Hepatic Encephalopathy Update: Reports from the 2013 International Liver Conference

HEPATOLOGY Center of Educational Expertise

Project ID: 13-0001-NL-1

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The studies presented have not been validated by peer reviewers, but are platform presentations, posters, etc. presented at a scientific meeting. Use caution in drawing conclusions until published in peer-reviewed journals.

Objectives:

After reading and studying this newsletter, the participant should be able to:

- Recognize the debilitating effects of covert hepatic encephalopathy in patients with cirrhosis
- Assess the results of selected studies relating to the diagnosis and treatment of hepatic encephalopathy presented at the 2013 Conference of the European Association for the Study of the Liver

Although minimal hepatic encephalopathy (MHE) is a defined and often detected condition, most physicians did not give a great deal of consideration to treating it until recently, perhaps because the term “minimal” implied a limited need for treatment. However, an abundance of recently generated data suggesting that MHE adversely impacts employability,[1,2] driving capacity,[3,4] and many domains of health-related quality of life[5-7] in patients with MHE contradict this view. Additionally, more than 50% of patients will go on to develop overt HE within 30 months.[8] In recognition of the dangerous consequences of MHE, the name of the condition has recently been changed to covert HE (CHE), a position endorsed by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism.[9] One of the obstacles to management of CHE is an absence of cost-effectiveness data to support routine treatment despite empirical evidence demonstrating the ability of currently available HE therapies, such as lactulose and rifaximin, to improve quality of life,[6,7] driving capacity,[10] and performance on psychometric tests, including the inhibitory control test. It is important to note that most of the trials from which these data were generated were placebo controlled and therefore not burdened by problems associated with trials of treatments for overt HE (OHE) where placebo arms were thought to be unethical.[11] Cost-effectiveness may be less controversial in the treatment of patients at risk for recurrent bouts of OHE is based on preventing or reducing hospitalizations. However, since cost issues are more difficult to reconcile with the reversal of MHE or CHE due to difficulties in estimating costs of reducing quality of life, poor driving capacity, and other consequences of CHE. This newsletter will review selected research related to HE reported at the 48th Annual Meeting of the European Association for the Study of the Liver, which took place in Amsterdam, The Netherlands, on April 24-28, 2013.[12]

Advances in Diagnostic and Prognostic Methods in Hepatic Encephalopathy

The diagnosis of CHE is based on psychometric and/or neuro-physiological tests which are not widely used outside of research settings because they are time consuming, expensive, and may require experienced personnel. In the poster presentation by Galvin et al, 86 cirrhotic patients underwent transient elastography (TE), an established non-invasive tool commonly used to determine the severity of hepatic fibrosis, and completed the Psychometric Hepatic Encephalopathy Score (PHES) to investigate whether TE could be effective in identifying patients most likely to have MHE.[13] According to PHES results, 34% of patients had MHE. Additional study

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results indicated that the TE-based liver stiffness measurement (LSM) was significantly greater in those with MHE than in those without MHE (median 38.6 kPa vs 17.3 kPa; P=0.002). Receiver operating characteristic (ROC) curve analysis demonstrated an area under the curve value of 0.785. At a cutoff value of 20.8 kPa, specificity of MHE detection was 79% and sensitivity was 67%. The study authors concluded that TE could be used to risk stratify patients for the presence of MHE and suggested that all patients with a LSM >20.8 kPa should either be tested for MHE or empirically treated.

