three papers reported analyses that assessed the cost-effectiveness in the treatment of HE with long-term rifaximin.51–53

Clinical efficacy of rifaximin

Prevention of recurrent HE

A large randomized trial from 2010 with 299 patients concluded that rifaximin reduces the risk of new episodes of HE and decreases hospitalizations due to HE in patients with previous episodes of overt HE.15 Included patients were nonresponders to the nonabsorbable disaccharide lactulose. The mean duration of treatment was 130 days. The overall results showed a number needed to treat of four patients. Accordingly, to prevent one episode of overt HE, four patients needed treatment with rifaximin for 130 days. Long-term treatment with rifaximin was assessed in an open-label extension of this trial. The extension trial also found a reduction in hospitalizations and episodes of HE.43,45 In accordance with these findings, a prospective cohort study including 69 patients with previous HE found that long-term treatment with rifaximin decreases portal hypertension and reduces the risk of complications to cirrhosis.42 A prospective
Table 1 Overview of the literature

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Primary outcomes</th>
<th>Significant trial results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efimiadi et al31</td>
<td>20</td>
<td>Gut flora</td>
<td>No statistical comparison reported</td>
</tr>
<tr>
<td>De Marco et al27</td>
<td>32</td>
<td>HE grade, s-ammonia, and blood biochemistry</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Testa et al28</td>
<td>20</td>
<td>s-ammonia, NCT, and gut flora</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Riggio et al24</td>
<td>75</td>
<td>Breakthrough of HE, s-ammonia</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Song et al33,26</td>
<td>64</td>
<td>Mental status and s-ammonia</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Williams et al38</td>
<td>54</td>
<td>PSE index, EEG, and s-ammonia</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Di Piazza et al27</td>
<td>14</td>
<td>Asterixis; trail-making test</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Venturini et al27</td>
<td>18</td>
<td>Benzo diazepine-like compounds</td>
<td>Benzo diazepine-like compounds lowered in rifaximin</td>
</tr>
<tr>
<td>Festi et al31</td>
<td>59</td>
<td>Asterixis, s-ammonia, and EEG</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Miglio et al24</td>
<td>60</td>
<td>s-ammonia, trans-aminases, and trail-making test</td>
<td>Improved trail-making test in rifaximin group</td>
</tr>
<tr>
<td>Parini et al39</td>
<td>30</td>
<td>HE grade and s-ammonia</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Pedretti et al36</td>
<td>30</td>
<td>Neuropsychometric tests, EEG, PSE index, and s-ammonia</td>
<td>Lower s-ammonia in the rifaximin group</td>
</tr>
<tr>
<td>Fera et al30</td>
<td>40</td>
<td>Mental state, A-cancellation-test (neuropsychometric test), trail-making test,</td>
<td>Mental state improved in rifaximin group, trail-making test improved in lactulose group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EEG irregularities, and s-ammonia</td>
<td></td>
</tr>
<tr>
<td>Paik et al35</td>
<td>54</td>
<td>HE index, s-ammonia, and NCT</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Massa et al32</td>
<td>40</td>
<td>Mental state, a-cancellation test, trail-making test, and s-ammonia</td>
<td>Improvement in mental status and trail-making test in the rifaxim group</td>
</tr>
<tr>
<td>Buccı and Palmieri16</td>
<td>58</td>
<td>Mental state, a-cancellation test, EEG, and PSE index</td>
<td>Improvement in EEG irregularities and a-cancellation test in rifaxim group.</td>
</tr>
<tr>
<td>Loguerco et al32</td>
<td>26</td>
<td>Mental state, asterixis, NCT, s-ammonia</td>
<td>Decrease in s-ammonia level in the rifaximin-lactitol group</td>
</tr>
<tr>
<td>Mas et al38</td>
<td>103</td>
<td>s-ammonia, NCT, EEG, and PSE index</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Bass et al39,30</td>
<td>93</td>
<td>s-ammonia, NCT, mental state, PSE index, and asterix</td>
<td>Improvement in asterixis in rifaximin group</td>
</tr>
<tr>
<td>Bass et al31</td>
<td>299</td>
<td>HE episodes and hospitalizations</td>
<td>Decreased number of recurrent episodes of HE and hospitalization rates in rifaximin group</td>
</tr>
<tr>
<td>Sidhu et al39</td>
<td>94</td>
<td>HRQL, SIP score, and NCT</td>
<td>Decrease in SIP score in rifaximin group</td>
</tr>
<tr>
<td>Bajaj et al42</td>
<td>42</td>
<td>Biochemistry, neuropsychometric testing, driving capacity, and sickness impact</td>
<td>Improvement in sickness impact profile and fewer driving errors in rifaxim group</td>
</tr>
<tr>
<td>Sharma et al27</td>
<td>120</td>
<td>Mortality, recovery of HE, and hospitalization</td>
<td>Lower mortality and hospitalization duration in rifaximin group</td>
</tr>
<tr>
<td><strong>Prospective trials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vlachogiannakos et al12</td>
<td>69</td>
<td>Prevention of HE, portal hypertension, and complications to cirrhosis</td>
<td>Lower risk of developing HE and complications to cirrhosis in rifaxim group</td>
</tr>
<tr>
<td>Irima et al25</td>
<td>78</td>
<td>Prevention of recurrent HE; hospitalizations</td>
<td>No significant difference among treatment groups</td>
</tr>
<tr>
<td>Tandon et al41</td>
<td>115</td>
<td>Antibiotic resistant infections and antibiotic exposure</td>
<td>No data on rifaximin treatment alone</td>
</tr>
<tr>
<td>Sanyal et al35,36</td>
<td>392</td>
<td>Infection rates and antibiotic use</td>
<td>No statistical comparison reported</td>
</tr>
<tr>
<td>Bajaj et al42,22</td>
<td>82</td>
<td>Incidence of breakthrough HE</td>
<td>No statistical comparison reported</td>
</tr>
<tr>
<td>O’Leary and et al46</td>
<td>175</td>
<td>Recurrent infections and use of antibiotics</td>
<td>Higher rates of rifaxim use in patients with recurrent infections</td>
</tr>
<tr>
<td><strong>Retrospective analyses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levey and Phillips2</td>
<td>145a</td>
<td>Hospitalization rates, HE grade, asterixis, and adverse events</td>
<td>Decreased hospitalization rates, decreased asterixis, and fewer patients with HE grade 3–4 during rifaxim treatment</td>
</tr>
<tr>
<td>Neff et al47</td>
<td>39</td>
<td>Hospitalization rates, economic data, and MELD score</td>
<td>No statistical comparison between groups reported</td>
</tr>
<tr>
<td>Mantry and Munsaf30</td>
<td>65</td>
<td>Hospitalizations</td>
<td>Reduced risk of hospitalization during rifaxim treatment</td>
</tr>
<tr>
<td>Neff et al47</td>
<td>203</td>
<td>Prevention of HE; MELD score</td>
<td>No comparison between groups performed</td>
</tr>
<tr>
<td>Neff47</td>
<td>45,480</td>
<td>Treatment patterns and use of rifaximin</td>
<td>No statistical comparison between groups reported</td>
</tr>
<tr>
<td>Neff et al48</td>
<td>211</td>
<td>Development of Clostridium difficile infections</td>
<td>No control group; no Clostridium difficile infections</td>
</tr>
</tbody>
</table>

