LIVER

# A Randomized, Double-Blind, Controlled Trial Comparing Rifaximin Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy

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OBJECTIVES: **Hepatic encephalopathy (HE) is associated with poor prognosis in cirrhosis. Drugs used in the treatment of HE are primarily directed at the reduction of the blood ammonia levels. Rifaximin and lactulose have shown to be effective in HE. We evaluated the efficacy and safety of rifaximin plus lactulose vs. lactulose alone for treatment of overt HE.**

METHODS: **In this prospective double-blind randomized controlled trial, 120 patients with overt HE were randomized into two groups: (group A lactulose plus rifaximin 1,200 mg/day; *n*=63) and group B (lactulose (*n*=57) plus placebo). The primary end point was complete reversal of HE and the secondary end points were mortality and hospital stay.**

RESULTS: **A total of 120 patients (mean age 39.4±9.6 years; male/female ratio 89:31) were included in the study. 37 (30.8%) patients were in Child–Turcotte–Pugh (CTP) class B and 83 (69.2%) were in CTP class C. Mean CTP score was 9.7±2.8 and the MELD (model for end-stage liver disease) score was 24.6±4.2. At the time of admission, 22 patients (18.3%) had grade 2, 40 (33.3%) had grade 3, and 58 (48.3%) had grade 4 HE. Of the patients, 48 (76%) in group A compared with 29 (50.8%) in group B had complete reversal of HE (*P*<0.004). There was a significant decrease in mortality after treatment with lactulose plus rifaximin vs. lactulose and placebo (23.8% vs. 49.1%, *P*<0.05). There were significantly more deaths in group B because of sepsis (group A vs. group B: 7:17, *P*=0.01), whereas there were no differences because of gastrointestinal bleed (group A vs. group B: 4:4, *P*=nonsignificant (NS)) and hepatorenal syndrome (group A vs. group B: 4:7, *P*=NS). Patients in the lactulose plus rifaximin group had shorter hospital stay (5.8±3.4 vs. 8.2±4.6 days, *P*=0.001).**

CONCLUSION: **Combination of lactulose plus rifaximin is more effective than lactulose alone in the treatment of overt HE.**

*Am J Gastroenterol* 2013; 108:1458–1463; doi:10.1038/ajg.2013.219; published online 23 July 2013

## INTRODUCTION

Hepatic encephalopathy (HE) is a serious but potentially reversible disorder with a wide spectrum of neuropsychiatric abnormalities and motor disturbances that range from mild alteration of cognitive and motor function to coma and death (1). It is a challenging complication of advanced liver disease and is estimated to occur in 30 to 45% of patients with liver cirrhosis and in 10–50% of patients with transjugular intrahepatic portosystemic shunts (2). Bustamante *et al.* (3) reported the survival probability of 42% at 1 year of follow-up and 23% at 3 years in patients with cirrhosis with a first episode of acute HE. The primary treatment of HE is the identification and treatment of the precipitating factors. The majority of the drugs used in the treatment of HE are primarily directed at the reduction or elimination of the increased neurotoxic ammonia levels. Lactulose, a nonabsorbable disaccharide, remains the mainstay treatment for HE (4). Despite the widespread use of lactulose, evidence supporting its efficacy for the treatment of HE is limited. A systematic review of the literature found lactulose to be more effective than placebo in improving HE, but with no effect on mortality (5). However, when only the highest quality studies were included, no significant effect on improvement of HE was seen with lactulose therapy.

Rifaximin, a semisynthetic derivative of rifamycin, is minimally absorbed. It has broad-spectrum *in vitro* activity against

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**Received 13 January 2013; accepted 6 May 2013**

Gram-positive and Gram-negative aerobic and anaerobic enteric bacteria, and has a low risk of inducing bacterial resistance. No dosage adjustments are necessary in patients with liver dysfunction or renal insufficiency (6,7). With minimal systemic bioavailability, rifaximin may be more conducive to long-term use than other, more bioavailable antibiotics with detrimental side effects. It has been proven to prevent the episode of HE and decrease the risk of hospitalization (8). In randomized studies, rifaximin was more effective than nonabsorbable disaccharides and had efficacy that was equivalent to or greater than that of other antibiotics used in the treatment of acute HE (9–17). In their recent meta-analysis, Eltawil *et al.* (18) reported that rifaximin is as effective as other conventional oral agents for the treatment of HE with a better safety profile. There is a paucity of data on the evaluation of a combination of rifaximin plus lactulose in the treatment of HE. In this study, we evaluated the efficacy and safety of rifaximin plus lactulose vs. lactulose alone for treatment of overt HE.

