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Advances in Hepatic Encephalopathy From EASL 2014

A Review of Selected Presentations From the 49th Annual Meeting of the European Association for the Study of the Liver

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With Expert Commentary by:

Steven L. Flamm, MD
Professor of Medicine and Surgery
Division of Gastroenterology and Hepatology
Chief of the Liver Transplantation Program
Northwestern University Feinberg School of Medicine
Chicago, Illinois

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Advances in Hepatic Encephalopathy From EASL 2014

O19 Prophylaxis of Hepatic Encephalopathy in Acute Variceal Bleed in Patients With Cirrhosis: An Open Label Randomized Controlled Trial of Lactulose Versus Rifaximin[1]

S Maharshi, BC Sharma, S Srivastava, A Jindal

Acute variceal bleeding (AVB) is a precipitating factor for hepatic encephalopathy (HE) that can be prevented with prophylactic measures. Although lactulose is known to be useful for prophylaxis of HE following AVB, data have been lacking on the role of rifaximin in this setting. To gain further insight, Dr Sudhir Maharshi and colleagues from the Govind Ballabh Pant Hospital in New Delhi, India, randomized 53 adult cirrhotic patients with AVB, but without HE, to either lactulose or rifaximin prophylaxis.[1] Patients received standard treatment with AVB (per the Baveno V guidelines[2]). The primary endpoint was development of HE within 5 days of randomization. Results were presented at the 49th Annual Meeting of the European Association for the Study of the Liver (EASL), which took place April 9 to 13, 2014 in London, United Kingdom.

Dr Maharshi and his team found no significant differences in the characteristics of AVB, arterial pressure, and time to endoscopy between the treatment groups. There was no significant difference in the rate of HE, which occurred in 5 of 27 patients receiving lactulose and 4 of 26 patients receiving rifaximin. The mortality rate was also similar between groups, with 3 deaths occurring in each. Dr Maharshi and colleagues concluded that lactulose and rifaximin are equally effective for prophylaxis of HE in patients with cirrhosis and AVB.

P440 Outcomes of Rifaximin Plus Lactulose Versus Lactulose Alone in Treatment of Overt Hepatic Encephalopathy[3]

ML Gill, T Niaz, H Aziz, S Khan

Rifaximin and lactulose are each used to reduce ammonia levels in HE. In a study reported at EASL 2014, Dr Muzzaffar L. Gill of the Maroof International Hospital in Islamabad, Pakistan, examined whether a combination of the 2 agents would improve outcome.[3]

The study enrolled 200 patients with HE (30% with grade 2, 35% with grade 3, and 35% with grade 4). Patients were equally divided into 2 treatment groups: 1 group received rifaximin at a dosage of 550 mg twice daily and lactulose at a dose of 30 to 60 mL 2 to 3 times daily, and the other group received lactulose at the same dosage plus placebo. The treatment period was 10 days. The primary endpoint of the study was resolution of HE. The secondary endpoints were hospital stay and mortality.

The rate of complete resolution of HE was 75% in the combination group vs 45% in the lactulose monotherapy group (P=.005). The mortality rate was also lower in the combination group compared with the lactulose monotherapy group (20% vs 40%; P<.05). The combination group spent less time in the hospital; the average hospital stay was 4±2 days for the combination group vs 7±3 days in the lactulose monotherapy group (P=.005). Given these results, Dr Gill and his team concluded that the combination of rifaximin plus lactulose is more effective than lactulose alone in the treatment of HE.

P452 Mortality Associated With Hepatic Encephalopathy in Patients With Severe Liver Disease[4]

CL Morgan, S Jenkins-Jones, A Radwan, P Conway, A Reynolds, CJ Currie

To better characterize mortality risk for patients with HE, a multicenter team from Cardiff, United Kingdom, evaluated Clinical Practice Research Datalink records of patients diagnosed with liver disease between 1998 and 2012. The findings were reported by Dr Christopher L. Morgan of Pharmatelligence in Cardiff, United Kingdom, during a poster session at EASL 2014.[4]

The study identified 17,030 patients with liver disease, among whom 551 had HE. The data were analyzed via 2 Cox proportional hazard models. The first model evaluated the entire liver disease cohort, with HE treated as a binary time-dependent variable in quarterly segments. In the second model, 389 HE patients (71%) were compared with matched controls without HE.