Notes: 1Reports on the same prospective trial, a follow-up of the randomized trial by Bass et al; 2roll-over analysis where patients are initially treated with lactulose for 6 months followed by rifaximin for 6 months; 3published as abstracts; 4dose-finding trial, no control group; 5only abstract in English.

Abbreviations: EEG, electroencephalography; HE, hepatic encephalopathy; HRQL, health-related quality of life; MELD, Model of End Stage Liver Disease; NCT, number connection test; PSE, portal systemic encephalopathy; SIP, sickness impact profile.
study of 78 patients recovering from HE found that rifaximin is superior to lactulose in reducing HE-related hospitalization, but that lactulose was equally effective in preventing new episodes of HE. Reduced hospitalization rates and decreased recurrence of HE were also found in four retrospective analyses comprising a total of 452 patients on maintenance therapy.24,46-49

### Treatment of minimal HE

Two randomized trials comprising a total of 136 patients assessed the effect of rifaximin versus placebo on minimal HE.14,38 The primary endpoint in one trial was driving performance, whereas the other assessed reversal of minimal HE. Duration of treatment was 8 weeks. None of the included patients in these trials had previous episodes of HE. Only three patients developed overt HE during the study period (two patients in the placebo group and one patient in the rifaximin group). Data are inconclusive on whether rifaximin can prevent overt HE in patients with minimal HE. Both trials found some evidence of improved manifestations of minimal HE. The overall results were promising, but not conclusive.

