

HEPATOLOGY Centers of Educational Expertise

Project ID: 11-0014-NL-3

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Objectives:

- To describe the spectrum of neuropsychiatric manifestations seen in cirrhotic patients with hepatic encephalopathy
- To review the diagnosis and treatment of overt hepatic encephalopathy and recognize the importance of initiating prophylactic therapy following an episode of overt hepatic encephalopathy
- To assess the importance of diagnosing minimal hepatic encephalopathy in cirrhotic patients and to describe the benefits of treatment of minimal hepatic encephalopathy

Increasing awareness of the importance of early diagnosis and appropriate medical intervention for patients with hepatic encephalopathy (HE) was apparent at Digestive Disease Week 2011, where multiple studies of this debilitating complication of advanced liver disease were reported in oral and poster sessions. Several presentations covered new diagnostic techniques, while others focused on treatment and patient management during and after hospitalization. This newsletter will summarize selected presentations.

Minimal hepatic encephalopathy

Near Infrared Spectroscopy (NIRS) was utilized in a study of minimal HE presented by Nakanishi et al.¹ This technique, often used by anesthesiologists, noninvasively measures cerebral blood volume as an oxygenated hemoglobin (oxy-Hb) concentration. The technique is applicable in the treatment of patients with cirrhosis because there is evidence of reduced cerebral oxygen consumption and blood flow in overt HE. The aim was to evaluate the cerebral oxygen metabolism of cirrhotic patients with minimal HE utilizing NIRS. The study included 29 patients with cirrhosis, 16 of whom had minimal HE based on EEG. Patients underwent a word fluency test during which the responsive increase in oxy-Hb concentration was compared between patients with and without minimal HE. The maximum increase in oxy-HB was significantly lower in those with minimal HE compared to those with normal EEGs $(0.26 \pm 0.12 \text{ mMmm vs. } 0.32 \pm 0.22 \text{ mMmm})$. In addition, the time course change in oxy-Hb was different between the groups; minimal HE was associated with a gradual rise of oxy-Hb throughout the task compared to a steep and repetitive increase in cirrhotic patients without minimal HE. The investigators concluded that changes in brain oxygen were poorly related to word fluency in patients with minimal HE compared to those with normal cognition. While the advantages of NIRS are its non-invasiveness, low cost, and high time resolution, further studies are needed before this technique can be used clinically.

Patients with cirrhosis and minimal HE have poor driving skills, complicated by impaired insight into their driving ability. An improvement in this insight may reinforce physician recommendations against driving and reduce risk of harm from motor vehicle accidents. Bajaj and colleagues utilized cognitive testing and driving simulation to evaluate personal insight into the driving skills of 65 patients with cirrhosis.²



Patients were asked to rate their driving skills on a Likert scale from 0-10 (self-assessment of driving skill [SADS]) before and after driving simulation and to undergo cognitive testing. The cognitive battery included digit symbol, line tracing, serial dotting, number connection A/B, block design, and inhibitory control tests. Driving simulation included training, testing (outcomes = crashes, speeding), and navigation (outcomes = illegal turns and crashes) components. While 31% of patients reported an accident or a moving violation in the past year, this did not affect their pretest SADS compared to patients without these offenses (8 vs. 8; P=0.79). Half of the patients were diagnosed as having minimal HE using the inhibitory control test (ICT); 45% were diagnosed as having minimal HE using the remaining tests. SADS test results are summarized in Table 1:

Median SADS score prior to testing and simulation	7
Median SADS score after testing and simulation	5
Percent of patients with decreased SADS	25%
Percent of patients with decreased SADS whose ICT test was abnormal	40%
Percent of patients with decreased SADS whose ICT test was normal	15%

Table 1. Self-assessment of driving skill before and after driving simulation and cognitive testing in cirrhotic patients.