## METHODS

This was a prospective double-blind randomized controlled trial done in a tertiary care center, and enrollment started from October 2010 to September 2012. Patients aged 18–80 years with liver cirrhosis and overt HE were enrolled in this study. Cirrhosis was diagnosed on clinical basis involving laboratory tests, endoscopic evidence, sonographic findings, and liver histology, if available. Patients with serum creatinine >1.5 mg/dl on admission, active alcohol intake <4 weeks before present episode, other metabolic encephalopathies, hepatocellular carcinoma, degenerative central nervous system disease or major psychiatric illness, and significant comorbidity were excluded from the study.

### Study design

The severity of HE was graded according to West Haven criteria (1). The primary therapeutic diction was the identification and treatment of the precipitating factors such as control of gastrointestinal bleeding, preventing benzodiazepine, sedatives, and specific diuretics overdosage and antibiotics treatment of infections such as spontaneous bacterial peritonitis or other septic conditions. Once the patient met the inclusion criteria, randomization was performed using tables of computer-generated random numbers. Patients were randomized immediately after taking brief clinical history and sending all relevant investigation at baseline and after taking into account all excluding criteria. Blinding was done with respect to rifaximin and not for lactulose as it causes diarrhea and the dose has to be adjusted accordingly. Patients, investigators, and study staff (nurse) were blinded to treatment assignments. Group A patients were treated with rifaximin, one 400 mg capsule three times a day, and lactulose, 30–60 ml/three times a day, so that patient passes two to three semisoft stools in a day. Group B patients were treated with lactulose 30–60 ml/three times a day so that patient passes two to three semisoft stools in a day and one placebo capsule (sugar) three times a day. Treatment was given through nasogastric tube under strict intensive care monitoring and continued till complete recovery of HE or a maximum of 10 days for HE. However, patients were followed till they get discharged from the hospital or died during hospital stay. Once the patients were cured of HE, then patients who were in group A or group B were continued on same medications, that is, combination of rifaximin and lactulose in group A and lactulose in group B. In case of treatment failure, patients in group B were given rifaximin and those in group A were given L-ornithine and L-aspartate. Treatment envelopes with randomization code were distributed to the treating nurse by the statistician who was aware of treatment and this was done to prevent mixing of rifaximin and placebo. Baseline laboratory assessments included complete blood count, liver function test, kidney function test, serum electrolyte, blood sugar, prothrombin time, international normalized ratio, arterial ammonia, viral markers (hepatitis B surface antigen and anti-hepatitis C virus), and abdominal ultrasound with Doppler. Ascitic fluid analysis was done for spontaneous bacterial peritonitis. Child–Turcotte–Pugh (CTP) and model for end-stage liver disease (MELD) scores were calculated using standard clinical and laboratory measures. Recovery of HE was assessed twice daily independently by two expert hepatologists (B.C.S. and S.S.).

The primary end point of the study was complete reversal of HE as per West Haven criteria. The secondary end points were mortality and hospital stay. Written informed consent was taken from first-degree relative of the patient. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethical committee.

### Statistical analysis

This was a time-bound study with an estimated 120 patients being enrolled as per the initial protocol (ClinicalTrials.gov. identifier: NCT 01218568). Data were expressed as mean±s.d. For a comparison of categorical variables, $\chi^2$ and Fisher's exact tests were used, and for continuous variables, Mann–Whitney test was used as appropriate. The probability level of $P<0.05$ was set for statistical significance. Statistical analysis was performed with SPSS software, version 19 (SPSS, Chicago, IL).

## RESULTS

A total of 172 patients with cirrhosis and HE were screened. Of these, 52 patients were excluded because of serum creatinine >1.5 mg/dl at admission ($n=24$), active alcohol intake <4 weeks before present episode ($n=12$), hepatocellular carcinoma ($n=3$), and significant comorbidities ($n=13$). Finally, 120 patients (mean age 39.4±9.6 years; male/female ratio 89:31) who met the inclusion criteria were included in the study. Of these, 63 patients received a combination of lactulose and rifaximin (group A) and 57 patients received lactulose plus placebo (group B) along with other standard treatments, which included antibiotics (ceftriaxone 2 g/day or according to sensitivity of culture report), electrolyte correction, and control of gastrointestinal bleed (**Figure 1**).