### Treatment of overt HE

Eighteen randomized trials have assessed the effect of rifaximin on overt HE. One trial was a dose-finding study,28 one trial included patients after transjugular intrahepatic portosystemic shunt,24 and one trial was a crossover design.22 Sixteen trials included a control group of placebo, disaccharides, or other antibiotics.16-19,23,25,26,29-36,54 Treatment duration lasted from 5 to 21 days. Trials are characterized in Table 1. A thorough evaluation of the quality, relevance, and clinical efficiency of these studies lies beyond the scope of this paper.

### Safety of rifaximin treatment

Randomized trials have focused on rifaximin for the treatment of acute overt HE. The trials found that the safety of rifaximin was equal to that of comparative treatments. Few side effects such as nausea, diarrhea, vomiting, abdominal discomfort, and flatulence were reported in the rifaximin group. The risk of these adverse events was lower in the rifaximin group compared with the lactulose group.16,33 Safety assessment is summarized in Table 2.

The risk of adverse events was similar to that of placebo and did not increase with prolonged treatment up to 6 months.14,15

In a prospective cohort study, the effect of rifaximin on complications to liver cirrhosis was assessed during a follow-up period of 5 years.41 The study found that complications such as hepatorenal syndrome, spontaneous bacterial peritonitis, and HE was significantly reduced

### Table 2 Safety assessment of rifaximin

<table>
<thead>
<tr>
<th>Study</th>
<th>Adverse events – rifaximin</th>
<th>Adverse events – control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of patients</td>
<td>Mild</td>
</tr>
<tr>
<td>Randomized trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bucci and Palmieri16</td>
<td>30</td>
<td>9</td>
</tr>
<tr>
<td>Loguerio et al17</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Massa et al11</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Mas et al18</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Palk et al19</td>
<td>32</td>
<td>1</td>
</tr>
<tr>
<td>De Marco et al17</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Parini et al19</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Pedretti et al21</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Bajaj et al14</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Bass et al19</td>
<td>48</td>
<td>NA</td>
</tr>
<tr>
<td>Bass et al15</td>
<td>140</td>
<td>406</td>
</tr>
<tr>
<td>Sidhu et al22</td>
<td>49</td>
<td>12</td>
</tr>
<tr>
<td>Sharma et al27</td>
<td>63</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>528</td>
<td>453</td>
</tr>
<tr>
<td>Prospective studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vlachogiannakos et al23</td>
<td>23</td>
<td>NA</td>
</tr>
<tr>
<td>Irinia et al40</td>
<td>66</td>
<td>NA</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>NA</td>
</tr>
<tr>
<td>Retrospective studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantry and Munsaf8</td>
<td>65*</td>
<td>1</td>
</tr>
<tr>
<td>Leevey and Phillips2</td>
<td>145*</td>
<td>569</td>
</tr>
<tr>
<td>Total</td>
<td>210</td>
<td>570</td>
</tr>
</tbody>
</table>

Notes:
- *Retrospective design (patients received both treatments consecutively).
- Abbreviation: NA, not assessed.
among patients receiving rifaximin. Rifaximin also reduced mortality. Eleven adverse events were registered in the group of
patients receiving rifaximin (n=23 patients) and 58 adverse
events were registered in the control group (n=46 patients).
In an open-label extension of a randomized trial assessing
the effect of rifaximin on recurrent HE, 299 patients were
included. The duration of therapy was at least 6 months. All
patients received rifaximin, including those originally ran-
donized to rifaximin as well as patients originally random-
ized to placebo. The number of serious adverse events and
nonserious adverse events was similar to the placebo period
of the randomized trials and did not change with time.43
A retrospective study assessed the efficacy of rifaximin
in 65 patients.46 Charts of patients who were treated with
lactulose and subsequently rifaximin were analyzed. The
analyses showed that rifaximin reduced the number and dura-
tion of hospitalizations due to HE. Furthermore, rifaximin
was better tolerated. The number of adverse events associated
with rifaximin was scarce or nonexistent and no drug-related
serious adverse events were reported in the lactulose or
rifaximin treatment period.
Concerns have been raised regarding the long-term
treatment with broad-spectrum antibiotics in a vulnerable
group of patients. No Clostridium difficile infections were
observed in 211 patients receiving rifaximin for more than
6 months.48 Stable infection rates during long-term treatment
with rifaximin were reported in a prospective cohort study
of 392 patients.45 However, a prospective study including
283 patients found that proton pump inhibitors, rifaximin,
and antibiotics for the prevention of spontaneous bacterial
peritonitis were predictors of recurrent infections in patients
with cirrhosis.44 Another prospective study of 115 infections
occurring in 746 patients found that systemic antibiotics,
but not oral nonabsorbable antibiotics, were predictors of
antibiotic-resistant infections.41

