Hepatic Encephalopathy Update: Reports from the 64th Annual Meeting of the American Association for the Study of Liver Diseases

Centers of Educational Expertise

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Objectives:

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

- Recognize the currently available therapeutic options for hepatic encephalopathy, as well as challenges in diagnosing hepatic encephalopathy, particularly covert hepatic encephalopathy
- Assess the results of selected studies relating to the diagnosis and treatment of hepatic encephalopathy presented at the 64th Annual Meeting of the American Association for the Study of Liver Diseases

Introduction

Hepatic encephalopathy (HE), a term used to describe a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction, after exclusion of other known brain diseases, can be considered to be either overt (OHE) or minimal (MHE) in severity.¹ Recently, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism recommended that MHE be referred to as covert HE (CHE) due to its dangerous consequences,² such as increased progression to OHE, poor quality of life, and a high risk of traffic violations and accidents.³ Although consensus has not yet been reached, CHE is often considered to be a preclinical stage of OHE⁴ and may be present in 60% to 80% of patients with cirrhosis.⁵ Currently, there is no system that can be used to diagnose a patient with the specific stages of HE objectively through the entire spectrum.⁶ However, unlike OHE, which can be diagnosed based on its signs and symptoms in a clinical setting, a diagnosis of CHE requires specialized psychometric or neurophysiologic testing.⁷ Unfortunately, these tests are copyrighted and require a psychologist for administration and interpretation, making them largely unsuitable for regular clinical settings.7 It should be noted that the diagnosis of HE using psychometric tests has been particularly difficult in the US due to a lack of tests with established norms.⁷ Despite diagnostic challenges, treatments are available for HE, the majority of which are directed toward the gut.7 Currently, lactulose, a nonabsorbable disaccharide that is fermented in the colon and rifaximin, a nonabsorbable antibiotic, represent the most widely used therapeutic options for HE.7 Although both acidification of colonic contents and mass evacuation of bacteria have been proposed,8 the exact mechanism of action by which lactulose mediates its effects on HE has yet to be elucidated. Rifaximin (RFX) has been used to treat HE and has resulted in positive outcomes.9-12 This newsletter will review selected research related to HE reported at the 64th Annual Meeting of the American Association for the Study of Liver Diseases, which took place in Washington, DC, on November 1-5, 2013.13

Advances in the Diagnosis of Hepatic Encephalopathy

The accurate diagnosis of CHE can be difficult to make, in

part due to the relative paucity of short screening tools.¹⁴ Recently, a Stroop smartphone application (EncephalApp_ Stroop) has been shown to be a short, valid, and reliable tool for screening CHE.¹⁵ In the poster presentation by Bajaj







and colleagues, results of a study designed to validate the EncephalApp_Stroop for the diagnosis of CHE using agebased cut-off values were described.¹⁶ Cirrhotics (n=75) and healthy controls (n=100) underwent cognitive testing using standard batteries and the two-part EncephalApp_Stroop, comprised of the Stroop Off (OffTime) state (subjects press the correct color in which "#" signs are presented) and the Stroop On (OnTime) state (subjects press the correct color of a word regardless of the word's meaning). As shown in Table 1, controls performed significantly better than cirrhotics on standard tests.

| Tasks | Control patient (n=100) scores | Cirrhotic patient (n=75) scores | P value |
|---|-----------------------------------|------------------------------------|---------|
| Standard cognitive batteries | | | |
| Number connection test-A | 23 seconds | 43 seconds | <0.0001 |
| Number connection test-B | 59 seconds | 114 seconds | <0.0001 |
| Digit symbol test | 78 correct pairs achieved | 53 correct pairs achieved | <0.0001 |
| Block design test | 42 designs copied correctly | 22 designs copied correctly | <0.0001 |
| EncephalApp_Stroop OffTime+OnTime task | 132 seconds | 206 seconds | <0.0001 |

Table 1. Results from a study of 175 people, 75 of whom were cirrhotics, showing scores on standard cognitive test batteries and the EncephalApp_Stroop OffTime+OnTime task.¹⁶

According to the results of the standard cognitive test batteries, 40% of the cirrhotic patients had CHE. Because results from the EncephalApp_Stroop OffTime+OnTime task were correlated with age (r=0.6, P<0.0001) in controls, their results were further analyzed by age (> or <45 years). Based on that analysis, performance was considered impaired if the OffTime+OnTime score was >145 seconds in patients <45 years of age and >190 seconds in patients >45 years of age. Regarding CHE diagnosis, use of these age-adjusted cutoffs demonstrated that 52% of cirrhotic patients had impaired performance. Using standard tests as a reference, the sensitivity of the age-variable cut-off was 90% and the specificity was 78%. The study authors concluded that their use of new, age-based cut-off values for the EncephalApp_ Stroop were highly sensitive for CHE screening and could also be used to guide future dedicated testing in cirrhosis. The Encephal_App Stroop is freely available from the iTunes App Store and can be used on the iPhone, but not Android phones.