Mortality during the follow-up period was significantly higher among the HE patients (55%) compared with patients without HE (41%; 6693 of 16,479 evaluable patients; P<.001). The hazard ratio of HE modeled as a time-dependent variable was 1.43 (95% CI, 1.20-1.70; P<.001). In the second Cox proportional hazard model, among the 389 patients with HE, 226 (58%) died during the follow-up period compared with 126 controls (32%). The hazard ratio for time to death was 2.28 (95% CI, 1.82-2.87; P<.001). The findings revealed that HE substantially increased mortality risk in patients with chronic liver disease.

P500 Minimal Hepatic Encephalopathy Is Independently Associated With Poor Survival and Increased Rate of Hospitalization: A Prospective Study of 170 Patients[5]

K Patidar, L Thacker, M White, N Noble, RK Sterling, R Stravitz, A Sanyal, I Bouneva, M Siddiqui, V Luketic, M Fuchs, D Heuman, H Gilles, J Wade, JS Bajaj

Minimal HE was independently associated with an increased risk of hospitalization and death in a study presented by Dr Kavish Patidar of the Virginia Commonwealth University in Richmond, Virginia.[5] To define the impact of minimal HE on development of overt HE, hospitalization, and death in patients with liver cirrhosis, a standard cognitive battery was administered to 170 cirrhotic patients. Among these patients, 57% had minimal HE, 45% had hepatitis C virus, and 20% were alcoholics.

Patients were followed for a median of 55.5 months. During this time, 30% developed overt HE. Median time to development of overt HE after the initial patient visit was 8.5 months (range, 2.0-18.0 months). Among the patients who developed overt HE, 42% were hospitalized; the median time from development of overt HE to hospitalization was 10 months (range, 3.0-26.0 months). Thirteen percent of overt HE patients died, at a median of 21.5 months after they developed the condition (range, 10.0-34.0 months). The composite rate of death/transplant was 19%; these events occurred at a median of 25 months (range, 10.0-34.0 months) after the initial visit.

A Cox regression analysis showed a worse outcome for patients with minimal HE, even after controlling for the Model for End-Stage Liver Disease (MELD). Compared with patients without minimal HE at baseline, patients with minimal HE had twice the risk of developing overt HE (hazard ratio [HR], 2.1; 95% CI, 1.01-4.5) and being hospitalized (HR, 2.5; 95% CI, 1.4-4.5), 5 times the risk of dying (HR, 4.9; 95% CI, 1.03-23.8), and 3 times the risk of undergoing transplantation or dying during follow-up (HR, 3.4; 95% CI, 1.2-9.7). Dr Patidar concluded that these results demonstrate a strong need for strategies to identify and manage minimal HE.

P456 Systems Biology Analysis of Probiotic *Lactobacillus* GG in Cirrhotic Patients With Minimal Hepatic Encephalopathy: A Randomized Double-Blind, Placebo-Controlled Trial[6]

JS Bajaj, D Heuman, P Hylemon, A Sanyal, R Sterling, R Stravitz, P Puri, M Sikaroodi, LR Thacker, J Wade, PM Gillevet

To evaluate the safety and tolerability of probiotics approved under the US Food and Drug Administration Investigational New Drug policies for use in minimal HE, a multidepartmental team from the Virginia Commonwealth University in Richmond, Virginia, compared *Lactobacillus* GG with placebo in 30 patients with compensated cirrhosis and minimal HE. The effects of the probiotic on inflammation and endotoxemia, cognition, the microbiome, and the urine metabolome were evaluated. The study findings were reported at EASL 2014 by Dr Jasmohan S. Bajaj during a poster session.[6]

Patients were randomized to receive *Lactobacillus* GG (n=14) or placebo (n=16) twice daily. A standard probiotic-free diet and a multivitamin were prescribed. Patients were monitored throughout an 8-week period. Serum, urine, and stool samples were collected at baseline and at the end of the study. Tolerability, endotoxin and systemic inflammation, the quality of the microbiome, the serum and urine metabolome, and the biofluid bile acid profile were assessed before and after the study.

Endotoxemia and elements that encourage a reduction in tumor necrosis factor in the microbiome (a reduction in *Enterobacteriaceae* and an increase in *Lachnospiraceae* and *Clostridiales*) were seen in only those patients who were receiv-

Table 1. Change From Baseline in the Gut Microbiome in Patients With Minimal HE

	***Lactobacillus* GG (n=14)**		**Placebo (n=16)**		
	Baseline	**Week 8**	**Baseline**	**Week 8**	***P* Value**
Enterobacteriaceae[a] (%)	4.7	1.8	2.7	2.6	<.05
Lachnospiraceae[b] (%)	8.5	12.5	11.01	11.6	<.005
Clostridiales XIV[b] (%)	1.4	2.2	2.6	1.8	<.05

[a]Nonautochthonous.

[b]Autochthonous.