Patient acceptability and adherence
to treatment with rifaximin
Randomized trials provide limited information on patient
adherence to rifaximin. Two trials have reported mean
adherence rates to treatment between 84% and 92%.44,45
In comparison, a trial on lactulose reported that adherence
rates were 54%.55 In a retrospective study, patients received
rifaximin and lactulose for a time period of 6 months. The
study defined compliance as adherence with at least 75%
of medication. The results showed that 92% of patients in the
rifaximin group and 31% of patients in the lactulose group
were compliant.2

Various factors play a part in adherence to medication
in cirrhosis and HE. Fatigue and confusion and the lack of
social support are likely to have a negative influence on
compliance. Complex dosage regimens may also add to the
lack of adherence.56

Cost-benefit issues
At this point, no analyses on adherence to self-paid rifax-
im are available. For the individual patient, the price of
the drug has a substantial impact on adherence. Redeeming
prescriptions at the pharmacy depends on economic means.
The majority of third-party coverage in the US and other
large markets often means that patients pay a smaller out-
of-pocket copayment rather than the full cost. Although the
monthly savings are about US$100, the costs of rifaximin
remain higher than lactulose.20,57

Decreased hospitalization rates have been the subject
of analyses of cost-efficiency in cirrhosis. A retrospective
analysis of 39 patients found that the cost per person per year
was lower if patients were treated with rifaximin compared
with lactulose.49 In contrast, a decision analysis from 2007
found that rifaximin monotherapy was not cost-effective
based on the average wholesale prices. Instead, lactulose
monotherapy and “rifaximin-salvage therapy,” combining
rifaximin and lactulose in patients with no initial response
to lactulose, proved cost-efficient.52 Based on an estimated
patient adherence to rifaximin of 95%, a cost-effectiveness
analysis on the diagnosis and treatment of minimal HE
was performed. The analysis evaluated data regarding the
effect of HE on the prevention of motor vehicle accidents.
The results showed that rifaximin was not cost-effective
unless prices fell to US$353 per month from the current
US$1,259 per month.20,51

Although the costs of rifaximin are much higher than
lactulose or lactitol, there seems to be evidence supporting
the use of rifaximin to prevent new events of HE hospi-
talizations due to HE episodes or other complications to
cirrhosis. Rifaximin used as rescue therapy may lead to
savings on health care costs.53 However, the use of rifaxi-
min will in large terms move the economic burden from
the health care system to the individual patient. The result may
induce greater heterogeneity in outcomes such as mortality
and admission rates among patients with cirrhosis and HE.
Patients will be divided into those who can afford rifaxi-
min and those who cannot. It has been argued that since
Alfa Wassermann S.p.A (Bologna, Italy) holds a patent on
rifaximin that expires in 2024, prices are unlikely to decrease
before that date.58
Discussion

Summary of main results
The majority of trials and studies on rifaximin have assessed the effects on overt HE. Several trials evaluated shorter treatment regimens lasting only days. The trials have included: patients with acute or chronic recurrent overt HE, transjugular intrahepatic portosystemic shunt patients at risk of developing HE, minimal HE with no previous episodes of HE, as well as HE prevention. Other studies include decision analyses of health care expenses. The trials and studies vary markedly in quality and design. Overall, in spite of these concerns, there seems to be evidence supporting the beneficial effects of rifaximin. Rifaximin may benefit patients with overt HE and be effective in the prevention of recurrent episodes of HE. Long-term treatment is not associated with an increased risk of adverse events. The risk of *Clostridium difficile* or other infections may not be increased. However, the evidence is not clear. During recent years, a number of analyses on hospitalization rates have suggested that rifaximin decreases both the number of hospitalizations and the duration of hospital stays. These results suggest that rifaximin may be competitive with lactulose from a socioeconomic perspective. However, the literature cannot address these questions in an exhaustible manner. Prospective and randomized trials with prolonged follow-up are still needed to clarify the beneficial effects of rifaximin in long-term maintenance treatment.

