# Moving Ahead: Advances in Hepatic Encephalopathy Awareness, Diagnosis, and Management

HEPATOLOGY Centers of Educational Expertise

Project ID: 11-0014-NL-2

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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

## Hepatic encephalopathy: A common complication of liver cirrhosis

Hepatic encephalopathy (HE) reflects a spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known brain diseases.[1] Two forms of hepatic encephalopathy are recognized; minimal hepatic encephalopathy (MHE) and overt hepatic encephalopathy (OHE). Patients with MHE have no clinical symptoms of HE, but have subtle deficits in cognitive function that can be detected by psychometric or neurophysiologic testing. OHE is characterized by symptoms ranging from a trivial lack of awareness to loss of consciousness, and is usually assessed using the West-Haven grading system (Table 1).[2,3]

| Grade | Features |
|---|---|
| 0 | No abnormalities detected |
| I | Trivial lack of awareness<br>Euphoria or anxiety<br>Shortened attention span<br>Impairment of addition or subtraction |
| II | Lethargy or apathy<br>Disorientation for time<br>Obvious personality change<br>Inappropriate behavior |
| III | Somnolence to semi-stupor<br>Responsive to stimuli<br>Confused<br>Gross disorientation<br>Bizarre behavior |
| IV | Coma, unable to test mental state |

**Table 1. West Haven criteria for grading mental state in patients with cirrhosis. Adapted from Bajaj JS, et al. *Aliment Pharmacol Ther.* 2011;33:739-747.**

It is estimated that approximately 1% of the population of the United States has histological cirrhosis.[4] MHE will affect up to 60% of those with cirrhosis, while 30% to 45% of cirrhotic patients will develop OHE.[5] Both MHE and OHE are associated with a poor prognosis; patients diagnosed with MHE are at increased risk for the development of OHE, while those with OHE have a survival probability of only 42% at 1 year and 23% at 3 years without liver transplantation.[6,7]

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While the pathogenesis of HE is undoubtedly multifactorial, abnormal ammonia metabolism is the most frequently implicated factor. Ammonia, produced by the enzymatic cleavage of protein by colonic bacteria, is absorbed into the portal circulation. The inability of the compromised liver to adequately metabolize ammonia along with portosystemic shunting results in increased ammonia levels in the systemic circulation.[8] Elevated plasma ammonia levels are associated with cerebral edema and increased intracranial pressure.[2]

## Drugs approved for the treatment of hepatic encephalopathy

Drugs currently approved for the treatment of HE along with their drug class and indication are listed in Table 2.[9]

| Drug Name | Drug Class | Indication |
|---|---|---|
| Lactulose | Poorly absorbed disaccharide | • Decrease blood ammonia concentration<br>• Prevention and treatment of portal-systemic encephalopathy |
| Rifaximin | Nonaminoglycoside semi-synthetic, nonsystemic antibiotic | • Reduction in risk of OHE recurrence in patients ≥18 years of age |
| Neomycin | Aminoglycoside antibiotic | • Adjuvant therapy in hepatic coma |

**Table 2. Agents approved for the treatment of HE. Adapted from U.S. Food and Drug Administration GI Drugs Advisory Committee Meeting, February 23, 2010. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisory%20Committee/UCM203247.pdf. Accessed 05/18/11.**

Lactulose is currently the mainstay of therapy for HE and approximately 70% to 80% of patients with acute or chronic HE improve with lactulose treatment. Lactulose is a nonabsorbable disaccharide that is metabolized by bacterial flora in the colon to lactic acid and acetic acid, thus lowering the colonic pH. The lowered pH creates a hostile environment for bacteria involved in the production of intestinal ammonia and favors the formation of the nonabsorbable $NH_4+$ from $NH_3$, thus trapping $NH_3$ in the intestinal lumen and effectively reducing plasma ammonia concentrations.[2] In addition, the cathartic effect of lactulose can increase fecal nitrogen excretion with up to a 4-fold increase in stool volume.[10] Lactulose can be administered by mouth, through a nasogastric tube, or rectally as a retention enema. The dose of lactulose in conscious patients (45 g/day to 90 g/day) should be titrated to achieve 2 to 3 soft stools per day. Abdominal cramping, flatulence, and diarrhea are the primary side effects of lactulose.[10] While lactulose is usually well tolerated, it can induce diarrhea leading to patient non-compliance.[11]

