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Treatment of Patients with Hepatic Encephalopathy: Review of the Latest Data from EASL 2011

A Review of Selected Presentations from
the 46th Annual Meeting of the European Association
for the Study of the Liver
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With a commentary by

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists, hepatologists, nurse practitioners, and physician assistants involved in the care of patients with hepatic encephalopathy (HE).

Statement of Need/Program Overview: The management of patients with HE is a considerable therapeutic challenge for clinicians. Advances in diagnosis, evaluation, treatment, predictors of response, overall management, and emerging data regarding current and novel therapies for HE continue to evolve. Physicians need to be aware of all these variables that can influence treatment choices and outcomes.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Outline challenges in the detection and treatment of various stages of HE.
2. Describe the significance of using rifaximin to reduce the risk of HE-related hospitalizations and breakthrough HE.
3. Implement strategies for the proper diagnosis of patients with liver disease and potential complications.
4. Describe quality of life, pharmacokinetic, and ammonia reduction data in patients with HE.

Faculty: **Nathan Bass, MD, PhD,** is Professor of Medicine in the Division of Gastroenterology at the University of California, San Francisco, in San Francisco, California.

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Introduction

Hepatic encephalopathy (HE) is a potentially serious disturbance in central nervous system function that can result from hepatic insufficiency.[1] Depending on its cause, HE can be categorized as either type A, which occurs in patients with acute liver failure; type B, which occurs in patients with bypass shunts; or type C, which occurs in patients with chronic liver disease.[2]

HE results from a complex process that involves overproduction and impaired metabolism of multiple neurotoxins. In general, HE occurs when decreased hepatic function and/or portal-systemic shunts allow nitrogenous substances from the gut to enter the systemic circulation. When these substances enter brain tissue, they can impair normal neurotransmission, causing changes in consciousness and behavior. As a result, HE can cause a wide range of neuropsychiatric symptoms, including confusion, disorientation, poor coordination, bizarre behavior, and coma.

Pathogenesis and Clinical Consequences of HE

Ammonia is thought to be a central player in the development of HE, as researchers have long recognized that ammonia levels are increased in patients with acute and chronic liver disease.[3] Ammonia is derived from both intestinal flora and alternative sources such as enterocytes in the small bowel and colon, which can produce a significant amount of ammonia when they metabolize glutamine.[4]

The exact mechanisms underlying ammonia-induced neurologic dysfunction have not been completely elucidated, but cerebral edema appears to be involved in this process. Glutamine (derived from glutamate and ammonia) is produced within astrocytes in the brain. This glutamine attracts water and causes swelling of astrocytes.[2] Ammonia can also directly cause oxidative and nitrosative stress in astrocytes, and it may activate various cellular signaling pathways, leading to upregulated cytokine production, inflammatory responses, and impaired intracellular signaling.[5] In addition to ammonia, other toxins implicated in the development of HE include neurosteroids, benzodiazepine-like molecules, the bacterial byproducts indole and oxindole, mercaptans, short-chain fatty acids, false neurotransmitters, manganese, and gamma-aminobutyric acid.

Clinical manifestations of HE can vary from mild neuropsychological abnormalities to acute confusion and/or coma. The most frequent disturbances associated with HE are mild cognitive abnormalities that can only be detected with psychometric or neurophysiologic testing.[1] Because of the wide range of neuropsychiatric symptoms in HE, clinical trials of this condition are hampered by the challenge of assessing patients' symptoms. For example, episodes of altered consciousness can occur spontaneously and are influenced by other factors, including infection, hypoxemia, gastrointestinal hemorrhage, and electrolyte disturbances.[1] In fact, the majority of HE episodes are precipitated by an event such as an infection.[6] Clinicians should therefore be alert to several precipitating factors, including infection, gastrointestinal bleeding, dehydration, constipation, electrolyte imbalances, and sedative use.[2,6-9] If detected, these conditions should be treated promptly.

Treatment Strategies

The treatment of HE is focused on several strategies that address both the proposed mechanisms of the disease and precipitating factors. One recent review stated that treatment strategies should focus on management of precipitating factors, reduction of ammonia and other toxins, modulation of fecal flora, modulation of neurotransmission, correction of nutritional deficiencies, and reduction of inflammation.[2]

Given the role of ammonia in the pathogenesis of HE, treatment strategies have long focused on reducing the production and absorption of ammonia. The standard approach for reducing ammonia levels in type C HE has been to administer nonabsorbable disaccharides such as lactulose or lactitol. A 2004 meta-analysis of 22 trials found that nonabsorbable disaccharides provided no significant survival benefit and were less effective than antibiotics for improving HE, but more recent studies have suggested that nonabsorbable disaccharides may indeed have a benefit for preventing HE recurrences.[10-12] Nonabsorbable disaccharides are thought to reduce ammonia levels through several mechanisms. They acidify and speed the passage of the fecal stream through the colon and promote the growth of beneficial intestinal bacteria. Acidification causes ammonia molecules to be protonated into charged ammonium ions that are poorly absorbed across colonocytes.

Ammonia levels can also be reduced via the use of systemic ammonia scavengers, such as intravenous sodium benzoate and sodium phenylacetate, or the phenylacetate prodrug oral sodium phenylbutyrate.[2] These compounds combine with glycine or glutamine to form water-soluble compounds that are excreted through the kidneys. However, there are limitations to these agents: They are not approved by the US Food and Drug Administration (FDA) for this use; they depend on adequate renal function for ammonia excretion; and the large therapeutic doses that are required can lead to a significant sodium load, which can contribute to fluid retention and poor palatability. Newer approaches for reducing ammonia are therefore being evaluated, including novel ammonia scavengers and orally ingested activated charcoal.