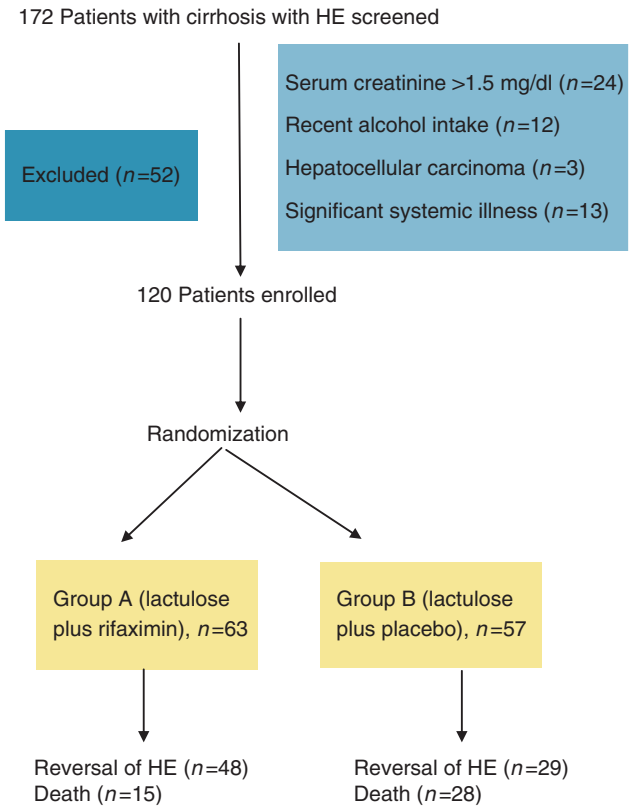


**Figure 1.** Consort flowchart for the study. HE, hepatic encephalopathy.

Etiology of liver cirrhosis was alcohol in 72 (60%), hepatitis B in 22 (18.3%), hepatitis C in 7 (5.8%), and other causes in 19 (15.9%) patients (autoimmune hepatitis in 2; primary biliary cirrhosis in 1; and cryptogenic cirrhosis in 16 patients). A total of 37 (30.8%) patients were in CTP class B and 83 (69.2%) were in CTP class C (**Table 1**). Mean CTP score was 9.7±2.8 and the MELD score was 24.6±4.2. Of the patients, 22 (18.3%) had grade 2, 40 (33.3%) had grade 3, and 58 (48.3%) had grade 4 HE at the time of admission (**Table 1**). Baseline hemogram, liver function test, renal function test, serum electrolyte, and arterial ammonia level were comparable in the two groups (**Table 2**). Of the 120 patients, 55 patients had episodes of HE in the past, with 30 in group A and 25 in group B. Median episodes in either group was 1 (range 0–2) with no significant difference in either group (**Table 1**). Previous episodes of HE were treated with lactulose and correction of precipitating factors if any. There was no case of refractory HE in patients who were enrolled in this study. Only 10 (16%) patients in group A and 8 (14%) patients in group B were on regular lactulose for secondary prophylaxis of HE before the present episode ($P$ = nonsignificant (NS)) and none of the patients were on rifaximin.

### Recovery of HE

In all, 48 (76%) patients in group A compared with 25 (44%) patients in group B had complete reversal of HE ($P = 0.004$) within 10 days. There was no significant difference in precipitating factor of HE in the two groups (**Table 3**). Patients in lactulose plus rifaximin group had shorter hospital stay as compared

**Table 1. Baseline characteristics of study patients**

| Parameter | Total ($n$=120) | Group A (rifaximin + lactulose), $n$=63 | Group B (lactulose + placebo), $n$=57 | $P$ value |
|---|---|---|---|---|
| Age (years) | 39.4±9.6 | 40.4±8.5 | 37.5±10.5 | NS |
| Male/female | 89:31 | 47:16 | 42:15 | NS |
| *Etiology* | | | | |
| Alcohol | 72 (60%) | 40 (63.4%) | 32 (56.1%) | NS |
| HBV | 22 (18.3%) | 10 (15.9%) | 12 (21.1%) | |
| HCV | 7 (5.9%) | 3 (4.8%) | 4 (7%) | |
| Other | 19 (15.8%) | 10 (15.9%) | 9 (15.8%) | |
| CTP B | 37 (30.8%) | 20 (24.1%) | 17 (29.8%) | NS |
| C | 83 (69.2%) | 43 (75.9%) | 40 (70.2%) | |
| CTP score | 9.7±2.6 | 9.9±2.8 | 9.4±2.5 | NS |
| MELD | 24.6±6.2 | 24.9±6.6 | 23.8±5.18 | NS |
| Baseline HE grade (1/2/3/4) | 0/22/40/58 | 0/10/20/33 | 0/12/20/25 | NS |
| H/o previous HE | 55 (45.8%) | 30 (47.6%) | 25 (43.9%) | NS |
| Median episode of HE | 1 (0–2) | 1 (0–2) | 1 (0–2) | NS |