Advances in the Treatment of Hepatic Encephalopathy

Flamm and colleagues reported the results of a study aimed at evaluating baseline factors predictive of imminent

complications of cirrhosis and examining the effects of RFX in reducing the risk of complications.¹⁷ To accomplish this aim, data from a 6-month, randomized, double-blind trial of RFX (550 mg administered twice daily) versus placebo (PBO) were evaluated in a post-hoc analysis that stratified 299 patients with a recent history of recurrent HE. All of the subjects were in remission at enrollment according to their baseline Model for End-Stage Liver Disease (MELD) and International Normalized Ratio (INR) scores (MELD≥12 and INR≥1.2 vs MELD<12 and INR<1.2) and the presence versus absence of ascites. The time to first complication, including HE, was assessed. Study results revealed that the mean MELD scores were higher in the 106 patients with ascites (RFX group: 14.1, PBO group: 14.0) compared with the 193 patients with no ascites (RFX group: 12.5, PBO group: 12.0). Additionally, the hazard ratio for risk of any complication in patients with ascites in the RFX group compared with the PBO group was 0.58 (P=0.045, 42% relative risk reduction; Figure 1).



Figure 1. Survival probability plots from 299 patients with a recent history of recurrent HE but in remission at enrollment in a 6-month, randomized, double-blind trial of RFX versus PBO. Hazard ratios for any complications were lower in the group of patients that did not have ascites at baseline.¹⁷

Although study results also showed that patients without ascites experienced fewer overall complications, RFX was nevertheless found to be effective relative to PBO (P<0.001, 65% relative risk reduction). The hazard ratio for RFX versus PBO was 0.40 (P<0.001, 60% relative risk reduction) in the 153 patients with MELD scores ≥12 and INR scores ≥1.2. RFX was also found to confer a 76% reduction in relative risk in the 54 patients with MELD scores <12 and INR scores <1.2. The study authors concluded that complications of cirrhosis were more likely in patients with ascites, or with MELD≥12 and INR≥1.2, although RFX significantly reduced the risk of complications in all subgroups. Furthermore,







they suggested that future prospective studies would be necessary to assess the ability of RFX to prevent complications of cirrhosis.

Although it is known that RFX is a nonabsorbable antibiotic used for the treatment of HE,¹⁸ its limited systemic absorption and antibacterial spectrum¹⁹ make RFX an intriguing candidate medication for spontaneous bacterial peritonitis (SBP) prophylaxis as well. The limited data available regarding the potential effect of RFX on the incidence of SBP in patients with cirrhosis and ascites was addressed in a poster presentation by Shokoohi and colleagues who reported on the proportion of SBP in 139 adult cirrhotic patients with ascites seen in a hepatology clinic at least twice from 2005 to 2012. The study authors compared subjects receiving RFX, with or without lactulose, with those receiving lactulose only.²⁰ Selected patient characteristics are displayed in Table 2.

| Selected patient characteristics | RFX (with or without lactulose) group (n = 79) | Lactulose-only group (n = 60) |
|--|---|----------------------------------|
| Average duration of follow-up (months) | 20.2 | 18.8 |
| Average age (years) | 53.5 | 58.2 |
| Average MELD score | 15.2 | 13.6 |

Table 2: Selected characteristics of 139 adult cirrhotic patients with ascites, seen in a hepatology clinic at least twice from 2005 to 2012, treated with RFX (with or without lactulose) or lactulose only.²⁰ MELD = Model for End-Stage Liver Disease; RFX = rifaximin.