Prebiotics and probiotics have also been studied for the treatment of HE. Prebiotics promote the growth of potentially beneficial bacterial strains, thus reducing the resources available for potentially harmful bacterial strains.[13] Probiotics, particularly *Lactobacilli* and *Bifidobacteria*, may also provide benefit in HE, primarily in patients with minimal disease.[14] One approach that has demonstrated efficacy in a randomized, placebo-controlled study is administration of both a prebiotic and a probiotic to produce an effective synbiotic.[13]

Antibiotics have also been used to treat HE. The presumed mechanism of action for antibiotics in HE is modulation of bacterial flora, but this mechanism has not been clearly elucidated. Other possibly beneficial effects of antibiotics in HE include reducing small intestinal bacterial overgrowth, reducing ammonia levels, and reducing inflammation. One antibiotic that has recently demonstrated a significant benefit in a randomized, placebo-controlled trial is rifaximin, a compound related to rifamycin. In patients with HE who were already receiving lactulose, rifaximin was found to significantly reduce the risk of HE recurrences and HE-related hospitalizations over a 6-month period.[15] Based in part on this data, rifaximin recently received an FDA indication for reducing the risk of overt HE (OHE) recurrences.

Finally, another treatment strategy for HE involves correcting nutritional deficiencies. This process can involve supplementation of individual nutritional components or a more general approach.[16] For example, L-ornithine L-aspartate (LOLA), which is used outside the United States as a treatment for HE, replenishes substrates for the urea cycle and glutamine synthesis. Other strategies involve correction of amino acid ratios, which can be altered in patients with cirrhosis, and special diets such as a restricted- or vegetable-protein diet. Finally, given the link among infection, inflammation, and HE, some clinicians have suggested that anti-inflammatory treatments may have a role in the treatment of HE.[17]

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Highlights from the 2011 EASL Meeting

Clinical Consequences of Hepatic Encephalopathy

Minimal Hepatic Encephalopathy: Predictive Factor of Falls in Patients with Cirrhosis. Prospective Study

E Román, G Soriano, J Córdoba, M Torrens, C Villanueva, X Torras, V Vargas, C Guarner

Minimal hepatic encephalopathy (MHE) is the least severe—and most common—manifestation of HE. Although neurologic examination of individuals with MHE will reveal normal findings, psychometric or neurophysiologic testing can reveal cognitive abnormalities that may affect attention, vigilance, and executive function.[1-3] MHE is predictive of OHE and poor prognosis and is associated with an increased risk of traffic accidents and poorer quality of life.[4,5] In addition, a retrospective analysis showed that MHE is associated with an increased risk of falls among patients with cirrhosis.[6] Falls are associated with adverse clinical, social, and economic consequences; they increase the risk of fracture, increase morbidity and mortality, and negatively affect quality of life.[7,8]

In the current study, Román and colleagues prospectively evaluated the association between MHE and falls in patients with cirrhosis. This study enrolled patients with cirrhosis who did not have acute or chronic OHE and who had not been hospitalized in the past month due to decompensation. Patients were excluded if they had hepatocellular carcinoma, neurologic disease, or cognitive impairment; if they could not perform psychometric tests or were actively consuming alcohol; or if they had severe comorbidities. MHE was diagnosed using the psychometric hepatic encephalopathy score (PHES). Investigators contacted patients and their relatives every 3 months to assess the incidence of falls, severity of falls, need for healthcare due to falls, incidence of OHE, and mortality. Patients were followed for a total of 1 year.

The study enrolled 130 patients, but 8 patients were excluded from the analysis because their follow-up duration was shorter than 1 month. Among the 122 evaluable patients, 42 patients (34%) met the definition for MHE. The mean follow-up time was significantly shorter among patients with MHE compared to those without MHE (9.2 months vs 10.6 months; P=.01). Multiple patient characteristics were also significantly different between patients with MHE and those without MHE: Patients with MHE were more likely to be older and/or female, to have received a transjugular intrahepatic portosystemic shunt (TIPS), and to have lower hemoglobin and/or serum sodium levels (Table 1). Patients with MHE were also more likely to have had previous encephalopathy and/or previous falls and were more likely to be using antidepressants or lactitol/lactulose.

Overall, 16% of patients experienced a fall during the 1-year follow-up period. The incidence of falls was significantly higher among patients with MHE compared to those without MHE (35.7% vs 6.2%; P<.001; Figure 1). The mean number of falls per patient was 0.7 versus 0.08, respectively (P=.009). Among patients who experienced falls, there was no significant difference in the severity of fall-related injuries. Patients with MHE were more likely than those without MHE to require healthcare due to falls (16.7% vs 2.5%, respectively; P=.006) and to require hospitalization due to falls (7.1% vs 0%, respectively; P=.03).

An analysis of patient characteristics according to the incidence of falls revealed several factors that were significantly predictive of falls in a univariate analysis. These factors included female gender, presence of ascites, history of previous falls, antidepressant use, and MHE. In a multivariate analysis, only MHE remained significantly predictive of falls, with an odds ratio of 8.3 (95% confidence interval [CI], 2.7–25.1; P<.001). The probability of experiencing a fall over a 1-year period was 46.6% among patients with MHE and 6.7% among patients without MHE (P<.001). The investigators also observed a significant association among use of psychoactive drugs, falls, and MHE. Of the 21 patients who were taking psychoactive drugs, the incidence of falls was 62.5% among patients with MHE compared to 0% among patients without MHE (P=.003). Among the 101 patients who were not taking psychoactive drugs, the incidence of falls was 29.4% among those with MHE and 7.4% among those without MHE (P=.003). During the 1-year follow-up period, patients with MHE were also significantly more likely than those without MHE to develop acute encephalopathy (33.3% vs 8.7%, respectively; P=.001) or to die (19% vs 3.7%, respec-

Table 1. Characteristics of Cirrhotic Patients with Minimal Hepatic Encephalopathy (MHE) Versus Those without MHE

Characteristic	MHE (n=42)	No MHE (n=80)	*P*-value
Mean age	66.7 years	61.8 years	.003
Sex Male Female	 43% 57%	 75% 25%	<.001
Mean body mass index	25.2 kg/m^2	26.4 kg/m^2	.23
Mean Child-Pugh score	6.6	6.2	.12
Mean MELD score	11.5 points	11.3 points	.78
Etiology Alcohol Virus Alcohol and virus	 42.8% 42.8% 14.2%	 62.5% 27.5% 10%	.07
TIPS	14.2%	2.5%	.02
Previous encephalopathy	40.4%	17.5%	.006
Previous falls	40.4%	11.2%	<.001
Mean hemoglobin level	121.2 g/dL	133.5 g/dL	.001
Mean serum sodium level	137.3 mmol/L	139 mmol/L	.02
Antidepressant use	19%	3.7%	.008
Sedative use	11.9%	16.2%	.52
Diuretic use	76%	66.2%	.25
Beta blocker use	38%	47.5%	.32
Lactitol/lactulose use	45.2%	17.5%	<.001
Mean arterial pressure	91.1 mmHg	91.1 mmHg	.98

MELD=Model for End-Stage Liver Disease; TIPS=transjugular intrahepatic portosystemic shunt.

