Advances in the Diagnosis of Hepatic Encephalopathy

OHE can be diagnosed based on clinical recognition of the distinctive neurologic features of HE, knowledge that underlying cirrhosis is present, exclusion of all other etiologies of neurologic and/or metabolic abnormalities, and identification of precipitating factors. Severity of OHE can be assessed using West Haven Criteria. In contrast, patients with CHE have no clinical signs or symptoms; diagnosis of CHE is only possible through specialized psychometric and neurological testing.

Unfortunately, no consensus on diagnostic criteria or diagnostic tests for CHE has been established.

Montagnese and colleagues reported results of a study aimed at investigating the degree of agreement and the prognostic value of neurophysiological (EEG), psychometric (Psychometric Encephalopathy Score, PHES), and psychophysical (Critical Flicker Frequency, CFF) test results in 132 cirrhotic outpatients. Forty-seven patients (36%) were clinically diagnosed as having mild OHE, and 85 patients...
did not have OHE on the day of the study. EEG, PHES, and CFF test results were abnormal in a greater percentage of those clinically diagnosed as having OHE than in those diagnosed as non-OHE.

Table 1. Comparison of neurophysiological (EEG), psychometric (Psychometric Encephalopathy Score, PHES), and psychophysical (Critical Flicker Frequency, CFF) test results in cirrhotic outpatients clinically diagnosed as having mild overt hepatic encephalopathy (OHE) or not having OHE.11

Of the 85 patients with no OHE, 22 (26%) had an abnormal EEG, 14 (16%) had an abnormal PHES, and 26 (31%) had abnormal CFF test results. The test results suggest that 16% to 31% of the non-OHE patients could be diagnosed as having CHE, depending on which test is utilized for diagnosis. Interestingly, only 15 (18%) non-OHE patients had more than one abnormal test result, indicating that agreement between EEG, PHES, and CFF as diagnostic tools for CHE is poor. Patients with a history of OHE had slower EEG (theta power; 37±19 vs 25±16%, P<.001) and worse PHES scores (-2.9±3.9 vs -1.5± 3.5, P=.05) than their counterparts with no history of OHE; CFF test results were comparable regardless of the OHE history. Patients were followed prospectively for 11±7 months; during this time, 10 patients died, 10 were transplanted, and 29 developed OHE. The presence of OHE (P=.004), abnormal EEG (P=.008), and an abnormal PHES (P=.04) at baseline predicted the subsequent occurrence of OHE; CFF did not. The authors concluded that the agreement between neurophysiological, psychometric, and psychophysical test results for the diagnosis of HE is poor. EEG alterations appear to be most strongly associated with both previous and subsequent OHE episodes.

A poster presentation reported on the feasibility of using a blood biomarker for diagnosing the presence of CHE in patients with cirrhosis as an alternative to neuropsychological testing.12 Different amino acids, cyclic guanosine monophosphate (cGMP), nitrites and nitrates, and 3-nitrotyrosine were selected for analysis based on studies in animal models of HE. These were measured in 63 controls, 43 cirrhotic patients without CHE, and 44 patients with CHE. CHE was diagnosed utilizing PHES. Of the compounds tested, three of the blood biomarkers – 3-nitrotyrosine, citrulline, and methionine – demonstrated significantly increased levels in patients with CHE compared to patients without CHE.

Table 2. Concentrations of 3-nitrotyrosine, citrulline, and methionine in cirrhotic patients with CHE compared to cirrhotic patients without CHE and control subjects with normal liver function.13 CHE = covert hepatic encephalopathy.