Study results showed that the proportion of SBP, 3.8% (n=3) in the RFX (with or without lactulose) group compared with 20% (n=12) in the lactulose-only group, was statistically significant (odds ratio [OR] 0.16, 95% confidence interval [CI] 0.03-0.65, P=0.004). Furthermore, RFX (with or without lactulose) remained a statistically significant preventive factor in the incidence of SBP after adjusting for age, gender, MELD score, serum sodium, and etiology of liver disease (OR 0.12, 95% CI 0.03-0.49, P=0.003). The study authors concluded that RFX was associated with a decreased incidence of SBP in patients with HE and ascites. They also asserted that it may be possible to consolidate therapy for HE and SBP prophylaxis by using RFX, although they noted that further studies would be necessary to confirm their findings and to explore the potential role for RFX in the secondary prophylaxis of SBP.

Lutz and colleagues presented a poster in which they reported on a study of the characteristics of SBP with respect to RFX coadministration.²¹ All patients receiving

a diagnostic paracentesis in their department from March 2012 to April 2013 were prospectively checked for SBP. Additionally, all clinical data -- including previous episodes of SBP, etiology of liver disease, type of SBP prophylaxis, prior use of RFX, concomitant complications of cirrhosis, as well as laboratory results and bacteriological findings -- were recorded. The 159 patients with advanced liver cirrhosis were divided in three groups: those who did not receive antibiotic prophylaxis (n=115); those who were prescribed RFX (n=27); and those who used systemic antibiotic prophylaxis (n=17). Study results indicated that 32 patients developed SBP, which was culture-positive in 15 cases (47%). Of these 32 patients, SBP occurred in 8/27 patients (30%) who received RFX and in 24/115 (21%) patients who received no prophylaxis at all. None of the 17 patients on systemic antibiotic prophylaxis developed SBP (P=0.04 vs no prophylaxis and P=0.02 vs RFX). In striking microbiological findings, enteric bacteria were predominantly identified in the ascites of patients without any prophylaxis (9/11, 82%), whereas bacteria exclusively from the oropharyngeal cavity were detected in patients receiving RFX (4/4, 100%; P=0.01). The study authors concluded that pretreatment with RFX might prevent SBP caused by enteric bacteria but not caused by bacteria from the oropharyngeal flora. Furthermore, they asserted that systemic antibiotics seemed to be more effective than RFX in the prevention of SBP and thus should remain the standard of care until data from randomized trials are available.

Although contemporary treatment for HE consisting predominantly of lactulose and RFX is helpful in most patients,7 the cost-effectiveness of these treatments remains uncertain. Therefore, Congly and associates conducted a cost-utility analysis using a Markov model to compare three prophylaxis strategies: (1) lactulose alone, (2) lactulose followed by RFX salvage in patients for whom lactulose is ineffective, and (3) RFX therapy in combination with lactulose upfront.²² The base case scenario of the model was designed to mirror data from a phase 3 registration trial (RFHE-3001) in which RFX was compared with placebo in conjunction with lactulose in maintaining remission in patients with a prior history of HE. In addition, the model employed a 5-year time horizon with 3-month cycles; model estimates were derived from the RFHE-3001 data as well as other published literature, with costs being based on a third party payer's perspective. Experimental results from the model predicted that 24.5% of patients receiving lactulose alone would be alive at the end of the 5-year study period compared with 30% for RFX salvage and 31.8% for RFX plus lactulose. Mean total healthcare costs were projected to be \$67,009 for lactulose, \$73,551 for RFX salvage, and \$91,647 for RFX plus lactulose, with 6.1%, 30.4%, and 49.6% of the total







cost being attributable to the medication (lactulose and/ or RFX), respectively. Treatment with lactulose alone was found to be both the least effective and least costly strategy, whereas the addition of RFX, either initially or after a second recurrence, led to both improved outcomes and increased costs. Additional results from the model indicated that the incremental cost-effectiveness ratio for RFX salvage, compared with lactulose alone, was \$38,833 per qualityadjusted life-year (QALY) and \$94,680 per QALY for RFX upfront (Table 3).

| Strategy | Cost [\$] | Incremental Cost [\$] | Effectiveness [QALY] | Incremental Effectiveness [QALY] | ICER [\$/QALY] | | | | |
|--------------------------|-----------|--------------------------|-------------------------|--|----------------|--|--|--|--|
| Lactulose | 67,009 | - | 1.99 | - | - | | | | |
| Salvage | 73,551 | 6,542 | 2.16 | 0.17 | 38,833 | | | | |
| Rifaximin + Lactulose | 91,647 | 24,638 | 2.25 | 0.26 | 94,680 | | | | |

Table 3. Results from a Markov model comparing three HE prophylaxis strategies: (1) lactulose alone, (2) lactulose followed by RFX salvage in patients for whom lactulose is ineffective, and (3) RFX therapy in combination with lactulose upfront.²² ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Using a one-way sensitivity analysis, the costs of hospitalization and the costs of RFX were found to be the biggest drivers of the model. The study authors concluded that, based on their model, the addition of RFX may be cost-effective as part of the management strategy for HE, depending on the willingness of payers to support such a strategy.