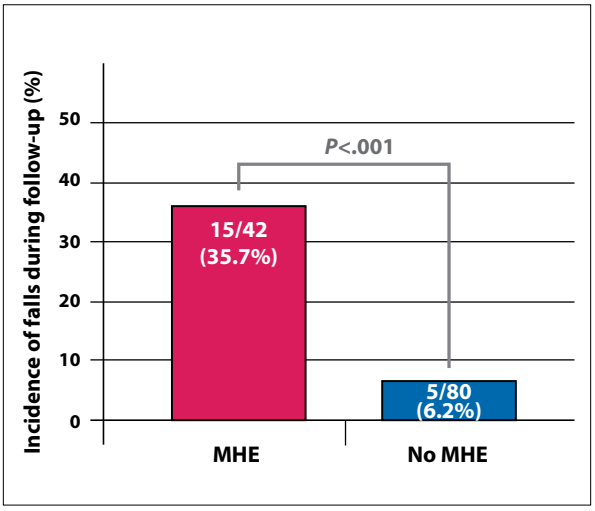

Figure 1. Incidence of falls in patients with minimal hepatic encephalopathy (MHE) and those without MHE.

tively; *P*=.008). Overall, this study confirmed that MHE is significantly associated with an increased risk of falls, OHE, and mortality.

Synergistic Roles of Hepatic Encephalopathy and Obstructive Sleep Apnea in Disturbance of Sleep Architecture in Patients with Cirrhosis

M Kappus, L Moses, DM Heuman, JS Bajaj

Sleep disturbances can severely compromise quality of life in patients with cirrhosis. The effects of HE on sleep are not completely understood, however, particularly in the setting of obstructive sleep apnea (OSA), which is becoming increasingly prevalent given rising obesity rates. In the current study, Kappus and colleagues investigated the association among HE, OSA, and sleep disturbances in patients with cirrhosis. The investigators

conducted a retrospective review of 46 patients with cirrhosis and sleep-related complaints who had undergone polysomnography between 2007 and 2010 at a single institution.

The evaluable population included 46 patients with cirrhosis; 93% of patients were male; patients' mean age was 58 years; and the median Model for End-Stage Liver Disease (MELD) score was 8 points. The primary causes of cirrhosis were hepatitis C virus infection (50%) and alcohol use (19%); other causes included nonalcoholic steatohepatitis (NASH) and cryptogenic cirrhosis. The mean body mass index (BMI) of enrolled patients was 34.4 kg/m^2. Concomitant conditions included hypertension (93%) and diabetes (43%). All patients had been referred for a sleep study because of subjective sleeping difficulties, including snoring (41%) and daytime sleepiness (32%). OSA was present in 89% of patients, and controlled HE (defined as the use of lactulose and/or rifaximin) was present in 21% of patients. All patients with HE also had OSA. No differences were noted between patients with HE and those without HE in terms of BMI, diabetes, or hypertension.

A review of the sleep study results found severe sleep disruptions in the majority of patients. Most of the time when patients were asleep, they were in early-stage sleep (N1/N2), with little time spent in deeper sleep (N3/N4); specifically, 11% of the time asleep was spent in N1, 57% in N2, 3% in N3, and 0.4% in N4. In 67% of patients, no N3/N4 sleep was observed. Rapid eye movement (REM) sleep accounted for 11% of the time spent asleep. The median sleep efficiency was 77%, with 29 hypopneas, 5 apneas, 67 arousals, and 23 periodic limb movements.

MELD scores were significantly correlated with the incidence of periodic limb movements (P=.04) and the proportion of time spent in N1 sleep (P=.037). The investigators also found a significant association between controlled HE and sleep disturbances: The proportion of time spent in early-stage sleep was significantly higher among patients with OSA and HE than among those with OSA alone (77% vs 65%, respectively; P=.007). Moreover, patients with HE and OSA were significantly more likely to have no detectable N3/N4 sleep compared to patients with OSA alone (100% vs 29%, respectively; P=.021). The investigators concluded that the presence of HE was associated with significantly greater sleep impairments among patients with cirrhosis and OSA compared to patients with OSA alone. These disturbances manifested as disruptions in deep sleep and a shift toward earlier stages of sleep.

Psychometric, Wake- and Sleep-EEG Features of Patients with Cirrhosis and Induced Hyperammonaemia

ID Raduazzo, A Bersagliere, S Schiff, A Gatta, P Amodio, P Achermann, S Montagnese

In another study that examined the effects of HE on sleep, Raduazzo and colleagues investigated the associations among elevated ammonia levels, HE, and sleep disturbances in patients with cirrhosis. In this study, researchers induced hyperammonaemia using an amino acid challenge, in which an amino acid mixture with a composition comparable to blood was orally administered to mimic the episodic HE that occurs after gastrointestinal bleeding. This amino acid challenge provides a reproducible model of episodic, type C HE as assessed by reaction time and electroencephalographic (EEG) measurements.[9]

Raduazzo and colleagues compared clinical, psychometric, and EEG parameters before and after hyperammonaemia induction in 10 cirrhotic patients without OHE (mean age=54 years) and 10 matched, healthy volunteers (mean age=49 years). Causes of cirrhosis included viral hepatitis (6 patients), alcohol (3 patients), and alcohol plus viral hepatitis (1 patient). On Day 1 of the study, participants submitted questionnaires, sleep diaries, and actigraphs. On Days 4 and 8, participants underwent amino acid challenge, neuropsychiatric assessments, and polysomnography.