A significantly higher rate of getting lost on the navigation task was seen in those who had a decrease in SADS compared to those with no change in SADS (median 1 vs. 0, P=0.04), and the percent reduction in SADS correlated significantly with the number of illegal turns (r=0.4; P=0.01) and navigation crashes (r=0.38; P=0.03). The percent reduction in SADS also significantly correlated with digit symbol errors (r=0.38) and line tracing errors (r=0.38). The authors concluded that cirrhotic patients gain insight into impairment of driving skills after experiencing navigation errors during driving simulation or performing poorly on cognitive tests.

The aim of a study by Vazguez-Elizondo et al was to establish the prevalence of minimal HE as determined by a psychometric battery of tests (Psychometric Hepatic Encephalopathy Test Score [PHES]) and Critical Flicker Frequency (CFF) testing in a cohort of patients with cirrhosis (N=104).³ An additional aim was to evaluate the impact of minimal HE on 2-year survival. The investigators prospectively recruited 104 patients and administered PHES and CFF tests to each subject. They classified minimal HE as a score >2 SD + over controls for PHES and a score <38 Hz for CFF. Subjects were followed for 2 years, and univariate logistic regression and Kaplan-Meier curves were used to identify variables associated with 2-year mortality. The population consisted mainly of alcohol-induced cirrhosis (69.2%; n=72), and 44% of thes were Child Class A. The prevalence of minimal HE was 55.8% (n=58) by either PHES or CFF criteria; PHES was abnormal in 32.7% (n=34), CFF was abnormal in 34.6% (n=36), and both tests were abnormal in 11.5% (n=12). Minimal HE with PHES testing was not associated with age, but was related to educational level

(r=0.333, *P*=0.001). In contrast, minimal HE with CFF was related to age (r=-0.93, *P*=0.049), but not to educational level. Upon Cox regression analysis, both Child Class C status (OR 10.9, 95% Cl 4.4-27.2, *P*<0.001) and minimal HE detected by both tests (OR 6.1, 95% Cl 1.8-20.1, *P*=0.003) are predictors of decreased 2year survival. The authors concluded that the prevalence of minimal HE in this population was comparable to that of other published studies, and that Child C status and a diagnosis of minimal HE by both CFF and PHES are of prognostic significance for 2-year survival in patients with cirrhosis.

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Inpatient management of HE

While the use of head CT is common in patients who are being evaluated for possible HE, there is little evidence supporting this practice. Bhandari et al presented a study in which the aim was to study the utility of head CTs in the diagnosis of HE.⁴ Charts of all adult cirrhotic patients admitted to a university hospital over a 3year period were analyzed for demographics, etiology of cirrhosis, model for end-stage liver disease (MELD) scores, biochemical data, encephalopathy grade, neurologic exam findings, and CT findings. The study involved 67 patients who were admitted for 147 episodes of HE where a head CT was performed. Overall, the prevalence of intracranial findings in HE was 4% (6/147) and 0.7% (1/142) in the absence of trauma or focal neurologic findings. The other 141 CTs did not reveal an acute abnormality. None of the clinical variables associated with disease severity, laboratory data, or HE severity had a statistically significant impact on CT findings. The authors concluded that, in patients with cirrhosis who present with HE without trauma or focal neurological findings, the yield of a head CT in determining the cause of change in mental status is extremely low. A head CT is not only costly, but confers a significant radiation exposure risk. The diagnostic evaluation to determine the precipitating cause of HE should include a thorough history, and a detailed neurologic exam, as well as supportive laboratory studies to evaluate for electrolyte disorders, occult infections, gastrointestinal bleeding, metabolic disturbances and drug intoxication. A head CT should be performed in the setting of trauma or focal findings on neurologic exam.