HE, hepatic encephalopathy.

Data from Bajaj JS et al. EASL abstract P456. *J Hepatol.* 2014;60(suppl 1):S221.[6]

Table 2. Minimal HE Concordance and Diagnosis Rates With the EncephalApp–Stroop Test

Site	OnTime+OffTime (±SD)	Cut-Off (seconds)	Cirrhotics Impaired (%) (κ compared with Virginia cutoffs)	
			Virginia (n=137)	Ohio (n=39)
Virginia	148±27	202	36	35
Ohio	151±29	209	31 (κ 0.80)	27 (κ 0.89)
Arkansas	151±30	211	28 (κ 0.78)	26 (κ 0.82)

HE, hepatic encephalopathy; SD, standard deviation.

Data from Allampati S et al. EASL abstract P458. *J Hepatol.* 2014;60(suppl 1):S221.[7]

ing the probiotic (Table 1). The level of aminomalonate also was reduced among these patients, and factors supporting ammonia-detoxification products were increased. Correlations between hippurate/asparagine/glutamate and *Enterobacteriaceae* were reduced, and correlation with anti-inflammatory interleukin-13 and *Enterobacteriaceae* was increased. The primary adverse event was diarrhea, which occurred more frequently but was self-limited in patients receiving the probiotic.

The findings led Dr Bajaj and colleagues to conclude that *Lactobacillus* GG is safe and well-tolerated. It was associated with a reduction in systemic inflammation and endotoxemia, and had a beneficial effect on the composition and function of the gut microbiome in patients with minimal HE.

P458 Validation of EncephalApp_Stroop for Minimal Hepatic Encephalopathy Screening: A Multi-Center US Study[7]

S Allampati, A Duarte-Rojo, L Thacker, M White, N Noble, A Unser, RS O'Shea, CR Flud, JS Klair, JS Bajaj

The EncephalApp–Stroop Test is a smartphone-based Stroop test that gauges mental impairment. Although it has been presented as a screening test for minimal HE, multicenter validation was lacking. At EASL 2014, Dr Sanath Allampati of the Cleveland Clinic in Cleveland, Ohio, reported results from a multicenter study that aimed to establish normative values for the test and determine sensitivity for the diagnosis of minimal HE.[7]

The Stroop test was first described more than 75 years ago as a way to measure mental speed and flexibility.[8] The EncephalApp–Stroop Test employs the same principles as the original test. In the first part (known as "OffTime"), the goal is to correctly identify the color of a series of pound marks. In the second part (known as "OnTime"), test takers must correctly identify the color of a word that signifies a different color (eg, the word *red* written in blue letters). The OffTime task measures psychomotor speed, and the more complex OnTime task measures psychomotor speed and cognitive flexibility. The lower the score, the better the performance.

The study enrolled 176 outpatients with cirrhosis from the Cleveland Clinic and participating sites in Virginia and 134 healthy, age-matched controls from centers in Virginia, Arkansas, and Ohio. All subjects took psychometric tests to determine their Psychometric Hepatic Encephalopathy Score (PHES), which is the gold-standard measurement for the quantification of minimal HE. All subjects also underwent testing with the EncephalApp–Stroop Test. Minimal HE was indicated by a standard deviation (SD) of 4 or more beyond controls on the PHES, and an SD of 2 beyond controls on the EncephalApp–Stroop Test OffTime+OnTime composite measurement.

Based on control plus a 2 SD OffTime+OnTime score, EncephalApp–Stroop Test cutoffs were 202 seconds for Virginia controls, 211 for Arkansas controls, and 209 for Ohio controls (206 seconds for all controls). A high concordance of an abnormal EncephalApp–Stroop Test among patients at these 3 sites was seen (Table 2). In comparison, the rate of specificity and sensitivity was 81% at a 183-second cutoff, with an area under the curve (AUC) of 0.90, for PHES. The findings suggest that the EncephalApp–Stroop Test has value as a screening test for minimal HE.

O169 Rifaximin Versus Lactulose in the Treatment of Minimal Hepatic Encephalopathy in Patients With Cirrhosis: A Prospective, Randomized, Active-Comparator, Non-Inferiority Trial[9]

O Goyal, SS Sidhu, RA Parker, J Prasad, H Kishore, A Sood, V Mehta, RS Chhin

Minimal HE has a significant impact on health-related quality of life (HRQOL) in patients with cirrhotic liver disease. A multicenter Indian and British team compared whether treatment with rifaximin or lactulose was associated with better neuropsychometric test performance and HRQOL in these patients. The findings of the team's prospective, randomized, single-blind, noninferiority trial were reported by Dr Omesh Goyal of the Dayanand Medical College and Hospital in Ludhiana, India, at EASL 2014.[9]

The study tested 351 patients with cirrhotic liver disease for minimal HE, which was defined as a derangement beyond 2 SDs of normal on 2 neuropsychologic tests. The diagnosis was made in 112 patients (32%), who were ran-

domized to receive 3 months of treatment with lactulose at dosages ranging from 30 mL/day to 120 mL/day (n=55) or rifaximin at a dosage of 1200 mg/day (n=57).