At baseline, no psychometric or wake EEG abnormalities were noted, although patients with cirrhosis had significantly slower EEGs compared to healthy volunteers (P<.05), as well as significantly worse psychometric performance in terms of PHES and Sternberg scores (P<.05). The amino acid challenge was associated with a significant increase in ammonia levels; this increase peaked at 4 hours in all participants. Ammonia levels remained elevated for a longer duration in patients with cirrhosis.

The amino acid challenge did not result in any significant changes in psychometric performance; however, worsening of the wake EEG was observed in 2 patients with cirrhosis (but not in healthy volunteers). In terms of sleep changes, induced hyperammonaemia caused opposite effects in healthy controls compared to patients with cirrhosis: In healthy controls, induced hyperammonaemia was associated with an increase in the sleep EEG delta and a decrease in the sleep EEG beta, indicating deeper sleep; in contrast, patients with cirrhosis showed a decrease in the sleep EEG delta and an increase in the sleep EEG beta,

indicating lighter, more disturbed sleep. Moreover, the amino acid challenge was associated with a nonsignificant increase in the length of non-REM sleep among healthy controls (from 30.4 minutes to 49.3 minutes; *P*=.08). Overall, the investigators concluded that hyperammonaemia may cause disturbances in sleep homeostasis among patients with cirrhosis.

Diagnosis of Hepatic Encephalopathy

Breath Ammonia Testing of Healthy Subjects and Patients with Cirrhosis

R Adrover, D Cocozzella, E Ridruejo, A Garcia, J Romé, A Adrover, M Zicavo, JJ Podestá

HE, even MHE, can have well documented adverse effects on quality of life. Although OHE is associated with neuropsychiatric abnormalities that are detectable using clinical tests, the abnormalities associated with MHE are only detectable using specific psychometric tests. However, accurate detection of MHE is important, as lactulose treatment has been shown to improve cognitive function and quality of life in patients with MHE.[10] Therefore, a rapid, accurate test for diagnosing MHE would be beneficial.

Given the association between ammonia levels and HE, researchers have considered using breath ammonia testing as a tool for diagnosing HE. If such testing proves accurate, measurement of breath ammonia levels could offer a rapid, low-cost, noninvasive method for diagnosing and classifying HE. To evaluate the feasibility of breath ammonia testing in this setting, Adrover and colleagues compared breath ammonia levels among 3 groups: healthy individuals, cirrhotic patients without OHE, and cirrhotic patients with OHE. Breath ammonia testing was performed after fasting and within 15 minutes of brushing teeth. Ammonia levels were expressed using a device with an electronic sensor that yielded results in millivolts; these results were then mathematically converted to parts per billion (ppb).

To be included in this study, healthy individuals could not have signs or symptoms of acute or chronic illness, a history of chronic illness, or a need for regular medication usage. Specific exclusion criteria included chronic nonhepatic illness such as cardiac or renal insufficiency, associated cardiovascular disease or pulmonary illness, diabetes, chronic obstructive pulmonary disease, celiac disease, and HE greater than grade 2.

The evaluable study population included 106 subjects: 55 patients with cirrhosis and 51 healthy controls. Mean age was significantly lower in healthy controls compared to patients with cirrhosis (44 years vs 58 years; *P*<.001), but there were no significant differences between the 2 groups in terms of gender (64% male vs 53% male, respectively), average body weight (74.5 kg vs 74.2 kg, respectively), or BMI (25.8 kg/m^2 vs 26.5 kg/m^2, respectively). Causes of cirrhosis included alcoholic liver disease (40%), chronic hepatitis C virus infection (31%), primary biliary cirrhosis (7%), cryptogenic cirrhosis (7%), autoimmune hepatitis (4%), hepatitis B virus infection (4%), NASH (4%), and Wilson disease (2%). Among patients with cirrhosis, OHE was present in 18 individuals (33%). Cirrhotic patients with OHE and those without OHE did not differ in terms of gender, mean age (59 years vs 58 years, respectively), or mean BMI (26 kg/m^2 vs 27 kg/m^2, respectively).

Among healthy controls, the mean breath ammonia level was 151.4 ppb; this value did not differ significantly based on gender or age. Mean breath ammonia levels were significantly higher in patients with cirrhosis compared to controls (169.9 ppb vs 151.4 ppb; *P*=.00001). In addition, mean breath ammonia levels were significantly higher in cirrhotic patients with grade 1–2 OHE compared to cirrhotic patients without OHE (184.1 ppb vs 162.9 ppb; *P*=.0011). To differentiate between healthy subjects and patients with cirrhosis, the investigators assessed the area under the receiver operating characteristic curve and identified a cutoff value of 165 ppb. Among patients with cirrhosis, a cutoff value of 175 ppb was found to differentiate between patients with OHE and those without OHE.

Subgroup analyses of the patients with cirrhosis found no differences in the frequency of OHE or breath ammonia levels according to disease severity as assessed by MELD scores (<15 points vs ≥15 points)—either overall or based on gender, age, or BMI. Among patients with cirrhosis, breath ammonia levels did not differ between the 27 patients with ascites and the 28 patients without ascites. When patients with cirrhosis were subdivided by Child-Pugh score (CPS; <8 points vs ≥8 points), a significant difference in the prevalence of OHE was observed (*P*=.026), but the difference in breath ammonia levels between these 2 groups was not significant. The investigators concluded that breath ammonia testing appears to be feasible and useful, but further studies are needed to validate this technique.

A Multidimensional Approach to the Diagnosis of Hepatic Encephalopathy: Focus on Heart Rate Variability

D Pavanello, AR Mani, A Biancardi, S Schiff, A Gatta, P Amodio, S Montagnese

Heart rate variability (HRV), which reflects the physiologic fluctuations of the heart cycle over time, has been shown to correlate with the presence and degree of HE in patients with cirrhosis.[11] Pavanello and colleagues therefore conducted studies to further investigate the association between HRV and HE and to assess whether HRV could be used as a tool for diagnosing HE.