Rifaximin is a minimally absorbed oral antibiotic that has broad-spectrum in vitro activity against gram-positive and gram-negative aerobic and anaerobic enteric bacteria and has a low risk of inducing bacterial resistance. With minimal systemic bioavailability, rifaximin may be more conducive to long-term use than other, more bioavailable antibiotics. Rifaximin acts by reducing ammonia-producing enteric bacteria in patients with HE. The dose of rifaximin is 550 mg twice daily (BID) and it can be used as monotherapy or in conjunction with lactulose in the treatment of HE. The side effects of rifaximin in a large clinical study were similar to a placebo control group.[11] Other antibiotics (neomycin, metronidazole, and vancomycin) have been used to treat HE, but the potential for adverse events with these agents limits their use as first-line therapies.[10]

## Overt hepatic encephalopathy

In patients with cirrhosis and portosystemic shunting, a known precipitating factor and a typical clinical presentation is usually sufficient to make a diagnosis of OHE after other causes of neurological and/or metabolic abnormalities are excluded.[8] Common precipitating factors include gastrointestinal bleeding, infection, dehydration, psychotropic medications, and surgery.[2] Treatment of OHE consists of identifying and correcting the precipitating factor(s). Therapeutic agents that reduce colonic ammonia production and/or increase excretion of ammonia from the colon are useful for improving the mental status as the precipitating factors are simultaneously being corrected (Figure 1).[12]

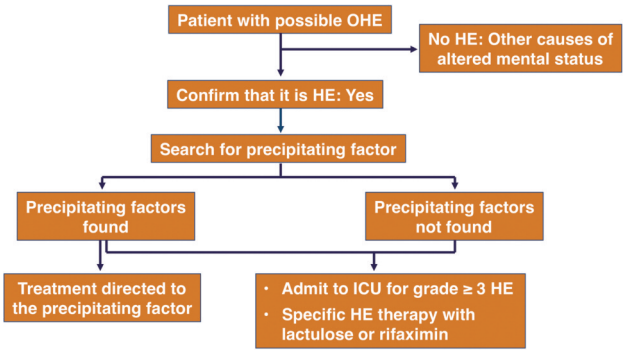


**Figure 1. Algorithm for in-patient diagnosis and treatment of OHE. Adapted from Bajaj JS. *Aliment Pharmacol Ther.* 2010;31:537-547.**

Following an episode of OHE, prophylactic therapy for an indefinite period of time or until liver transplant is recommended. The goals of prophylactic therapy are to prevent recurrent episodes of OHE and to improve quality of life. Both lactulose and rifaximin have been used as long-term prophylactic therapy following an episode of OHE, either as monotherapy or in combination.[13] Sharma et al conducted an open label trial comparing lactulose (n = 70) to no treatment (n = 70) in patients who had recovered from an episode of OHE. Patients were enrolled within 1 week following recovery from an episode of HE. Patients in the lactulose arm received 20 g



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to 40 g of lactulose in 2 or 3 divided doses so that they passed 2 to 3 semisoft stools per day. The primary end point of the study was development of OHE. Patients received treatment until they achieved the primary end point or until they completed a minimum follow-up of 6 months after study enrollment. The median follow-up was 14 months (range 1 to 20 months) for 61 patients in the lactulose arm and 64 patients in the no-treatment arm; 13 patients were lost to follow-up. The probability of developing recurrent OHE in patients receiving lactulose or no treatment is illustrated in Figure 2.

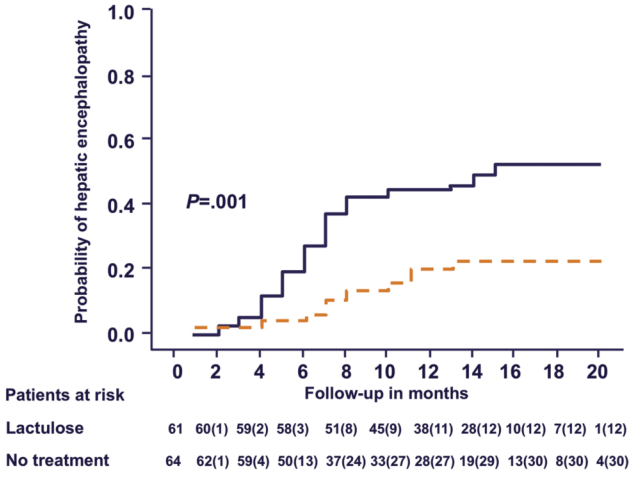


**Figure 2. Probability of developing a recurrent OHE episode in patients receiving lactulose (dashed line) or no treatment (solid line). Figures in parentheses indicate the cumulative number of subjects who developed OHE. Adapted from Sharma BC, et al. *Gastroenterology* 2009:137:885-891.**