Receiver operating characteristic (ROC) curve analysis demonstrated an area under the curve value of 0.96 (95% confidence interval [CI] 0.93-0.99) for 3-nitrotyrosine. At a cutoff value of 14 nM, specificity was 93%, sensitivity was 94%, and the positive and negative predictive values were both 91%. The authors concluded that the determination of serum 3-nitrotyrosine may be useful in identifying patients with CHE but that the results should be validated in a larger cohort. This study has been published.13

Advances in the Treatment of Hepatic Encephalopathy

Although lactulose has been used in the treatment of OHE and as secondary prophylaxis to prevent recurrent episodes of OHE, its use in primary prevention of HE in cirrhotic patients who have never had an episode of HE has not been studied. In the poster presentation by Agrawal et al, 120 cirrhotic patients who never had an episode of HE were randomized to receive lactulose or no lactulose.14 All patients were assessed by psychometry (number connection test A and B, figure connection test A and B if illiterate, digit symbol test, serial dot test, line tracing test, and CFF test) at study inclusion and after 3 months. Patients were followed monthly for development of OHE over a median follow-up of 12 months. Significantly fewer patients receiving lactulose prophylactically developed an episode of OHE compared to the untreated control group.

Table 3. Development of an episode of OHE or death in cirrhotic patients treated with prophylactic lactulose compared to controls who did not receive lactulose over a median follow-up of 12 months.14 CHE = covert hepatic encephalopathy; OHE = overt hepatic encephalopathy.
Liver Conference

Reports from the 2012 International Hepatic Encephalopathy Update: decreased OHE (log rank 13.35; liver transplant (log rank 5.1; be followed up with a randomized double-blind, placebo-controlled clinical trial.

In a 6-month randomized, double-blind, placebo-controlled trial of rifaximin in patients who were in remission from recurrent HE, Bass et al reported that a breakthrough episode of HE occurred in 22.1% of patients in the rifaximin group compared with 45.9% of patients in the placebo group. Hospitalization involving HE was also lower in the rifaximin-treated patients (22.6%) compared with the placebo group (13.6%). During a long-term open-label maintenance follow-up trial to the study published by Bass et al, a poster presentation by Sanyal et al reported rates of commonly occurring infections in rifaximin-treated patients. The open-label maintenance trial included 152 rollover patients from the original randomized trial along with 128 new patients. Median long-term rifaximin exposure was 427 (2-1427) days, or 510 person exposure years. The overall infection rate in patients using rifaximin long term was lower when compared with both the placebo and the rifaximin randomized control trial groups. Rates of commonly occurring infections in cirrhotic patients were either lower or remained stable during long-term administration.

Table 4. Infection rates during the 6-month randomized controlled trial (RCT) for patients receiving either placebo or rifaximin and rates for all rifaximin patients during the randomized trial and the open-label maintenance follow-up trial. * Rate is calculated as number of subjects/person exposure years (PEY).

<table>
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<tr>
<th>RCT Patients</th>
<th>Placebo (n=159) PEY = 46 (rate%)</th>
<th>Rifaximin (n=148) PEY = 50 (rate%)</th>
<th>All Rifaximin Patients (n=392) PEY = 510 (rate%)</th>
</tr>
</thead>
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<tr>
<td>Any infection</td>
<td>49 (1.32)</td>
<td>46 (1.33)</td>
<td>214 (0.72)</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>3 (0.06)</td>
<td>3 (0.06)</td>
<td>34 (0.07)</td>
</tr>
<tr>
<td>C. difficile infection</td>
<td>0</td>
<td>0 (0.48)</td>
<td>6 (0.012)</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>6 (0.13)</td>
<td>3 (0.06)</td>
<td>22 (0.044)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.022)</td>
<td>0 (0.008)</td>
<td>42 (0.084)</td>
</tr>
<tr>
<td>Sepsis/septic shock</td>
<td>5 (0.109)</td>
<td>2 (0.040)</td>
<td>31 (0.062)</td>
</tr>
<tr>
<td>Urinary tract/urinary</td>
<td>14 (0.320)</td>
<td>9 (0.187)</td>
<td>83 (0.193)</td>
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The use of antibiotics, both oral and intravenous, remained the same or decreased over time. The authors concluded that long-term treatment with rifaximin did not adversely affect infection rates or increase the use of antibiotics in cirrhotic patients with HE.