A total of 72 patients with cirrhosis underwent HRV testing, EEG, and neuropsychiatric assessment (using both paper-based methods [PHES] and computerized methods [Sternberg]). Blood samples were collected to measure levels of interleukin (IL)-6, C-reactive protein (CRP), tumor necrosis factor (TNF)-□, ammonia, indole, oxindole, hemoglobin, and sodium. The investigators then correlated HRV with multiple measures of HE, including EEG and both psychometric and laboratory indices of HE.

Reductions in HRV, primarily those observed via nonlinear methods, were associated with poorer hepatic function and neuropsychiatric performance. Reductions in HRV correlated significantly with EEG slowing ($P<.05$) and impaired cognitive performance on the computerized test ($P<.05$). HRV reductions were also associated with anemia ($P<.05$), hyponatremia ($P<.05$), and markers of inflammation, including abnormally high levels of IL-6 ($P<.01$) and CRP ($P<.01$). The researchers concluded that HRV reductions correlate significantly with electrophysiologic and psychometric indices of HE in patients with cirrhosis.

Treatment of Hepatic Encephalopathy

Long Term Efficacy and Survival in Patients Treated with the Gut-Selective Antibiotic Rifaximin (550 mg BID) for the Maintenance of Remission from Overt Hepatic Encephalopathy

KD Mullen, F Poordad, L Rossaro, M Jamal, J Talwalkar, S Huang, K Merchant, E Bortey, WP Forbes

In 2010, Bass and colleagues published results of a randomized, double-blind, placebo-controlled trial in which they showed that rifaximin can significantly reduce the risk of an HE episode over a 6-month period in cirrhotic patients who were in remission from recurrent HE.[12] Compared with placebo, rifaximin (550 mg twice daily) reduced the risk of HE breakthrough by 58% ($P<.0001$) and reduced the risk of HE-related hospitalization by 50% ($P=.01$).

To further investigate the efficacy and safety of rifaximin for management of HE, an open-label maintenance trial of rifaximin (550 mg twice daily) was initiated. This latter study included 322 patients: 70 patients from the randomized controlled trial who continued rifaximin, 82 patients from the randomized controlled trial who crossed over from the placebo arm, and 170 new patients. Patients were followed for approximately 16 months.

Both trials enrolled patients with a history of HE associated with cirrhosis or portal hypertension. In the randomized controlled trial, patients were enrolled if they met either of the following criteria: a Conn score of 0 or 1; or a Conn score greater than or equal to 2 with at least 2 episodes of HE within 6 months of screening (at least 1 episode verifiable by a physician). In the open-label trial, patients were enrolled if they met either of the following criteria: a Conn score of 0–2; or a Conn score greater than or equal to 2 with at least 2 episodes of HE within 12 months of screening (at least 1 episode verifiable by a physician). Exclusion criteria included active spontaneous bacterial peritonitis, daily prophylactic antibiotic therapy, gastrointestinal hemorrhage requiring hospitalization and transfusion of at least 2 units of blood within 3 months of screening, renal insufficiency, anemia, significant hypovolemia, or severe electrolyte abnormalities.

In the randomized controlled trial, 299 patients were assigned 1:1 to receive 6 months of treatment with rifaximin (550 mg twice daily; 140 patients) or placebo (159 patients). In the open-label study, all patients received rifaximin (550 mg twice daily), and follow-up visits were scheduled every 3 months. Concomitant lactulose use was permitted in both studies. Patient characteristics were similar across treatment groups with regard to age, gender, race, and HE history (Table 2). In the current analysis, the investigators reported outcomes from both studies independently, as well as from the population of 392 patients who were assigned to rifaximin in any part of the 2 trials.

Across both studies, the mean duration of drug exposure among rifaximin-treated patients was 476 days, yielding a total of 510 person-exposure years. Overall, rifaximin was associated with a 58% reduction in the risk of an HE breakthrough event compared to placebo (hazard ratio, 0.42; 95% CI, 0.28–0.64; $P<.0001$; Figure 2). HE event rates—calculated as the number of events per person-exposure years of study drug—ranged from 0.24–0.40 in patients who received rifaximin to 1.6 in placebo-treated patients.

Table 2. Patient Characteristics in Rifaximin Hepatic Encephalopathy (HE) Studies

Characteristic	All rifaximin-treated patients (n=392)	Randomized controlled trial	
		Rifaximin (n=140)	Placebo (n=159)
Mean age	57 years	56 years	57 years
Gender	59% male	54% male	67% male
Race	90% white	84% white	87% white
Geographic distribution North America Russia	 84% 16%	 72% 28%	 74% 26%
Mean duration of remission prior to study entry	96 days	69 days	73 days
Number of HE episodes in past 6 months 1 or 2 >2	 71% 29%	 69% 31%	 70% 30%
Conn score 0 1 2	 64% 33% 3%	 66% 34% 0%	 67% 33% 0%
Mean MELD score	12.8 points	13.1 points	12.7 points
Lactulose use	89%	91%	91%

MELD=Model for End-Stage Liver Disease.