The orientation log is a validated instrument to assess mental status in traumatic brain injury. Salam and colleagues presented a poster summarizing their study findings in which a modified version of this instrument, the Modified Orientation Log (MO-log), was utilized for assessing disease severity for inpatients with HE.⁵ The MO-log has 8 simple questions and a score ranging from 0 through 24 (24 being normal). Five questions are based on time, and 3 are based on place. The study included 52 HE patients admitted to 2 tertiary care hospitals. The MO-log assessments were done on admission and daily thereafter. Patient demographics, cirrhosis severity, prior HE, HE therapy, precipitating factors, daily MO-logs, admission West-Haven criteria (WHC) grade, sodium and ammonia at admission and discharge,



time to reach maximum MO-log score, and length of stay were assessed; death and re-admissions for HE were analyzed as outcomes. The first 24-hour change in MO-log was evaluated as a predictor of change. Most subjects were male and admitted for their second HE episode. The group as a whole was decompensated (median admission MELD was 20) and the majority of the precipitating factors were nonadherence to lactulose and sepsis. The median admission WHC grade was 3 and the mean MO-log score was 11±8. The average stay was 8 days; 10% of the patients died during their hospitalization. The majority of those discharged had a near-perfect MO-log \geq 23, but 40% were re-admitted for HE within 3 weeks of discharge. Face validity of the MO-log was significant, with negative correlation with the WHC and good predictive capability evidenced by a shorter length of stay in patients with any improvement (6 vs. 11 day, P=0.037) or those with >5-point improvement (5 vs. 9 days, P=0.016) in MO-log in the first 24 hours. Improvement within the first 24 hours was strongly associated with in-hospital mortality; 80% of those who died did not improve with 24 hours compared to only 27% who did not die (P=0.023). The authors concluded that the MO-log is an objective instrument to predict outcome in patients admitted with HE.

Management of HE is associated with significant morbidity and mortality in addition to high costs, with the highest percentage of these costs being spent on inpatient treatment. Bleibel and colleagues presented their findings from a study of the effect of implementation of an HE algorithmic treatment protocol on morbidity, mortality and cost of inpatient treatment of HE.⁶ The study took place in a university transplant center over a 17-month period and enrolled patients retrospectively and prospectively with a primary or secondary diagnosis of HE. The treatment algorithm for HE outlined the doses, frequency and route of administration of lactulose and/or rifaximin. Outcomes of the prospectively recruited patients were compared to those who were admitted in the 17 months preceding the study. Results are summarized in Table 2:

	Pre-Implementation	Post-Implementation	<i>p</i> value		
Number of patients	115	78	NA		
Total patient days	602	318	0.03		
Average length of stay	5.2	4.1	0.03		
Total ICU days	61	7	0.005		
ICU days (%)	10.1	2.2	0.02		
Number of deaths	2	1	0.06		
Mortality rate (%)	1.7	1.3	0.05		
Average cost per patient	\$9,409 (SD \$11,877)	\$6,765 (SD \$5,905)	0.02		

Table 2. Comparison of HE inpatient outcomes prior to and following the implementation of a treatment algorithm at a university transplant center.

The authors concluded that implementation of a treatment protocol for HE significantly reduced the average length of stay and the percentage of days spent in the intensive care setting; morbidity and mortality were also reduced. More than 90 days of hospitalization were saved, resulting in a cost-reduction of more than \$220,000.

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Transcranial Doppler ultrasonography (TCD) is a simple, noninvasive technique to measure cerebrovascular function and structural integrity. Cerebrovascular function is expressed as cerebrovascular reactivity (CVR) and structural integrity is expressed as the pulsatility index (PI). The aim of a study by Green and colleagues was to evaluate cerebral hemodynamics utilizing TCD in patients with compensated and decompensated cirrhosis and in patients with and without HE, compared to healthy controls.7 The study included 90 subjects, 30 with cirrhosis and no HE, 30 with cirrhosis and HE, and 30 healthy controls. As expected, patients with HE had further decompensated liver disease compared to those without HE. Decompensated liver disease (Child \geq 7 and MELD \geq 14) significantly increased the PI as compared with patients with Child ≤ 7 and healthy subjects (Table 3). This was accompanied by a low CVR compared with the other 2 groups. Patients with HE had evidence of deranged hemodynamics, with a higher PI and lower CVR compared with the non-HE and control subjects. The investigators concluded that altered cerebral hemodynamics could be seen in HE patients and was related to cirrhosis severity. This could also indicate structural vascular damage and arteriolosclerosis in these patients. TCD currently cannot differentiate between HE and other neurological conditions in cirrhosis, but appears to be a good tool to assess cirrhosis.