After 3 months of treatment, the rate of reversal of minimal HE was similar between the groups (67% for lactulose vs 65% for rifaximin). The adverse event profiles were also similar. HRQOL scores, assessed using the Sickness Impact Profile questionnaire,[10] significantly improved in both groups and showed noninferiority of rifaximin in comparison with lactulose. Rifaximin, however, was more cost-effective than lactulose.

P461 Utility of Bispectral Index Monitoring for Assessment of Presence and Severity of Overt and Minimal Hepatic Encephalopathy Before and After Treatment in Patients With Cirrhosis[11]

A Jindal, BC Sharma, S Sachdeva, R Chawla, S Srivastava, S Maharshi

The bispectral index appears to be a useful tool for diagnosing minimal HE and overt HE, grading HE, and monitoring improvement or decline of HE in patients with cirrhosis, according to a study from the Govind Ballabh Pant Hospital in New Delhi, India. The findings were reported by Dr Amit Jindal during a poster session at EASL 2014.[11]

To evaluate the utility of the bispectral index to diagnose minimal HE and overt HE, grade HE, and monitor improvement or decline in disease status, Dr Jindal and colleagues enrolled 200 patients with cirrhosis and various grades of minimal HE and overt HE (as assessed by psychometric tests and West Haven criteria, respectively). Thirty patients each had grade I, II, III, or IV overt HE, 60 had minimal HE, and 20 did not have overt HE or minimal HE. Monitoring with the bispectral index was performed at baseline in all study patients plus 20 healthy controls. Monitoring was then repeated after 1 week of lactulose therapy in patients with overt HE and 3 months of therapy in patients with minimal HE.

Table 3. Bispectral Index Values in HE Patients and Controls

Severity	Cut-Off	Value
Grade I	77.5	79.5±4.2
Grade II	70.5	67.5±4.3
Grade III	60.5	56.4±3.5
Grade IV	50.5	44.8±3.9
Minimal HE	90.5	85.0±4.3
No overt HE/minimal HE	NA	92.6±3.7
Controls	NA	93.75±2.8

HE, hepatic encephalopathy; NA, not applicable.

Data from Jindal A et al EASL abstract P461. *J Hepatol*. 2014;60(suppl 1):S223.[11]

The bispectral index values significantly differed depending on the type and grade of HE but were similar between patients with HE (overt or minimal) and controls (Table 3). Improvement or worsening of HE and minimal HE following treatment correlated with changes in the bispectral index values. The research team concluded that the bispectral index is useful for diagnosing, grading, and monitoring treatment of overt HE and minimal HE.

P513 A Simple Model for the Prediction of Overt Hepatic Encephalopathy in Cirrhotic Patients: Results of a Prospective Observational Study and Validation in an Independent Cohort[12]

C Pasquale, S Nardelli, I Pentassuglio, S Gioia, E Onori, N Piazza, P Amodio, M De Rui, S Schiff, A Farcomeni, M Merli, S Montagnese, O Riggio

Overt HE can be prevented with prophylaxis, thereby avoiding further complications and healthcare expenditures.[13] A multicenter Italian team of researchers sought to establish a method to identify which patients with cirrhosis are at greater risk of developing overt HE. Their study showed that a 2-variable model is adequate, although less accurate than a 3-variable model. The findings were reported by Dr Chiara Pasquale of the Policlinico Umberto I in Rome, Italy, during a poster session at EASL 2014.[12]

Dr Pasquale and colleagues reviewed variables related to overt HE development in 216 patients with cirrhosis throughout a follow-up of 14±11.6 months. A model was established and tested in an independent validation group of 112 patients with cirrhosis, with a follow-up of 12±9.5 months.

Factors in the multivariate analysis included the MELD score; placement of a transjugular intrahepatic portosystemic shunt or large portosystemic shunt; previous overt HE or minimal HE per PHES; and levels of albumin, bilirubin, creatinine, and sodium. The analysis revealed 3 significant risk factors for the development of overt HE: previous HE, positivity for minimal HE on PHES, and an albumin measurement of less than 3.5 g/dL (AUC, 0.76; specificity, 0.94). A second multivariate analysis that excluded positivity for minimal HE per PHES showed that albumin and previous HE were suggestive of risk (AUC, 0.73). The difference in AUCs was not statistically significant (P=.132), but the Net Reclassification Index was 0.3 (P=.04).