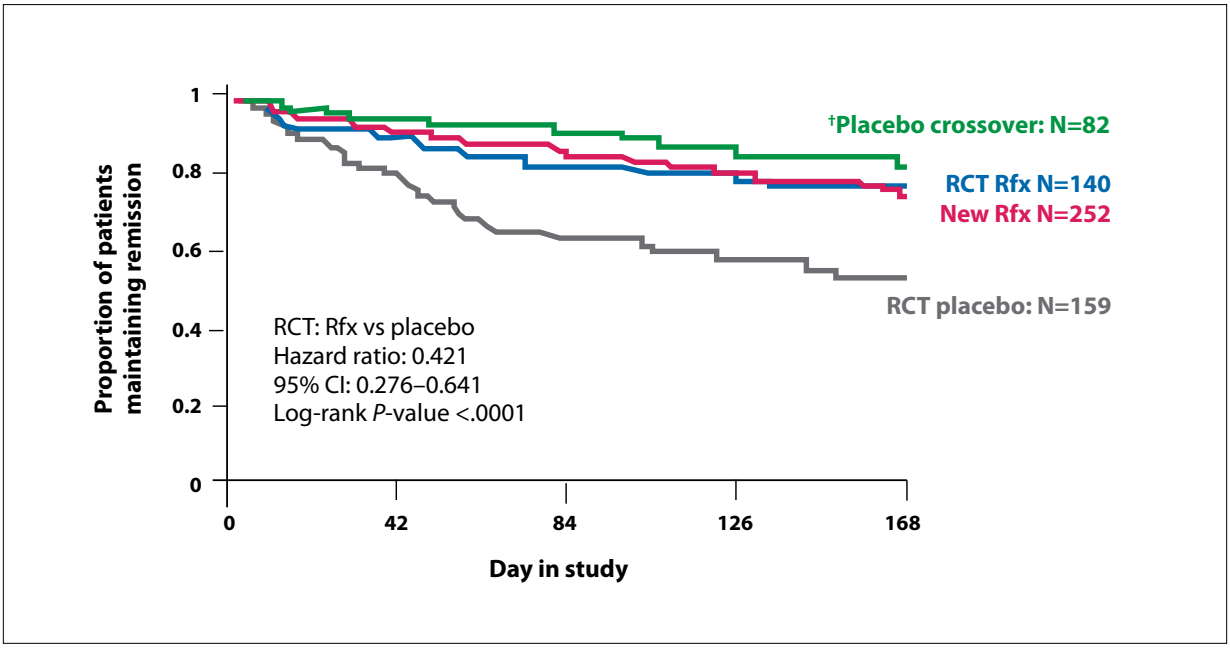

Figure 2. Treatment effect of Rfx: maintenance of remission from hepatic encephalopathy.

†Day 0 for these 82 patients coincides with randomization day into the open-label maintenance trial and first dose of Rfx. These patients were previously randomized to placebo in the RCT.

CI=confidence interval; RCT=randomized controlled trial; Rfx=rifaximin.

In the pooled analysis, rifaximin treatment was associated with a significant reduction in rates of hospitalization due to any cause (0.45 events per person-exposure years with rifaximin vs 1.31 with placebo; *P*<.0001) and rates of HE-related hospitalizations (0.21 vs 0.72, respectively; *P*<.0001). Rifaximin was also associated with a lower adverse event rate compared to placebo (0.71 vs 2.8, respectively), lower drug-related adverse event rate (0.11 vs 0.74, respectively), lower serious adverse event rate (0.48 vs 1.4, respectively), and lower rate of discontinuations due to adverse events (0.25 vs 0.98, respectively). Rifaximin was not associated with an increase in mortality rates. The investigators concluded that rifaximin provided long-term protection from HE breakthrough and reduced rates of hospitalization without adversely affecting patient survival.

Correlation of Platelet Count with Endotoxaemia in Cirrhotic Patients with Thrombocytopenia and Effects of Rifaximin

G Kalambokis, A Mouzaki, M Rodi, E Tsianos

Thrombocytopenia is a significant complication of cirrhosis. Studies in noncirrhotic individuals have shown that circulating endotoxins and proinflammatory cytokines can alter platelet homeostasis, causing thrombocytopenia. In patients with cirrhosis, high levels of circulating endotoxins and cytokines are associated with intestinal bacterial overgrowth and translocation. However, the association between thrombocytopenia and hypersplenism is not well understood. In the current study, Kalambokis and colleagues correlated endotoxin levels with platelet counts and spleen size. The investigators also assessed how rifaximin affects platelet counts in patients with cirrhosis and thrombocytopenia.

This study enrolled 25 cirrhotic patients with thrombocytopenia, defined as a platelet count of less than 150,000/µL. Blood samples were taken before and after a 4-week course of rifaximin treatment (1,200 mg/day; 15 patients) or no treatment (10 patients). To assess the relationship between endotoxin levels and thrombocytopenia, plasma endotoxin levels were measured in 10 additional cirrhotic patients without thrombocytopenia. To be enrolled in this study, patients had to have abstained from alcohol use for at least 6 months, and they could not have had an infection or variceal bleeding for at least 1 month prior to study entry.

At baseline, endotoxin levels were significantly higher among patients with thrombocytopenia compared to those without thrombocytopenia (2.76 EU/mL vs 0.64 EU/mL; *P*<.001). In patients with thrombocytopenia, endotoxin levels were significantly correlated with platelet count (*P*=.003) and, to a lesser degree, with spleen size (*P*=.02). A 4-week course of rifaximin treatment was associated with a significant increase in mean platelet count (from 83,100/µL to 99,600/µL) as well as significant reductions in levels of endotoxin, TNF-□, IL-1 □, and IL-6 (Table 3). A significant correlation was observed between increases in platelet counts and reductions in endotoxin levels (*P*=.04). The investigators concluded that rifaximin treatment was associated with significant improvements in platelet counts among cirrhotic patients with thrombocytopenia, which may be due to a reduction in endotoxemia.

Table 3. Changes in Endotoxin and Cytokine Levels After Rifaximin Treatment in Cirrhotic Patients with Thrombocytopenia

Mediator	Mean level at baseline	Mean level after rifaximin treatment	*P*-value
Endotoxin	2.5 EU/mL	1.3 EU/mL	.005
TNF-□	5.8 pg/mL	3.6 pg/mL	.02
IL-1 □	4.4 pg/mL	3.1 pg/mL	.04
IL-6	21.1 pg/mL	12.8 pg/mL	.01

IL=interleukin; TNF=tumor necrosis factor.

Chronic Hepatic Encephalopathy (HE) in Patients with Severe Liver Cirrhosis: Efficacy of the Wheat and Milk Protein Free Diet in the Reduction of Clinical Episodes

F Balzola, C Sanna, A Ottobrelli, M Torrani, S Martini, D Leotta, A Marchet, A Veneziani, B Capellero, D Boggio, R Galletti, A Mollo, B Bianco, M Rizzetto

The bowel is recognized as a source of toxic and immunologic brain damage in other gut-brain diseases, and a "leaky gut" (hyperpermeability) is common in cirrhosis. Given these findings, low protein diets and bowel cleansing have been used as treatments for HE. Furthermore, a diet that is free of wheat or milk proteins has been shown to reduce blood concentrations of exogenous opioid peptides derived from these proteins, which are known to have a direct central morphine-like action.