Twelve (19.6%) of 61 patients receiving lactulose and 30 (46.8%) of patients receiving no treatment developed OHE (*P*=0.001). Five of 61 patients (8%) receiving lactulose and 11 of 64 patients receiving no treatment died. All of the patients in the lactulose group remained compliant to therapy. Of the 61 patients receiving lactulose, 14 (23%) had diarrhea, 6 (10%) had abdominal bloating, and 8 (13%) had distaste to lactulose; the dose was reduced in these patients but not stopped. Ten of 64 patients (16%) in the no-treatment group reported constipation as an adverse event. The authors concluded that lactulose is effective for prevention of recurrence of OHE in patients with cirrhosis.[14]

Rifaximin has also been studied as a prophylactic therapy in patients who were in remission from recurrent OHE resulting from chronic liver disease. The study enrolled 299 patients, with 140 patients receiving rifaximin at a dose of 550 mg BID and 159 patients receiving placebo for 6 months. It should be noted that 91.4% of the patients in the rifaximin arm and 91.2% of the patients in the placebo arm received concomitant lactulose therapy during the study. The primary efficacy end point was the time to the first breakthrough episode of HE; the key secondary end point was the time to the first hospitalization involving HE.

A Kaplan-Meier estimate of the time to the first breakthrough episode of HE is illustrated in Figure 3.

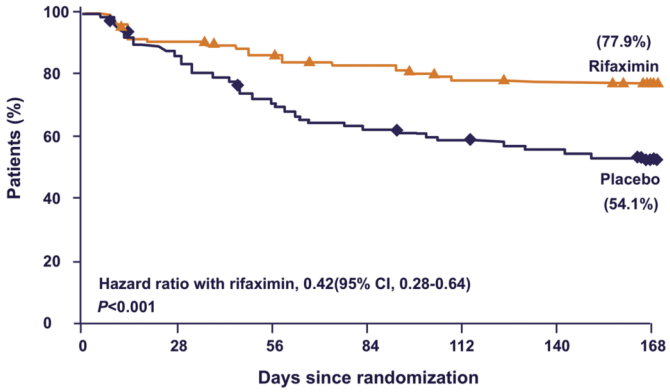


**Figure 3. Kaplan-Meier estimate of time to first recurrent breakthrough OHE epaisode. Adapted from Bass NM, et al. *N Engl J Med* 2010; 362:1071-1081.**

A breakthrough episode of HE occurred in 22.1% of patients in the rifaximin group as compared to 45.9% of patients in the placebo group. The hazard ratio for the risk of a breakthrough episode in the rifaximin group compared to the placebo group was 0.42 (95% CI, 0.28 to 0.64; *P*<0.001), reflecting a relative reduction in the risk of a breakthrough by 58% with rifaximin as compared to placebo over the 6-month study period. Hospitalization involving HE was necessary for 13.6% of patients in the rifaximin arm vs. 22.6% of patients in the placebo arm. The hazard ratio for risk of hospitalization in the rifaximin group vs. the placebo group was 0.50 (95% CI, 0.29 to 0.87; *P*=0.01), reflecting a reduction in risk by 50% with rifaximin compared to placebo. Nine patients in the rifaximin arm and 11 patients in the placebo group died during the study; most deaths were attributed to disease progression. The incidence of adverse events reported during the study was similar in both arms: 80% in the rifaximin group and 79.9% in the placebo group. The authors concluded that rifaximin has a protective effect against episodes of HE and also reduces the risk of hospitalization involving HE.[11]

## Minimal hepatic encephalopathy

MHE has a substantial negative effect on quality of life, daily functioning, and employment capability. In addition, it may impair the ability to drive, placing those with MHE at an increased risk for road traffic violations and accidents. Patients with a diagnosis of MHE are also at greater risk for progression to OHE.[15,16] No consensus on diagnostic criteria or diagnostic testing for MHE has been established.[17] Copyright issues with tests, time constraints, expense, and test standardization are among the roadblocks commonly listed as reasons for not screening those at risk for MHE.[2] Fortunately, several computerized psychometric tests are being developed to aid in the diagnosis of MHE that will enable clinicians to screen cirrhotic patients in an outpatient setting.[13]



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Several recent studies have demonstrated the beneficial effect of treating MHE in cirrhotic patients with lactulose or rifaximin. Prasad et al investigated the effect of treatment with lactulose compared to no treatment for 3 months in patients diagnosed with MHE utilizing psychometric testing. The study objectives were to measure the effect of lactulose on health-related quality of life (HRQOL) using the Sickness Impact Profile (SIP) and psychometric test results (2 number-connection tests, 2 figure-connection tests, a picture-completion test, and a block-design test). Thirty-one patients were assigned to receive lactulose (20 g/day to 40 g/day in 2 or 3 divided doses so that patient passed 2 to 3 semisoft stools/day); 30 patients received no treatment. Prophylactic therapy with lactulose for 3 months resulted in across-the-board improvement in HRQOL as measured by all scales of the SIP (Figure 4).