		Pulsatility Index	Cerebrovascular Reactivity
	Control	0.87 (0.78-0.96)	1.28 (1.06-1.68)
Child	$\textbf{Child} \leq \textbf{7}$	0.90 (0.83-1.05)	1.20 (0.82-1.52)
onnu	$\textbf{Child} \geq \textbf{7}$	1.07 (0.95-1.21)	0.82 (0.45-1.11)
	Р	0.000	0.000
	Control	0.87 (0.78-0.96)	1.28 (1.06-1.68)
MELD	$\text{MELD} \leq 14$	0.94 (0.83-1.06)	1.07 (0.60-1.40)
IVILLD	$\text{MELD} \geq 14$	1.06 (1.02-1.21)	0.86 (0.63-1.15)
	Р	0.000	0.015
	Control	0.87 (0.78-0.96)	1.28 (1.06-1.68)
UE	HE Absent	0.96 (0.83-1.13)	1.00 (0.60-1.53)
HE	HE Present	1.05 (1.00-1.16)	0.89 (0.59-1.15)
	Р	0.000	0.007

Table 3. Results of Transcranial Doppler ultrasonography insubjects categorized according to Child, MELD, and HE.

Management of HE upon discharge

Results from a randomized, double-blind, placebo-controlled trial of rifaximin in HE were the topic of 2 presentations.^{8,9} The first dealt with health-related quality of life (HRQL) in cirrhotic patients with recurrent HE while the second reported on gastrointestinal



adverse events in those on concomitant lactulose and rifaximin vs. rifaximin monotherapy for the prevention of recurrent HE. Overall, the trial showed that rifaximin significantly reduced the risk of overt HE by 58% vs. placebo over 6 months (P<0.0001) in patients with cirrhosis and recurrent HE. In the trial, patients with cirrhosis who had \geq 2 episodes of HE (Conn score \geq 2) within 6 months of screening and who were currently in remission (defined as a Conn score = 0 or 1), were randomized to either rifaximin 550 mg BID (n=140) or placebo (n=159). Concomitant lactulose therapy was permitted in both groups.

The impact of HE and rifaximin treatment of HRQL was assessed using the Chronic Liver Disease Questionnaire (CLDQ). The CLDQ consists of 29 items in 6 domains: Abdominal Symptoms, Fatigue, Systemic Symptoms, Activity, Emotional Function, and Worry. CLDQ scores are ranked on a 7-point scale, with higher scores indicating a better HRQL. The questionnaire was administered at baseline and every 4 weeks through the end of treatment. Time weighted averages (TWA) were calculated by normalizing the area under the CLDQ score vs. time; these were compared across treatment groups, and between patients with and without recurrent HE events during the study for the overall CLDQ and for each CLDQ domain. The baseline HRQL of patients with recurrent HE was profoundly impaired as measured by mean CLDQ scores when compared to healthy individuals and was similar to cirrhotic patients awaiting liver transplantation (previously reported). After therapy, mean TWA scores of overall and individual domains were significantly higher in the rifaximin group compared to placebo (Table 4). Worsening HRLQ was found to be indicative of recurrent HE. The authors concluded that rifaximin significantly improved the HRQL in cirrhotic patients with recurrent HE and HRQL worsening could indicate impending HE recurrence.

	Mean Baseline	Mean Post-Treatmer	P Value*			
	CLDQ Scores	Rifaximin (n=140)	Placebo (n=159)	r value		
Overall	4.3	3.7	2.9	0.0093		
Abdominal Symptoms	4.7	4.1	3.3	0.0090		
Fatigue	3.3	3.2	2.5	0.0087		
Systematic Symptoms	4.6	3.9	3.2	0.0160		
Activity	4.1	3.7	2.8	0.0022		
Emotional Function	4.5	3.9	3.0	0.0065		
Worry	3,9	3.5	2.8	0.0436		

Table 4. Mean baseline and mean post-treatment Chronic LiverDisease Questionnaire scores in patients with cirrhosis andrecurrent HE.