Balzola and colleagues undertook a prospective study in which they evaluated the efficacy of a wheat or milk protein–free diet in a group of patients with untreatable chronic HE who were awaiting liver trans-

plantation. Of the 16 patients enrolled in this study, 11 were male; the patients' mean age was 54 years. Patients were prescribed a normoproteic diet that was free of wheat or milk proteins; they continued any HE medical treatments while on this diet.

After 4 weeks on this special diet, consistent clinical improvement was seen in 14 patients (87%). After 3 months, complete resolution of HE was maintained in these 14 patients, 1 patient continued to experience some lethargy, and HE persisted in 1 patient. Only 1 patient in this study required hospitalization due to HE; in a control group of 10 patients with HE who did not receive a special diet, the mean number of hospitalizations due to HE was 1–3 per month.

Although the investigators reported significant improvements in global cognitive status with the wheat and milk protein–free diet, this improvement was not associated with significant EEG changes. A rechallenge with wheat and milk led to an immediate HE event in 1 patient. Although these findings are preliminary, they suggest that a wheat and milk protein–free diet may be considered as an adjunctive treatment for HE. However, the investigators noted that longer controlled trials are needed to validate these findings.

Functional Core Modulation Following Treatment of Minimal Hepatic Encephalopathy with L-ornithine L-aspartate: A Potential Novel Mechanism of Action

MJ McPhail, R Leech, VP Grover, J Fitzpatrick, NS Dhanjal, BK Saxby, K Wesnes, HC Thomas, RJ Wise, SD Taylor-Robinson

McPhail and colleagues reported results from a single-arm study in which they evaluated the functional effects of a 4-week course of LOLA in patients with MHE. This study enrolled 21 patients with well compensated, mixed-etiology cirrhosis and previous MHE (as defined by PHES). Patients underwent clinical, laboratory, and psychometric evaluations at baseline and after 4 weeks of LOLA treatment.

Treatment with LOLA was not associated with any clinical or biochemical changes. However, LOLA treatment was associated with significant psychometric improvements from baseline, including significant mean differences in PHES scores (P=.008), Cognitive Drug Research scores (P=.003), speed of memory (P=.005), and quality of executive memory (P=.002).

LOLA is known to be associated with altered function in core metabolic and structural regions of the brain, including significant blood oxygenation level–dependent changes in the posterior cingulate and ventral-medial prefrontal cortex. In this study, these changes correlated with quality of episodic memory scores after LOLA therapy. The improved psychometric performance observed after LOLA treatment also correlated with increased activation of the visual cortex. However, no locoregional changes in brain volume were noted, which suggests that a mechanism other than improvement in low-grade cerebral edema may explain the psychometric improvements observed after LOLA treatment.

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Commentary

Nathan Bass, MD, PhD

MHE is an important emerging area of research and discovery in the field of hepatology, but this condition still poses a significant diagnostic challenge for the clinician. Currently, the diagnosis of MHE requires specialized psychometric or neurophysiologic testing; the need to establish a diagnosis of MHE has become increasingly indicated, however, given growing evidence regarding the negative impact of MHE on quality of life and risk of motor vehicle accidents. Patients with MHE are also at an increased risk for developing OHE and have higher rates of mortality.

The prospective study by Román and colleagues confirmed these latter risks in cirrhotic patients with MHE and identified a significant increase in the risk of falls in this population, with consequent utilization of healthcare and need for hospitalization. This study also found that patients with MHE were more likely to be older and/or female, to have undergone a prior TIPS procedure, and to suffer from anemia or hyponatremia. In addition, patients with MHE were more likely to be receiving HE treatment or antidepressant drugs. Importantly, the results of this study point to a strong association among MHE, antidepressant use, and risk of falls. This important new finding strongly suggests the need for caution when prescribing antidepressants in patients who have MHE or a history of HE. This finding also adds weight to the argument that we need to develop a readily applicable means to aid in the clinical diagnosis of MHE in patients with cirrhosis, as proper diagnosis of these patients is necessary in order to appropriately counsel patients and their families and to implement strategies to reduce the risk of falls.

Sleep disturbances are a common, problematic symptom in patients with HE. With the prevalence of obesity and obesity-related liver disease on the rise, the timely study by Kappus and colleagues probes the possible interaction between HE and OSA, which is commonly associated with obesity. Indeed, although this study was conducted in a relatively small group of patients with cirrhosis from a variety of causes—all of whom had subjective sleep disturbances and had undergone polysomnography—it revealed that 89% of these patients had OSA. This study also found that the presence of HE (in 21% of patients) significantly increased the severity of typical OSA-associated sleep disruption (shift from deeper to early-stage sleep and even loss of deep sleep), despite HE being controlled with treatment. This small but interesting and important study highlights another type of morbidity that affects patients with the combination of cirrhosis and obesity—morbidity that can profoundly impact cognition, functional capacity, and quality of life.

Complementing the findings of this study, the abstract presented by Raduazzo and colleagues suggests that hyperammonemia may be at least partly responsible for the shift to a lighter sleep pattern in patients with cirrhosis. They conducted sleep studies as well as EEGs and psychometric testing in 10 patients with cirrhosis but no HE and in 10 healthy, matched controls; testing was performed both at baseline and following the induction of hyperammonaemia by amino acid administration. Interestingly, hyperammonaemia in the HE-free cirrhotic patients had only a minor impact on EEGs while patients were awake and no effect on psychometric test performance. During sleep, however, these patients showed an EEG pattern of lighter, more disturbed sleep; this change was in complete contrast to the healthy volunteers, whose sleep EEG shifted to a pattern indicative of deeper sleep. Why induced hyperammonaemia affects the sleep patterns of patients with cirrhosis and healthy subjects so differently is unclear, but these results indicate an important role for ammonia in the production of the observed sleep disturbance seen in cirrhosis. These findings also illustrate the need for research into other factors that interact with hyperammonaemia to produce a selective susceptibility to sleep disturbance and possibly other clinical expressions of HE in cirrhotic patients.