Embolloization of large portal-systemic shunts was the topic of a poster presentation by Simón-Talero et al. Embolization of one dominant shunt was performed in 15 patients with portal-systemic shunts secondary to hepatic cirrhosis. The patients had exhibited episodes of OHE (<2 in 6 months) or persisting manifestations and were considered at low risk of gastrointestinal bleeding. A favorable outcome was defined as increased patient autonomy and a marked decrease in the number of episodes of HE during more than 6 months of follow-up. There were no complications following the procedure. Nine patients had a favorable response (8 completely autonomous, 1 partially dependent) and 6 had poor outcomes (1 death at 1 month, 1 partially dependent, 4 fully dependent) following shunt embolization. In the group with a favorable outcome, the number of days of HE decreased from 11 per 100 days to 0.15 per 100 days (follow-up 44 ± 41 months). HE did not decrease in the patients with a poor outcome (18 per 100 days vs 20 per 100 days) after a follow-up of 11 ± 9 months. Only one patient experienced an episode of gastrointestinal bleeding 5 years following embolization. Patients with a Child-Pugh score ≤7 (n=9) had a favorable response with the exception of one 83-year-old patient; all patients but one with Child-Pugh >7 had poor results following embolization (P=.01). The authors concluded that embolization of large portal-systemic shunts in patients with low risk of gastrointestinal bleeding is a safe procedure that causes an important improvement of HE in those with a Child-Pugh score ≤7.

This material was supported by an educational grant from Salix Pharmaceuticals, Inc.
**Persistence of Cognitive Impairment After OHE**

Evidence continues to grow that cognitive dysfunction may persist as a sequela despite apparent recovery from an OHE episode. Bajaj and colleagues utilized psychometric testing (PHES (number connection test A/B, digit symbol test, line drawing test) and block design test) and the computerized inhibitory control test to evaluate cognitive dysfunction in cirrhotics with prior OHE (n=32; median 2 episodes; all on lactulose) versus patients without prior OHE (n=131). Patients with prior OHE had significantly impaired test results in all tests except line drawing test errors, the serial dotting test time, and inhibitory control test lure rates.

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Prior OHE Patients (n=32)</th>
<th>Non-OHE Patients (n=131)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number connection test A</td>
<td>65</td>
<td>44</td>
<td>.02</td>
</tr>
<tr>
<td>Number connection test B</td>
<td>146</td>
<td>192</td>
<td>.01</td>
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<tr>
<td>Digit symbol test</td>
<td>18</td>
<td>45</td>
<td>&lt;.0001</td>
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<tr>
<td>Line drawing time</td>
<td>130</td>
<td>190</td>
<td>.02</td>
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<tr>
<td>Line drawing errors</td>
<td>49</td>
<td>31</td>
<td>.1</td>
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<tr>
<td>Serial dotting test</td>
<td>86</td>
<td>74</td>
<td>.2</td>
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<tr>
<td>Block design test</td>
<td>13</td>
<td>34</td>
<td>&lt;.0001</td>
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<td>Inhibitory control test Lures</td>
<td>16</td>
<td>15</td>
<td>.6</td>
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<tr>
<td>Weighted Lures</td>
<td>51</td>
<td>18</td>
<td>.01</td>
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<tr>
<td>Targets</td>
<td>77%</td>
<td>92%</td>
<td>.001</td>
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Table 5. Comparison of psychometric test results and inhibitory control test results in cirrhotic patients who had prior OHE episodes versus non-OHE cirrhotic patients. OHE = overt hepatic encephalopathy.

In addition, patients without prior OHE showed improvement in the second-half inhibitory control test results (decreased lure and weighted lure rates and an increased percentage of targets), whereas second-half test results for those with prior OHE did not improve. The inhibitory control test results suggest that patients without OHE were able to learn and improve from the first half to the second half, but those with prior OHE were unable to learn from their first-half experience. The authors concluded that cirrhotics with prior OHE exhibit persistent cognitive impairment that is not present in those without prior OHE. They suggest that this persistence could have important implications for transplant listing and for prevention of the first episode of OHE.

**Summary.** Without a liver transplant, 1-year survival following an episode of overt hepatic encephalopathy (OHE) is 42%, whereas 3-year survival is only 23%. Cognitive impairment in patients with cirrhosis begins before any signs or symptoms of OHE are actually apparent, a condition now called covert hepatic encephalopathy (CHE). CHE has previously been called subclinical HE or minimal HE. CHE can only be diagnosed with specialized testing, but guidelines have not yet been established for testing. Two EASL presentations dealt with the diagnosis of CHE: one suggested that EEG may be better than psychometric (PHES) or psychophysical (CFF) testing, and another proposed using serum levels of 3-nitrotyrosine as an alternative to neuropsychological testing.