CTP, Child–Turcotte–Pugh; HBV, hepatitis B virus; HCV, hepatitis C virus; HE, hepatic encephalopathy; H/o, history of; MELD, model for end-stage liver disease; NS, nonsignificant.

**Table 2. Baseline laboratory parameter of study patients**

| Parameters | Total (*n*=120) | Group A (*n*=63) | Group B (*n*=57) | *P* value |
|---|---|---|---|---|
| Hb (g%) | 8.2±2.2 | 8.1±1.9 | 8.4±2.6 | NS |
| Platelet (thousand/cmm) | 81,370±23,086 | 83,560±22,331 | 79,060±20,890 | NS |
| Bilirubin (m%) | 5.2±2.4 | 4.9±2.1 | 5.7±2.6 | NS |
| Albumin (g%) | 2.6±0.8 | 2.5±0.9 | 2.7±0.8 | NS |
| AST (IU/l) | 58.3±14.9 | 62.9±15.2 | 51.1±11.2 | NS |
| ALT (IU/l) | 65.2±16.4 | 68.1±17.9 | 59.4±13.2 | NS |
| ALP (U/l) | 109.2±38.7 | 101.2±36.4 | 118.4±39.2 | NS |
| INR | 2.8±1.5 | 2.7±1.4 | 2.9±1.8 | NS |
| Urea (g%) | 29.1±8.3 | 27.8±9.5 | 31.4±6.3 | NS |
| Creat (g%) | 0.8±0.4 | 0.9±0.5 | 0.7±0.4 | NS |
| Na (mEq/l) | 129.2±5.5 | 132.4±5.6 | 127.3±5.2 | NS |
| K (mEq/l) | 3.6±0.8 | 3.6±0.7 | 3.9±0.5 | NS |
| Art ammonia (μmol/l) | 122.8±25.4 | 132.6±29.8 | 115.7±22.7 | NS |

ALT, alanine transaminase; AST, aspartate transaminase; Creat, serum creatinine; Hb, hemoglobin; INR, international normalized ratio; K, potassium; Na, sodium; NS, nonsignificant.

**Table 3. Precipitating factors for hepatic encephalopathy**

| Precipitating factors | Group A (*n*=63) | Group B (*n*=57) | *P* value |
|---|---|---|---|
| SBP | 12 | 16 | NS |
| UTI with sepsis | 6 | 4 | NS |
| Pneumonia with sepsis | 2 | 3 | NS |
| GI bleed | 15 | 12 | NS |
| Constipation | 12 | 7 | NS |
| Electrolyte imbalance | 3 | 7 | NS |
| Unknown | 13 | 8 | NS |

GI bleed, gastrointestinal bleed; NS, nonsignificant; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection.

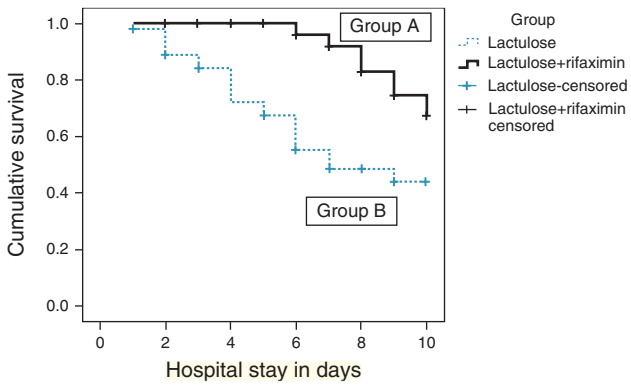


**Figure 2.** Kaplan–Meier survival for the two treatment groups assuming both groups were followed for 10 days.

with lactulose-alone group (5.8±3.4 vs. 8.2±4.6 days, $P=0.001$). There was a significant decrease in mortality in the lactulose plus rifaximin group (15 (24%)) vs. lactulose alone (28 (49.1%), $P<0.05$). There were significantly more deaths in group B because of sepsis (group A vs. group B: 7:17, $P=0.01$) whereas there were no differences because of gastrointestinal bleed (group A vs. group B: 4:4, $P=$NS) and hepatorenal syndrome (group A vs. group B: 4:7, $P=$NS). Assuming the two groups were followed for 10 days (**Figure 2**), we found that significantly more patients in group B died ($n=23$) as compared with group A ($n=13$; $P=0.03$).