Both models were validated in the second patient group. The AUC equaled 0.77 (95% CI, 0.56-0.91) for 3 variables, and the AUC equaled 0.76 (95% CI, 0.58-0.94) for 2 variables. Although the 2-variable model was slightly less accurate than the 3-variable model, the specificity was high. The research team concluded that the applicability and simplicity of the 2-variable model might compensate for the small reduction in accuracy.

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Advances in Hepatic Encephalopathy From EASL 2014: Commentary

Steven L. Flamm, MD
Professor of Medicine and Surgery
Division of Gastroenterology and Hepatology
Chief of the Liver Transplantation Program
Northwestern University Feinberg School of Medicine
Chicago, Illinois

Hepatic encephalopathy (HE) continues to be an important worldwide problem, and presentations at the 49th Annual Meeting of the European Association for the Study of the Liver (EASL) were from all over the world. In the United States, overt HE is treated with lactulose, a nonabsorbable disaccharide.[1] Rifaximin is approved for the prevention of recurrence.[2] The current care strategy is to use lactulose and rifaximin in patients with overt encephalopathy and then maintain rifaximin to prevent recurrence. Randomized studies evaluating the combination of rifaximin and lactulose vs one or the other for treatment of acute HE are lacking.

Prevention of recurrence was addressed at EASL 2014 by Dr Muzzaffar L. Gill of the Maroof International Hospital in Islamabad, Pakistan.[3] In this study, the combination of lactulose and rifaximin therapy was better than lactulose alone, a finding that will require confirmation. Dr Sudhir Maharshi and colleagues from the Govind Ballabh Pant Hospital in New Delhi, India, presented results from an uncontrolled study of rifaximin vs lactulose for prophylaxis against HE in patients with variceal bleeding.[4] Rates of HE prevention were similar with both agents, but the question remains regarding the degree to which they were effective. More research is needed using a more precise study design.

One of the more active areas of research presented at EASL 2014 concerned minimal HE. This condition is not diagnosed with clinical symptoms, but it is associated with significant subtle problems. Patients with minimal HE have poorer work productivity, quality-of-life deficits, and higher rates of traffic violations and accidents than cirrhotic patients without minimal HE.[5,6] The condition therefore represents an important issue.

The diagnostic strategies for minimal HE have not been standardized. An innovator in the field, Dr Jasmohan S. Bajaj of the Virginia Commonwealth University in Richmond, was involved in several studies presented at EASL 2014. One study examined minimal HE and its association with hospitalization and death.[7] The study found that patients with minimal HE had more than twice the risk of hospitalization and death than patients without minimal HE.

Researchers are challenged with attempting to identify ways to efficiently diagnose minimal HE. Dr Bajaj and colleagues presented a study on the EncephalApp–Stroop Test, which can be administered in the office setting and is easy

to perform.[8] A particularly innovative aspect of this test is that it is a smartphone app that is freely available. The study found that the test is accurate in diagnosing minimal HE. In fact, the EncephalApp–Stroop Test compared favorably to the standard, more complicated method of diagnosis.

Dr Bajaj's group also assessed the therapeutic effect of the probiotic *Lactobacillus* GG on minimal HE.[9] Many researchers suspect that HE, whether overt or minimal, is initiated by toxins released by colonic bacteria that are absorbed into the bloodstream.[10] If the colonic bacterial milieu can be favorably altered, minimal HE may be prevented. In the study reported at EASL 2014, Dr Bajaj and colleagues assessed the effects of *Lactobacillus* on patients with minimal HE.[9] They found that exposure to *Lactobacillus* reduced the amount of endotoxin in the bloodstream and increased the level of beneficial colonic bacteria in patients with minimal HE.

Another interesting EASL 2014 presentation concerned health-related quality of life. This large, single-blind study of patients with minimal HE compared rifaximin and lactulose.[11] The majority of patients improved, and at similar rates regardless of treatment. In my opinion, rifaximin might be the better therapeutic choice because it is much better tolerated than lactulose, which is a sweet syrup that causes diarrhea, nausea, cramping, and gassiness. Rifaximin, in contrast, has minimal side effects.

Conclusion

HE is a major health challenge in patients with chronic liver disease. We are making strides to understand it better. Diagnostic and treatment strategies for minimal HE, in particular, represent an exciting area of research. Further advances are expected to be announced at upcoming liver meetings.

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