*P value for rifaximin vs. placebo

The second presentation involving rifaximin included data from patients in the initial 6-month double-blind trial as well as data from new and rollover patients in an open-label trial.

Concomitant lactulose (daily doses ranged from 15 mL/day to 300 mL/day) was optional in both the randomized and open-label portions of the trial. Adverse event data were pooled from both portions of the trial to compare GI-related adverse events between patients treated with rifaximin plus lactulose (n=264) and patients

treated with rifaximin alone (n=84). The overall incidence of Glrelated adverse events was significantly greater in patients who received lactulose: 69% (183/264) of rifaximin patients treated with lactulose experienced at least one Gl-related adverse event vs. 49% (41/84) of patients treated with rifaximin alone (Table 5). The results suggest that concomitant lactulose resulted in higher incidences and event rates of Gl-related adverse events than when rifaximin was used alone.

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	Rifaximin 550 mg	g BID (n=84)	Rifaximin 550 mg BID + Lactulose (n=264						
	Events/100 PEY*	95% CI	Events/100 PEY*	95% CI					
Overall	43.6	33.7 - 53.5	72.4	66.2 - 78.2					
Nausea	8.5	3.8 - 16.0	23.0	17.9 - 28.7					
Abdominal Pain	7.4	3.0 - 14.7	15.8	11.5 - 21.0					
Vomiting	4.3	1.2 - 10.5	15.4	11.2 - 20.5					
Diarrhea	5.3	1.8 - 11.9	14.2	10.2 - 19.2					
Constipation	2.1	0.3 - 7.4	13.1	9.2 - 17.9					
Abdominal Pain Upper	2.1	7.5	4.6 - 11.5						
Abdominal Distension	1.1	0.0 - 5.8	7.1	4.3 - 11.0					

Table 5. Normalized rate of most frequent GI-related adverse events in patients with recurrent HE receiving either rifaximin monotherapy or rifaximin plus lactulose. *PEY: Person-years of rifaximin exposure.

The success of a Danish rehabilitation out-patient clinic (RC) for patients discharged after HE treatment was the topic of a presentation by Andersen et al.10 The clinic, established for alcoholic cirrhotic patients, allowed for frequent visits and easy access for contacting the clinic in the event of any liver-related or general symptom in order to prevent a recurrence of HE and to improve survival. Patients surviving HE were offered participation in the RC. They were seen by a nurse for a 1-hour interview at 1to 3-week intervals after discharge and by a doctor as needed. Clinical, psychological, and social problems were identified and addressed; alcohol consumption was recorded and alcohol cessation was encouraged at each visit. Patients developing minimal or overt HE were referred to the Liver Unit. Outcomes for 19 patients participating in the HE study were compared to outcomes of 14 patients discharged prior to establishment of the RC (control group). MELD score, age, proportion of patients with complications (esophageal varices, ascites), HE grade, ammonia levels, and other biochemical parameters were similar in the 2 groups; Child score was higher in the RC group compared to the control group (median [range] 13 [8-14] vs. 11 [7-13]; P=0.033) . The 1-year survival in the group participating in the RC was significantly higher than in the control group (16/19 [84%]) vs. 5/14 [36%]; P=0.012). The investigators concluded that the improved survival was due to a combination of decreased alcohol consumption and earlier referral to hospital when complications developed.



This material was supported by an educational grant from Salix Pharmaceuticals, Inc.



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Please select the one best answer by circling the appropriate letter.