Overall completeness and applicability of evidence
The effects of long-term treatment with rifaximin are evaluated in a randomized trial that included an extension period of several months. Prospective follow-up of this trial assessed rifaximin treatment for up to 1,400 days. This trial combined with prospective cohort studies and retrospective studies has found reasonable adherence and a small risk of adverse events associated with long-term rifaximin. Unfortunately, there are no randomized trials on hospitalization rates, mortality, complications, and infection rates in long-term rifaximin treatment. Furthermore, the retrospective studies are based on an American population and may not be generalizable to the use and distribution of the drug in the rest of the world. No trials address patient acceptability and adherence in the assessment of main outcomes or the actual use of rifaximin in a clinical setting.

Rifaximin was approved by the US FDA for travelers’ diarrhea in 2004. In 2010, rifaximin was approved for HE. A large study on the use of rifaximin in the US found that 12% of patients with an episode of overt HE received rifaximin either as single treatment (4%) or in combination with lactulose (8%). In 2011, this number increased to 22% (13% and 9% respectively). The clinical use of rifaximin in other parts of the world is not clarified, and compliance to rifaximin as redeemed prescriptions and actual adherence to medication remains unanswered.

Quality of the evidence
Several limitations apply to this overview, mainly based on the quality of trials, studies, and outcomes. Randomized trials are generally of high quality, but the variation in clinical outcomes impedes assessment and interpretation. In all other questions regarding hospitalization, infections, long-term acceptability, and adherence to medication, we are left with prospective cohorts with or without a control group and retrospective studies that may bias our conclusions.

Agreements and disagreements with other studies or reviews
Clinical trials and retrospective analyses assessed in this review are the foundation of several reports conducted within the area of treatment and prevention of HE. However, only a few reviews have focused on patient adherence and maintenance therapy. A recent report on minimal HE and prophylactic treatment proposes treatment to prevent not only motor vehicle accidents and quality of life, but also new episodes of overt HE. Probiotics, disaccharides, and rifaximin are suggested in no prioritized order. Another review suggests disaccharides as first-line treatment in overt HE and minimal HE, and in the case of recurrent HE or no improvement, addition of branched-chain amino acids or rifaximin. Still, recommendations of long-term treatment are lacking.

Authors’ conclusion
Rifaximin has potential beneficial effects in both overt HE and to prevent recurrent episodes of HE. Additional evidence is needed to determine the effects of rifaximin in clinical practice. In particular, the evidence supporting the use of rifaximin for minimal HE is weak. Knowledge about long-term maintenance treatment is scarce. The current cost of the drug may very well influence both the duration of treatment and adherence to medication.

Implications for practice
Rifaximin should be considered after the second episode of overt HE as well as during episodes of overt HE for patients who do not respond to standard treatment. Whether the treatment is second- or third-line after disaccharides and branched-chain amino acids has not been established.
Likewise, additional evidence on the combination of these treatments is needed. The current literature does not clearly support rifaximin being given continuously on a lifelong basis; due to this and the extensive cost of the drug, discontinuation ought to be considered in relation to the patients’ health and risk of complications.

Implications for research
This review identifies unresolved areas. Most importantly, data on patient adherence to prescribed medicine is needed. Secondly, the safety of prolonged treatment must be mapped out to improve our understanding of the risks and benefits of maintenance treatment. Clinical trials on rifaximin are conducted, but randomized trials or prospective controlled trials with clinical outcome measures such as mortality, complication rates, patient compliance, and adverse events, in a prolonged treatment design, are warranted.

Author contributions
Nina Kimer performed the literature searches, extracted data, and wrote the draft for this review; Aleksander Krag and Lise L Gluud validated the data extraction and contributed to the revision of the review. All authors approved the final version.

Disclosure
Lise L Gluud and Aleksander Krag report no conflicts of interest in the work. Nina Kimer has received rifaximin tablets and placebo from Norgine Denmark A/S in relation to an ongoing trial.

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