Mayer and colleagues conducted a study to follow-up on the recent finding of an association between a microsatellite in the promoter region of the phosphate activated glutaminase (GLS) gene and the risk of developing HE.[14] In their follow-up study, Mayer and colleagues investigated whether this genetic association would result in an increased risk of developing HE in patients with cirhosis.[15] To accomplish this aim, HE was quantified by critical flicker frequency (CFF) and *GLS* variants were genotyped by PCR-based assays with 5-nuclease and fluorescence detection in 158 patients. Study results revealed that 53% of the patients displayed abnormal CFF results and that the *GLS* genotype distributions of homozygous minor (20%), homozygous major (32%), and heterozygous (48%) alleles were consistent with Hardy-Weinberg equilibrium. CFF values significantly differed between the three genotypes such that the genotype distribution of patients with MHE or grade I HE in comparison to patients without HE suggested an association between the homozygous major *GLS* variant and the development of HE. Furthermore, results of a multivariate analysis indicated that homozygous carriers of the major *GLS* variant had a significantly higher risk than heterozygous patients to develop HE independent of age and presence of transjugular intrahepatic portosystemic shunt. The study authors concluded that carriers of the homozygous major *GLS* variant displayed significantly lower CFF results, supporting a potential role of variant *GLS* in the development of HE which could be used for the identification of susceptible patients and prevention of complications.

A poster presentation by Montagnese et al. reported on the prognostic benefit of the addition of an EEG-based index [mean dominant frequency (MDF)] to the Model End-Stage Liver Disease (MELD) score, as MDF scores below 7.3 Hz are indicative of HE, an important prognostic parameter not reflected in the MELD score.[16] EEG data with automated MDF determination were collected from 392 patients with decompensated cirrhosis and their MELD scores were calculated. To determine prognostic value, stand-alone/combined MELD and MDF indices were calculated using standard survival analysis techniques and findings were validated using a split sample technique such that the Cox regression curve was re-calculated in a random sample of 259 patients, with the remaining 133 patients serving as a test group. Of the 392 patients, 107 died or were transplanted for hepatic decompensation during the follow-up period. Study results revealed that both the MELD and the MDF predicted mortality on the Kaplan–Meier analysis and on the Cox model.

Variable	beta	SE (beta)	Wald T	P	O.R.
MELD	0.087	0.016	30.5	0.000	1.091 (CI: 1.058-1.126)
MDF	-0.306	0.068	20.2	0.000	0.737 (CI: 0.645-0.842)

Table 1. Results of a Cox regression curve model demonstrating that MELD and the MDF were both independent predictors of mortality in patients with decompensated cirrhosis.[16] MDF = mean dominant frequency; MELD = Model for End-Stage Liver Disease; O.R. = odds ratio.

Using the Cox regression parameters, a novel prognostic index (MELD-EEG) was devised and was found to have higher prognostic accuracy in predicting 12- and 18-month mortality compared to MELD (*P*=0.016 and 0.018, respectively) on a ROC-curve analysis. Additionally, the ROC-curve analysis demonstrated that MELD-EEG had a higher Youden index (12 months: 0.31 vs 0.18; 18 months: 0.35 vs 0.2) as well. The assessment of validation showed no significant differences between the reference and test groups. The study authors concluded that the addition of an automatically obtained EEG-based index improved the prognostic accuracy of MELD and asserted that confirmation of their findings was already underway.

Although the relationship between portal-systemic shunt and the occurrence of OHE has long been known, the relationship between spleno-systemic shunts (SSS) and CHE is less clear and was the topic of a poster presentation by Tonello et al.[17] The likelihood of CHE screening in relation to the presence of SSS and the relationship between SSS and quantitative CHE indices were assessed in 331 patients with cirrhosis, 88 of whom had SSS. The prevalence of CHE screening in all 331 patients was 13% and was higher in those with SSS (34% vs 5%; $\chi^2 = 47.2$, P<0.0001). Additional study results revealed significant differences in spectral EEG features (EEG frequency and slow delta activity) between patients with and without portal flow inversion in the entire population and in the SSS group (all P<0.05) and no differences in patients without portal flow inversion in relation to SSS. The study authors concluded that although a significant association was observed between the presence of SSS and the likelihood of CHE screening, EEG parameters did not differ between patients with and without SSS. They also suggested that flow inversion is a risk factor for CHE based on their finding that the EEG was slower in patients with inverted portal flow compared to those with SSS only.