### Predictors of nonresponse to therapy

Baseline characteristics of patients who did not respond to therapy were compared in the two groups. We found that patients who did not respond to lactulose and placebo therapy had higher baseline total leukocyte count as compared with patients who responded (7,534±3,659 vs. 5,858±2,206, $P=0.03$). Similarly, in the rifaximin and lactulose group, patients who did not respond had higher baseline HE grade as compared with patients who responded (**Table 4**). Taking overall patients in the two groups, we found on both univariate and multivariate analyses that baseline total leukocyte count ($P=0.024$) and treatment with lactulose + placebo ($P=0.0001$) were the only two independent predictors of nonresponse in patients with HE.

### Side effects related to drug therapy

There were no serious side effects related to lactulose and placebo or lactulose and rifaximin therapy. Diarrhea needing modification of lactulose therapy was required in eight patients

**Table 4. Predictors of nonresponse to therapy in the two groups**

| Parameters | Overall patients | | | Group A | | | Group B | | |
|---|---|---|---|---|---|---|---|---|---|
| | Response (*n*=73) | Nonresponse (*n*=47) | *P* value | Response (*n*=48) | Nonresponse (*n*=15) | *P* value | Response (*n*=25) | Nonresponse (*n*=32) | *P* value |
| Age | 38.8±9.8 | 42.3±9.7 | 0.06 | 39.2±10 | 44.4±10.2 | 0.08 | 38.0±9.6 | 41.4±9.7 | 0.2 |
| TLC | 6,058±3,827 | 7,742±3,723 | 0.01 | 6,163±4,199 | 8,186±3,949 | 0.10 | 5,858±2,206 | 7,534±3,659 | 0.03 |
| CTP | 10.9±1.9 | 10.7±2.0 | 0.68 | 10.8±1.9 | 11.0±2.1 | 0.75 | 11.1±1.8 | 10.6±2.1 | 0.37 |
| MELD | 22.1±3.8 | 22.0±3.9 | 0.86 | 22.5±3.1 | 21.1±2.9 | 0.19 | 21.4±3.4 | 22.4±4.3 | 0.35 |
| NH3 | 111.7±48.6 | 115.4±43.4 | 0.67 | 114.8±54.4 | 137.3±54.0 | 0.17 | 105.8±35.3 | 105.2±33.7 | 0.14 |
| Na | 136.4±6.1 | 137.6±4.7 | 0.25 | 136±6.1 | 138±4.5 | 0.18 | 137.1±6.2 | 137.4±4.8 | 0.81 |
| HE grade | 3.2±0.7 | 3.3±0.7 | 0.20 | 3.2±0.7 | 3.7±0.4 | 0.02 | 3.1±0.7 | 3.2±0.7 | 0.61 |

CTP, Child–Turcotte–Pugh; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; Na, sodium; NH3, ammonia; TLC, total leukocyte count.

in group A and in six patients in group B ($P$=NS). Abdominal pain was observed in four patients in each group ($P$=NS).

## DISCUSSION

This study shows that a combination of rifaximin plus lactulose was more effective than lactulose alone for improvement of HE and reduction in mortality. Traditionally, nonabsorbable disaccharides have been used as the first-line therapy for patients with HE, even if their effectiveness in comparison with placebo has not been proven (5). Rifaximin offers an attractive choice as the risk of bacterial resistance appears to be lower with rifaximin than with systemic antibiotics. Plasma levels of rifaximin are negligible; therefore, bacteria outside the gastrointestinal tract are not exposed to appreciable selective pressure.