1. Driving skills of cirrhotic patients with minimal hepatic encephalopathy:

a. Are usually not impaired

- b. May be impaired, but patients are frequently unaware of the impairment
- *c*. May be impaired, and most patients are well aware of the impairment

d. Are only impaired after progression to overt hepatic encephalopathy

2. A head CT in the initial evaluation of hepatic encephalopathy:

- a. Is seldom used in the US despite strong evidence of its utility
- **b.** Is recommended for all patients with suspected overt hepatic encephalopathy
- c. Seldom results in intracranial findings in cirrhotic patients who do not show evidence of trauma or focal neurological findings
- d. Is useful for determining disease severity

3. Implementation of a treatment protocol for patients with hepatic encephalopathy that outline doses, frequency, and route of administration of lactulose and/or rifaximin in a university transplant center:

- a. Had no effect on average length of stay, but decreased percent of days spent in the ICU
- b. Decreased the average length of stay, but had no effect on percent of days spent in the ICU
- c. Had no effect on either the average length of stay or percent of days spent in the ICU
- d. Significantly reduced both the average length of stay and the percent of days spent in the ICU

4. A study of health-related quality of life (HRQL) as measured by the Chronic Liver Disease Questionnaire (CLDQ) in patients with cirrhosis and recurrent hepatic encephalopathy who were treated for 6 months with rifaximin 550 mg BID or placebo (concomitant lactulose was permitted in both groups) found that:

- a. Rifaximin was significantly better than placebo in improving HRQL
- b. Rifaximin and placebo produced similar changes in CLDQ scores
- c. Baseline CLDQ scores of patients with recurrent hepatic encephalopathy prior to therapy were similar to those of healthy individuals
- d. There was no correlation between worsening HRQL and recurrence of hepatic encephalopathy

5. When comparing the use of rifaximin monotherapy to combination rifaximin use with lactulose, associated GI-related side effects occur with:

- a. Similar incidence for either therapy regimen
- **b**. Higher incidence in combination therapy
- c. Higher incidence in monotherapy
- d. Infrequent incidence with either therapy regimen



Hepatic Encephalopathy Update: Reports From Digestive Disease Week 2011

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.

	This learning objective did (or will) increase/improve my:	High Impact	Moderate Impact	No Impact	Not Applicable
• To describe the spectrum of neuropsychiatric	Knowledge				
manifestations seen in cirrhotic patients with	Competence				
hepatic encephalopathy	Performance	🗅			
	Patient Outcomes	🗖			
• To review the diagnosis and treatment of overt hepatic	Knowledge				
encephalopathy and recognize the importance of	Competence	🗅			
initiating prophylactic therapy following an episode of	Performance	🗅			
overt hepatic encephalopathy	Patient Outcomes	🗖			
• To assess the importance of diagnosing minimal	Knowledge				
hepatic encephalopathy in cirrhotic patients and to	Competence	🗖			
describe the benefits of treatment of minimal hepatic	Performance				
encephalopathy	Patient Outcomes	🗅			
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 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.

☐ Yes, please explain					
Was this activity scientifically sound and free of	mmercial bias* or influence?				
☐ Yes					
🗅 No, please explain 🛛					
Commercial bias is defined as a personal judgment ir	or of a specific product or service of a comm	nercial inte	rest.		
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 The educational activity has enhanced my professional 	Agree	Ayıtt	Disayiee	Disagree	Applicable	
effectiveness in treating patients	•••• 🗖					
$ullet$ The educational activity will result in a change in my practice behavior $\ldots\ldots$	🗅					

CLDF Chronic Liver Disease Foundation

This material was supported by an educational grant from Salix Pharmaceuticals, Inc.



 How will 	you change your	practice as a	result of p	articipating	in this activity	(select all	that apply)?
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 Create/revise protocols, policies, and/or procedures Change the management and/or treatment of my pati 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 the	ese changes.
Lack of experience	Reimbursement/insurance issues
Lack of resources (equipment)	Patient compliance issues
Lack of time to assess/counsel patients	No barriers
Lack of consensus of professional guidelines	□ Cost
Lack of opportunity (patients)	□ Other
Lack of administrative support	
 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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