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A retrospective study of 168 patients adult patients listed for liver transplantation between 2007 and 2011 presented by Coenraad et al found that the presence of HE was independently associated with increased mortality before transplantation.[18] The study used clinical data retrieved from patient records to calculate MELD and MELDNa scores and survival analyses were performed using Kaplan Meier and Cox proportional hazard regression analyses. Approximately half (49%) of the patients with HE and without HE (54%) underwent liver transplantation and those with HE had a higher MELD score at listing than patients without HE (20±9 vs 12±5, P<0.001). Results of the Kaplan–Meier survival estimate indicated that the presence of HE was independently associated with increased mortality before transplantation [Hazard Ratio (HR) 3.702 (95% confidence interval {CI} 1.496–9.162), P=0.005], even after adjusting for MELD and MELDNa scores in a multivariate analysis.

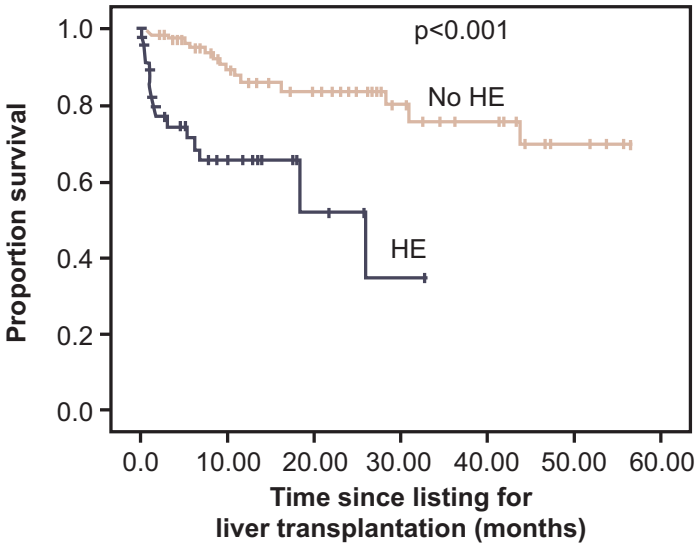

Figure 1. Kaplan–Meier survival estimate (months) of all patients until death according to the presence or absence of HE in patients listed for liver transplantation.[18] HE = hepatic encephalopathy.

Additionally, both the MELD [HR 1.095 (95% CI 1.031–1.163)] and MELDNa scores [HR 1.124 (95% CI 1.051–1.202] were also independent predictors of mortality. Although mortality was not increased in patients with HE grade 1 (HR 1.094), more severe HE was associated with a higher mortality risk such that the HRs for HE grades 2 and 3-4 were 4.973 and 28.413, respectively (both *P*<0.001). The study authors concluded that HE was an independent risk factor for mortality in patients awaiting liver transplantation and suggested that objective biomarkers for assessment of HE are needed, as HE patients might deserve higher priority.

Advances in the Treatment of Hepatic Encephalopathy

In a multicenter, prospective, double-blind, placebo-controlled trial, Simón-Talero et al assessed the efficacy of albumin administration on episodic HE, as albumin administration may modify factors that induce circulatory dysfunction, cause oxidative stress-mediated damage or enhance astrocyte swelling, and therefore precipitate episodic HE.[19] The proportion of 56 cirrhotic patients with an acute episode of HE randomized to treatment with either albumin or isotonic saline, in addition to standard treatment with laxatives and rifaximin, in which HE was resolved on day 3 was assessed. Additionally, survival and the mean length of the hospital stay were also examined.