This is the first double-blind randomized controlled trial comparing rifaximin plus lactulose vs. lactulose alone in the treatment of overt HE. Our study shows the superiority of rifaximin plus lactulose therapy over treatment with lactulose alone. We found that a combination of rifaximin with lactulose was more effective for treatment of overt HE (76% vs. 50.8%, $P$=0.007). Similarly, mortality after treatment with a combination of rifaximin plus lactulose was significantly lower as compared with lactulose alone (23.8% vs. 49.1%, $P$<0.05). Locally active antibiotics such as neomycin have long been proven to be effective in the treatment of HE. Conn *et al.* (19) and Atterbury *et al.* (20) in their studies showed that neomycin was equally effective as lactulose for treatment of acute nitrogenous portal systemic encephalopathy. Mas *et al.* (11) in their double-blind study comparing rifaximin and lactitol in the treatment of acute HE found that both were equally effective. Of the patients, 81.6% in the rifaximin group and 80.4% in the lactitol group showed improvement or total regression of episode. However, in this study, most of the patient had grade 1 and 2 HE and the study did not include patients with grade 4 HE. Bucci *et al.* (9) also showed equal efficacy of rifaximin and lactulose, with better tolerability and lack of side effects with rifaximin. Paik *et al.* (10) reported that both rifaximin and lactulose were effective in the majority of patients (84.4% and 95.4%, respectively) with significant improvement in blood NH3, flapping tremor, mental status, and psychometric test. In our study lactulose resulted in complete recovery of HE in 51% of patients as compared with 70–90% reported in previous published studies (10,11). This difference could be because of inclusion of higher number of patients with grade 3 and 4 HE in our study and also keeping complete recovery from HE as our primary end point and not improvement by grade 1 or 2 from baseline HE grade.

Bass *et al.* (8) have shown the efficacy of rifaximin in reducing the risk of HE. More than 90% of patients in their study received concomitant lactulose. Both rifaximin and lactulose have exclusive mechanisms of action. Lactulose lowers the colonic pH that favors formation of insoluble ammonium from soluble ammonia, resulting in reduced systemic absorption. In addition, lactulose causes a fourfold increase in fecal nitrogen excretion because of its cathartic effects. Small intestinal bacterial overgrowth in cirrhotic patients is common and is associated with systemic endotoxemia (21). Gupta *et al.* (22) found that the presence of small intestinal bacterial overgrowth was a significant predictor of development of minimal HE. In our earlier study we have found that small intestinal bacterial overgrowth is common in patients with low-grade encephalopathy (23).

Rifaximin contributes to restore gut microflora imbalance and is an important therapeutic agent in small intestinal bacterial overgrowth (24). These different mechanisms of action on gut flora and lowering blood ammonia can explain the synergistic action and better efficacy of a combination of rifaximin and lactulose in the treatment of HE as compared with lactulose alone. There was no significant adverse effect related to treatment with rifaximin. We found that baseline high total leukocyte count was a predictor of nonresponse in patients treated with lactulose and placebo but not with rifaximin and lactulose combination. This could partly be attributed to rifaximin as it decreases endotoxemia and thereby decreases inflammatory response. We found less mortality in the rifaximin and lactulose group mainly because of a decrease

in sepsis-related deaths (group A vs. group B: 7:17, $P=0.01$) that could be because of a decrease in gut-related endotoxin level in the blood. The strength of this study includes a large cohort of patients with overt HE with grades 3 and 4 that one comes across in clinical practice. The limitations were that we did not monitor the serial arterial ammonia level and serum endotoxin level during therapy. However, in routine practice, it is not monitored in the management of overt HE. Stool culture could have strengthened our study to see the effect of therapy on colonic bacteria. We conclude that a combination of rifaximin and lactulose is more effective than lactulose alone for treatment of overt HE in patients with cirrhosis.

### CONFLICT OF INTEREST

**Guarantor of the article:** Barjesh Chander Sharma, MD, DM.
**Specific author contributions:** study concept, data analysis, interpretation, and critical revision: Barjesh Chander Sharma and Praveen Sharma; data collection and editing of manuscript: Manish Kumar Lunia, Siddharth Srivastava, Rohit Goyal, and S.K. Sarin.
**Financial support:** None.
**Potential competing interests**: None.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ Lactulose is commonly used as a first-line therapy in the treatment of hepatic encephalopathy.
- ✓ Rifaximin has shown to be equally effective in the treatment of hepatic encephalopathy compared with lactulose.

### WHAT IS NEW HERE

- ✓ A combination therapy of lactulose and rifaximin is more effective in the treatment of hepatic encephalopathy.
- ✓ A combination therapy of rifaximin and lactulose decreases hospital mortality mainly by decreasing sepsis-related death.
- ✓ A combination therapy of lactulose and rifaximin also decreases hospital stay as compared with lactulose alone.
- ✓ A combination therapy of lactulose and rifaximin should be the standard of care for the treatment of hepatic encephalopathy.

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