HE remains a clinical diagnosis, but the clinician's skill is imperfect—to say the least—in terms of our ability to determine the presence and stage of subtle or mild HE, including MHE. In addition, it remains unclear whether laboratory testing will ever play a helpful role in the diagnosis and staging of HE. Blood ammonia has proven inadequate for this purpose; although blood ammonia levels are frequently elevated in patients with OHE, normal levels tend to be only partially reassuring regarding the absence of HE, and the clinical correlation between blood ammonia levels and HE severity is poor.

In their abstract, Adrover and colleagues describe a convenient, electrode-based technology for the measurement of breath ammonia levels and a pilot study in which they assessed its utility in the diagnosis of OHE. The significant aspects of this study were that breath ammonia levels differed significantly, and incrementally, between normal subjects and patients with cirrhosis, and again between cirrhotic patients without OHE and those with OHE. However, it was disappointing to note that the actual magnitude of the differences in breath ammonia levels between the categories tested were not impressive, and the levels were also not significantly different between the subgroup of cirrhotic patients with CPS less than 8 and those with scores equal to or greater than 8, despite a significantly higher prevalence of OHE among patients

with a CPS greater than or equal to 8. However, small numbers may have confounded the results in this study. As the authors suggest in their conclusion, more work is needed to assess and validate the utility of this promising test in the diagnosis and staging of HE.

Another approach to HE testing, which was reported by Pavanello and colleagues, took advantage of the observation that physiologic HRV is reduced in patients with HE, possibly reflecting the development of a degree of autonomic neuropathic dysfunction. These researchers found that HRV reduction correlated not only with other measures of HE (EEG slowing and impaired performance on computerized testing) in patients with cirrhosis but also with other factors known to be associated with a risk for HE, including biomarkers of inflammation (IL-6 and CRP), anemia, and hyponatremia. The value of this study lies both in its identification of new pathophysiologic associations in the mechanism of HE development and its discovery that HRV reduction could have potential value as part of a multicomponent physiologic testing protocol for HE—a concept that deserves further study.

Addressing the treatment of HE, Mullen and colleagues provided an interesting and important follow-up to the randomized controlled trial that first showed the clinical efficacy of rifaximin for preventing episodic OHE in cirrhotic patients who had a history of OHE and were already taking lactulose. The current abstract describes outcomes in a population of 392 patients who were taking rifaximin, either as part of the randomized trial or as part of the subsequent, long-term, open-label study that enrolled both new patients and patients from the rifaximin and placebo arms of the earlier randomized controlled trial. Using the placebo data from the randomized trial as a comparator, the key message of this study is that the pooled analysis of outcomes for the entire rifaximin-treated population showed reduced rates of both all-cause and HE-related hospitalization over approximately 16 months, which extends and confirms the data from the randomized controlled trial. In addition, the pooled analysis revealed novel observations: reductions in adverse event rate, serious adverse event rate, drug-related adverse event rate, and discontinuation rate due to adverse events for rifaximin versus placebo. Although this analysis is somewhat less than ideal—as it is based on a pooled analysis of data collected from both randomized and nonrandomized sources—it takes advantage of data from a large population of patients treated with rifaximin and strengthens earlier conclusions from the randomized controlled trial regarding this drug's efficacy, ability to reduce hospitalizations, and excellent safety profile in the management of HE.

There may be other advantages to the use of rifaximin related to this drug's impact on intestinal bacterial flora. Patients with cirrhosis develop thrombocytopenia, which is typically attributed to hypersplenism. However, other factors may also be involved in reducing platelet counts in these patients, including inflammatory cytokines and bacterial-derived endotoxin. Evidence for these mechanisms is provided in the study described by Kalambokis and collegues, in which levels of endotoxin and proinflammatory cytokines were reduced in 25 patients with cirrhosis who were treated with rifaximin for 4 weeks. In addition, this treatment was associated with a modest but significant rise in platelet counts. The implications of these findings go well beyond the demonstrated increase in platelet counts, and they raise interesting and important questions pertaining to both the mechanism of action of rifaximin in the treatment of HE—could the reduction in inflammatory signaling be a key element?—and the broader therapeutic potential of this drug in cirrhosis. The results of this small longitudinal study need to be confirmed through a placebo-controlled study.

Finally, 2 additional abstracts reported nutritional modification approaches, both of which also merit longer–term, controlled studies to properly evaluate their promise. Dietary protein reduction is one of the oldest treatment strategies for the management of HE, but it is no longer considered a viable option for 2 reasons: evidence for its lack of efficacy has been published; and depriving cirrhotic patients of protein may accelerate muscle wasting that can in turn create a greater susceptibility to chronic HE. Qualitative rather than quantitative alteration of dietary protein has met with more favor, including diets that emphasize vegetable protein sources and supplementation with branch-chain amino acids. Into this forum comes the report from Balzola and colleagues; preliminary results from their brief, uncontrolled study using a diet with a normal daily protein requirement but no wheat or milk proteins suggest a possible benefit of this dietary modification in patients with HE. The rationale for this approach is based on evidence for increased intestinal permeability ("leaky gut") in patients with cirrhosis, which could account for abnormal absorption of sedating, opioid-like peptides derived from wheat and milk proteins.

Exploiting a different nutritional strategy, McPhail and colleagues observed a benefit with LOLA, which was given over 4 weeks to 21 patients with MHE, and described neurophysiologic changes that may help to elucidate the basis for brain dysfunction in MHE. The therapeutic benefit of LOLA was evident on post-treatment psychometric testing, and accompanying alterations seen on functional magnetic resonance imaging suggested that the improvement in patient performance was not related to alterations in brain volume (and hence amelioration of low-grade cerebral edema) but rather through alteration in metabolic function in the posterior cingulate and ventral-medial prefrontal cortex.


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