	Albumin-Treated Patients (n=26)	Saline-Treated Patients (n=30)	*P* Value
Patients without HE at day 3 (%)	62.5	57.1	>0.05
Mean duration of the HE (days)	1.12	3.42	>0.05
Mean length of hospital stay (days)	8.6	10.3	>0.05
Mortality rate at 1.5 month follow-up (%)	7.7	36.7	0.01
Mortality rate at 3 month follow-up (%)	24	50	0.048

Table 2. Comparison of the percentage of patients without HE at day 3, the mean duration of the HE, the mean length of the hospital stay, and the 1.5 and 3 month follow-up mortality rates in cirrhotic patients with an acute episode of HE randomized to treatment with either albumin or isotonic saline.[19] HE = hepatic encephalopathy.

The two treatment groups did not differ in the percentage of patients without HE at day 3, the mean duration of the HE, or the mean length of the hospital stay. Conversely, the two treatment groups differed significantly in mortality rates at the 1.5 and 3 month follow-ups with lower rates observed for albumin-treated patients. The study authors concluded that albumin did not improve the evolution of HE during hospitalization. They also noted that the development of HE may identify a subgroup of patients with advanced cirrhosis that may benefit from the administration of albumin based on the observed differences in survival after hospitalization.

Although rifaximin, a gut-specific antibiotic, is effective in treating MHE, which has a presumed gut-based pathophysiology, its mechanism of action is unclear. A poster presentation reported on a systems biologic analysis of the microbiome, metabolome and cognitive change after rifaximin treatment in 20 cirrhotic patients with MHE to test the hypothesis that modulation of gut microbiota and

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their end-products by rifaximin would improve cognition in patients with MHE.[20] Study results revealed significant improvement in cognition (six of seven tests improved, P<0.01) and endotoxemia (0.55 to 0.48 Eu/ml, P=0.02) without MELD score change after treatment with rifaximin. Although significant increases in serum saturated (myristic, caprylic, palmitic, palmitoleic, oleic and eicosanoic) and unsaturated (linoleic, linolenic, gamma-linolenic and arachnidonic) acids post-rifaximin without urinary changes were observed, no significant microbial abundance changes were observed at the phylum/order level, with the exception of modest decreases in *Veillonellaceae* and increases in *Eubacteriaceae*. Additional study results from a network analysis indicated that the interaction of the microbiome and metabolome significantly shifted after treatment with rifaximin compared to baseline resulting in a significant reduction in network connectivity and clustering. Networks centered on potentially pathogenic and HE-associated taxa including *Enterobacteriaceae*, *Porphyromonadaceae* and *Bacteroidaceae* shifted from pathogenic to beneficial metabolite linkages and networks centered on autochthonous taxa such as *Lachnospiraceae*, *Ruminococcaeae* and Clostridium-ClusterXIV remained similarly linked to beneficial metabolites. The study authors concluded that rifaximin therapy changed gut bacterial linkages with metabolites without significantly changing microbial abundance and was associated with improved cognitive function and endotoxemia in MHE.

In an 8-week multi-center, double-blind, randomized, placebo-controlled, dose-ranging study (the ASTUTE study) (AST-120 Used to Treat Hepatic Encephalopathy), Bajaj et al. assessed the safety and tolerability of AST-120, a compound that has demonstrated efficient binding capacity for ammonia and other gut-based toxins, in 148 patients with CHE diagnosed using the global summary score on Repeatable Battery for the Assessment of Neuropsychological Status (RBANS).[21]

	AST-120 12g-Treated Patients (n=50)	AST-120 6g-Treated Patients (n=50)	Placebo-Treated Patients (n=48)
Change from baseline RBANS global-summary scores at week 8	3.27±7.97	4.51±7.72	4.57±9.50
Change from baseline venous ammonia levels at week 8 (mcg/dL)	-17	-14	+5
Frequency of treatment-emergent adverse events (%)	32	26	37.5

Table 3. Comparison of the change from baseline RBANS global-summary scores and ammonia levels at week 8 and the frequency of treatment-emergent adverse events in cirrhotic patients with CHE randomized to treatment with either AST-120 12g TID, AST-120 6g, or placebo.[21] RBANS = Repeatable Battery for the Assessment of Neuropsychological Status.