Summary

HE describes a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction; patients along the spectrum can be classified as having either OHE or MHE/CHE. CHE is a significant health problem, as it has been associated with increased progression to OHE, poor quality of life, and a high risk of traffic violations and accidents. Additionally, CHE may be present in 60% to 80% of patients with cirrhosis. The diagnosis of CHE requires specialized psychometric or neurophysiologic testing, which may be difficult to administer and interpret in regular clinical settings. Fortunately, treatments for HE directed toward the gut, such as lactulose and RFX, are available. Of the five American Association for the Study of Liver Diseases 2013 poster presentations summarized here, one pertained to improvements to a quick-screening tool designed to improve the diagnosis of CHE and four others were treatment-focused. Of the treatment-focused presentations, one evaluated baseline factors predictive of imminent complications of cirrhosis and examined the effects of RFX in reducing the risk of complications. Two other presentations were focused on the potential effects of RFX on the incidence of SBP in patients with cirrhosis and ascites. The final treatment-focused presentation examined the cost-effectiveness of lactulose and RFX using a Markov model to compare three prophylaxis strategies.







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Posttest

If you wish to receive acknowledgement of participation for this activity, please complete this posttest, evaluation form, and request for credit (pages 6-9) and fax to **973-939-8533**.

Required with 70% Passing. Must get 4 out of 5 answers correct.

- 1. Using standard cognitive tests as a reference, Bajaj et al determined that the sensitivity and the specificity of the EncephalApp_Stroop task in detecting CHE using their age-variable cut-off were:
 - a. 78% and 90%, respectively
 - b. 88% and 77%, respectively
 - c. 90% and 78%, respectively
 - d. 75% and 88%, respectively
- 2. In the study by Flamm et al, the hazard ratio for RFX versus PBO in the 153 patients with MELD scores \geq 12 and INR scores \geq 1.2 was 0.40 and represented a reduction in relative risk of:
 - a. 30%
 - b. 40%
 - c. 50%
 - d. 60%

3. In the study by Shokoohi et al, the proportions of SBP in the lactulose group compared with the RFX group were:

- a. 20% and 3.8%, respectively
- b. 4.8% and 30%, respectively
- c. 30% and 4.8%, respectively
- d. 3.8 % and 20%, respectively

4. The results of the study by Lutz et al revealed that:

- a. all of the 17 patients on systemic antibiotic prophylaxis developed SBP
- b. none of the 17 patients on systemic antibiotic prophylaxis developed SBP
- c. 2 of the 17 patients on systemic antibiotic prophylaxis developed SBP
- d. 15 of the 17 patients on systemic antibiotic prophylaxis developed SBP
- 5. Which of the three HE prophylaxis strategies modeled by Congly et al was found to be both the least effective and the least costly strategy?
 - a. RFX therapy in combination with lactulose upfront
 - b. Lactulose alone
 - c. Lactulose salvage in patients in whom RFX is ineffective
 - d. RFX salvage in patients in whom lactulose is ineffective







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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 currently available therapeutic options for hepatic encephalopathy, as well as challenges in diagnosing hepatic encephalopathy, particularly covert hepatic encephalopathy | Knowledge Competence Performance Patient Outcomes | | | | |
| Assess the results of selected studies relating to the diagnosis and treatment of hepatic encephalopathy presented at the 64th Annual Meeting of the American Association for the Study of Liver Diseases | 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 | |
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| 🖵 res, please explain | |
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Was this activity scientifically sound and free of commercial bias* or influence?

| 🖵 Yes | |
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* 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 | Disagree | Strongly | Not |
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| • | The educational activity has enhanced my professional effectiveness in treating patients | Agree | | | Disagree | Applicable |
| • | 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)?



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Evaluation

| Create/revise protocols, policies, and/or procedures Change the management and/or treatment of my patie 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 | g 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? | e, |
| • Comments to help improve this activity? | |
| • Recommendations for future CME/CPE topics. | |
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| l spent | hours on this program |





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Evaluation

If you wish to receive acknowledgement of participation for this activity, please complete this posttest, evaluation form, and request for credit (pages 6-9) and fax 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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