Several presentations dealt with treatment of HE. Significantly fewer cirrhotic patients who had never experienced an episode of OHE, when treated prophylactically with lactulose, developed OHE. The interesting observation that cirrhotic patients who were also diabetic and who received metformin appeared to be protected from the development of OHE warrants further study. A long-term open-label study of rifaximin used prophylactically in patients who had experienced an episode of OHE for the prevention of recurrent episodes found that the long-term use did not adversely affect infection rates or increase antibiotic use. For cirrhotic patients who had experienced multiple episodes of OHE or who had persistent symptoms, embolization of large portal-systemic shunts was found to be an effective intervention in 9 of 15 patients.
References


Hepatic Encephalopathy Update: Reports from the 2012 International Liver Conference

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Hepatic Encephalopathy Update: Reports from the 2012 International Liver Conference

Required with 70% passing.

1. Without a liver transplant, the estimated 1-year survival rate of cirrhotic patients following a first episode of overt hepatic encephalopathy is:
   a. <20%
   b. 42%
   c. 77%
   d. >90%

2. In the study by Montagnese and colleagues, which diagnostic test appeared to be most strongly associated with both previous and subsequent overt hepatic encephalopathy episodes?
   a. Psychometric Encephalopathy Score (PHES)
   b. Critical Flicker Frequency (CFF)
   c. Inhibitory Control Test
   d. EEG

3. What compound has been proposed as a potentially useful biomarker for diagnosing covert hepatic encephalopathy in patients with cirrhosis?
   a. Cyclic guanosine monophosphate
   b. 3-nitrotyrosine
   c. Alanine
   d. Ammonia

4. Which group of cirrhotic patients with concomitant diabetes appeared to be protected from developing overt hepatic encephalopathy?
   a. Patients receiving metformin with or without pioglitazone
   b. Patients receiving pioglitazone monotherapy
   c. Patients receiving dietetic treatment
   d. Patients receiving insulin

5. In the study by Simón-Talero et al., which treatment/procedure was found to be effective for controlling hepatic encephalopathy in patients exhibiting multiple episodes or persistent manifestations?
   a. Lactulose monotherapy
   b. Rifaximin monotherapy
   c. Lactulose and rifaximin combination therapy
   d. Embolization of large portal-systemic shunts
Evaluation

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

### Hepatic Encephalopathy Update: Reports from the 2012 International Liver Conference

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.

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<th>This learning objective did (or will) increase/improve my:</th>
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<th>No Impact</th>
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- **Recognize the debilitating effects of hepatic encephalopathy in patients with cirrhosis, including both covert and overt hepatic encephalopathy**

- **Assess the results of selected studies relating to the diagnosis and treatment of hepatic encephalopathy presented at the 2012 Conference of the European Association for the Study of the Liver**

### 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.
Hepatic Encephalopathy Update: Reports from the 2012 International Liver Conference

- The educational activity has enhanced my professional effectiveness in treating patients ............................ □ □ □ □ □
- The educational activity will result in a change in my practice behavior .......................... □ □ □ □ □

- 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
### REQUEST FOR CREDIT

If you wish to receive acknowledgement of participation for this activity, please fill in your contact information and fax back pages 7-10 to (973) 939-8533.

*Please do not use abbreviations.*

We need current and *complete* information to assure delivery of participation acknowledgement.

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**Degree** (please mark appropriate box and circle appropriate degree)
- [ ] MD/DO
- [ ] PharmD/RPh
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- [ ] RN
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**Full Name** (please print clearly)

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*Signature is required to receive statement of credit*

**Signature:** __________________________  **Date:** ________________

*Attestation to time spent on activity is required*

Purdue University College of Pharmacy designates this enduring material for a maximum of **1 AMA PRA Category 1 Credit(s)™**. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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