Study results revealed that although no significant changes were noted in the RBANS global-summary scores at week 8, a strong learning effect on RBANS (P<0.0001) was apparent between screening and baseline visits in all groups. In addition, no differences in PHES, clinical global assessment of HE or OHE/hospitalization events between groups were observed. Importantly, levels of venous ammonia significantly decreased from baseline in both treatment groups but increased in the placebo group. Lastly, the frequencies of treatment-emergent adverse events were similar for all groups. The study authors noted that theirs was the largest controlled trial yet conducted in CHE or MHE and concluded that AST-120 was well tolerated but did not achieve its primary endpoint of RBANS improvement. They suggested that the study results may have been confounded by the study design, which allowed for an improvement in neurocognitive measures prior to randomization. Lastly, the authors noted that ammonia levels improved significantly but independently of neurocognitive changes.

Summary

CHE, previously referred to as subclinical HE or MHE, is a condition defined by the presence of cognitive impairment in patients with cirrhosis that begins before signs or symptoms of OHE become apparent. Research indicates that a majority of patients will go on to develop OHE less than three years following a diagnosis of CHE. Therefore, prompt diagnosis of CHE is essential but remains challenging due to a need for specialized testing and an absence of evidence-based guideline recommendations. Of the EASL 2013 poster presentations summarized here, two pertained to experiments designed to improve diagnosis of CHE through the use of TE and genotyping for GLS variants. Additional presentations explored different prognostic indicators including the addition of an automatically obtained EEG-based index to the MELD score to improve its prognostic accuracy, the likelihood of

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CHE screening in relation to the presence of SSS and the relationship between SSS and quantitative CHE indices, and determination of whether HE could be considered an independent risk factor for mortality in patients awaiting liver transplantation. Several of the summarized EASL 2013 poster presentations addressed research on the treatment of HE. Specifically, one presentation describing a multicenter, prospective, double-blind, placebo-controlled trial to assess the efficacy of albumin on episodic HE reported that albumin did not improve the evolution of HE during hospitalization although observed differences in survival after hospitalization suggested that the development of HE may identify a subgroup of patients with advanced cirrhosis that could benefit from the administration of albumin. Additionally, a presentation that described a systems biology analysis of the microbiome, metabolome and cognitive change after rifaximin treatment in cirrhotic patients with MHE reported that rifaximin therapy changed gut bacterial linkages with metabolites without significantly changing microbial abundance and was associated with improved cognitive function and endotoxemia in MHE. Lastly, a presentation that described an 8-week multi-center, double-blind, randomized, placebo-controlled, dose-ranging study to assess the safety and tolerability of AST-120 in patients with CHE reported that ammonia levels improved significantly but independently of neurocognitive changes and that although AST-120 was well tolerated, the primary study endpoint was not achieved.

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Posttest

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1. Once CHE is identified, approximately what percentage of patients will go on to develop overt HE within 30 months?

a. 15%
b. 25%
c. 50%
d. 75%

2. In the study by Simón-Talero et al., which measure differed between albumin- and saline-treated patients?

a. Patients without HE at day 3
b. Mean duration of the HE
c. Mean length of hospital stay
d. Mortality rate at 1.5 month follow-up

3. In the study by Mayer et al., which GLS variant was associated with significantly lower CFF results?

a. Homozygous major
b. Homozygous minor
c. Homozygous
d. None of the above

4. The results of the ASTUTE trial demonstrated that AST-120:

a. Was well tolerated and achieved its primary endpoint of RBANS improvement
b. Was well tolerated but did not achieve its primary endpoint of RBANS improvement
c. Was poorly tolerated and did not achieve its primary endpoint of RBANS improvement
d. Was poorly tolerated and achieved its primary endpoint of RBANS improvement

5. The results of the study by Montagnese et al. demonstrated that:

a. The MELD, but not the MDF, predicted mortality on the Kaplan–Meier analysis and on the Cox model
b. Both the MELD and the MDF predicted mortality on the Kaplan–Meier analysis and on the Cox model
c. The MDF, but not the MELD, predicted mortality on the Kaplan–Meier analysis and on the Cox model
d. Both the MELD and the MDF predicted mortality on the Kaplan–Meier analysis but not on the Cox model

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Evaluation

Purdue University College of Pharmacy respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form.

How well did this activity meet the following learning objectives?

	This learning objective did (or will) increase/ improve my:	*High Impact*	*Moderate Impact*	*No Impact*	*Not Applicable*
• Recognize the debilitating effects of covert hepatic encephalopathy in patients with cirrhosis	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑
• Assess the results of selected studies relating to the diagnosis and treatment of hepatic encephalopathy presented at the 2013 Conference of the European Association for the Study of the Liver	***Knowledge***	❑	❑	❑	❑
	Competence	❑	❑	❑	❑
	Performance	❑	❑	❑	❑
	Patient Outcomes	❑	❑	❑	❑

Impact of the Activity

- Please indicate which of the following American Board of Medical Specialties/Institute of Medicine core competencies were addressed by this educational activity *(select all that apply)*:

❑ Patient care or patient-centered care
❑ Practice-based learning and improvement
❑ Interpersonal and communication skills
❑ Employ evidence-based practice
❑ Interdisciplinary teams
❑ Professionalism
❑ Quality improvement
❑ Medical knowledge
❑ System-based practice
❑ Utilize informatics
❑ None of the above

- The content of this activity matched my current (or potential) scope of practice.

❑ No _____
❑ Yes, please explain _____

- Was this activity scientifically sound and free of commercial bias* or influence?

❑ Yes _____
❑ No, please explain _____

** Commercial bias is defined as a personal judgment in favor of a specific product or service of a commercial interest.*

Impact of the Activity

	Strongly Agree	*Agree*	*Disagree*	*Strongly Disagree*	*Not Applicable*
• The educational activity has enhanced my professional effectiveness in treating patients	❑	❑	❑	❑	❑
• The educational activity will result in a change in my practice behavior	❑	❑	❑	❑	❑

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Evaluation

- How will you change your practice as a result of participating in this activity *(select all that apply)*?

❑ Create/revise protocols, policies, and/or procedures
❑ Change the management and/or treatment of my patients
❑ This activity validated my current practice
❑ I will not make any changes to my practice
❑ Other, please specify: _____

- What new information did you learn during this activity? _____

- Please indicate any barriers you perceive in implementing these changes.

❑ Lack of experience
❑ Lack of resources (equipment)
❑ Lack of time to assess/counsel patients
❑ Lack of consensus of professional guidelines
❑ Lack of opportunity (patients)
❑ Lack of administrative support
❑ Reimbursement/insurance issues
❑ Patient compliance issues
❑ No barriers
❑ Cost
❑ Other _____

- If you indicated any barriers, how will you address these barriers in order to implement changes in your knowledge, competency, performance, and/or patients' outcomes?

- Comments to help improve this activity?

- Recommendations for future CME/CPE topics.

To assist with future planning, please attest to time spent on activity:

I spent _____ hours on this program

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*Please do not use abbreviations. We need current and **complete** information to assure delivery of participation acknowledgement.*

Degree *(please mark appropriate box and circle appropriate degree)*

❑ MD/DO ❑ PharmD/RPh ❑ NP/PA ❑ RN ❑ Other _____

Full Name *(please print clearly)*

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Specialty:

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Date Completed: _____

Attestation to time spent on activity is required

❑ I participated in the entire activity and claim *1.0 AMA PRA Category 1 Credit(s)™*.

❑ I participated in only part of the activity and claim _____credits

❑ I do not wish to claim credits

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