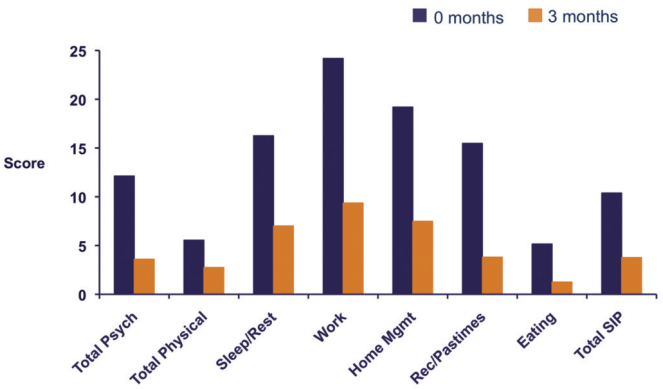
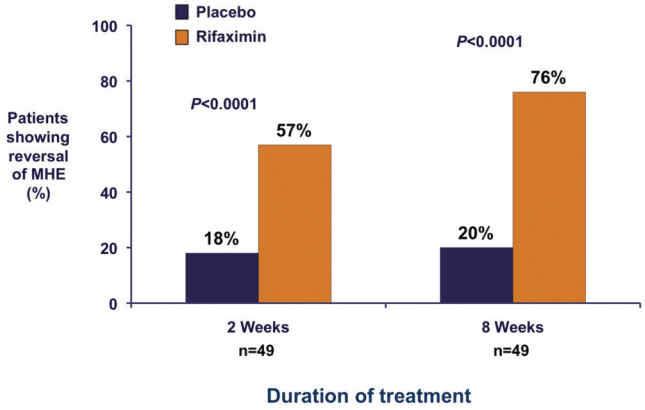



**Figure 4. Sickness Impact Profile (SIP) scores of cirrhotic patients with MHE before and after 3 months of therapy with lactulose. Each score ranges from 0 (best) to 100 (worst). Adapted from Prasad S, et al. *Hepatology*. 2007;45:549-559.**

The total SIP score in MHE patients receiving lactulose improved with 3 months of therapy (10.39 [95% CI, 9.36-11.43] before treatment vs. 3.77 [95% CI, 2.52-5.02] at the end of 3 months, *P*=0.002); the total SIP score in MHE patients receiving no treatment was unchanged (10.36 [95% CI, 8.98-11.73] before treatment vs. 10.39 [95% CI, 8.36-12.42] at the end of 3 months, *P*=NS). Of the 6 psychometric tests, the number of abnormal tests in the lactulose group decreased from 2.74 (95% CI, 2.40-3.08) before therapy to 0.75 (95% CI, 0.36-1.16) after 3 months of lactulose treatment; for the non-treatment group, the number of abnormal tests remained essentially the same at 2.47 (95% CI, 2.19-2.74) before treatment and 2.55 (95% CI, 2.16-2.94). Twenty six of 31 (84%) patients had reversal of MHE following 3 months of lactulose therapy compared to 12 of 30 (40%) untreated patients who no longer had MHE at the end of 3 months. One of 31 patients receiving lactulose developed an episode of OHE during therapy compared to 2 of 30 patients with no treatment.[15]

Rifaximin has also been studied in patients diagnosed with MHE. Sidhu et al. compared quality of life and reversal of MHE in 49 patients treated with rifaximin (1200 mg/day) with 45 patients who received placebo for 8 weeks. MHE was diagnosed with psychometric testing (number- and figure-connection tests, picture-completion, digit-symbol, and block-design tests). HRQOL was assessed using the SIP questionnaire. Psychometric tests were administered at baseline, at the end of week 2, and at the end of week 8. HRQOL was assessed at baseline and at the end of week 8. At the end of treatment, 76% of patients in the rifaximin group showed reversal of MHE compared to 20% in the placebo group (Figure 5).

**Figure 5. Reversal of MHE following administration of rifaximin or**




**placebo at 2 weeks and at 8 weeks. Adapted from Sidhu SS et al. *Am J Gastroenterol*. 2011;106:307-316.**

Rifaximin also resulted in an improved HRQOL while there was no change in the placebo group. The total SIP score decreased from 11.67 (95% CI, 10.31-13.03) to 6.45 (95% CI, 5.59-7.30) following 8 weeks of rifaximin therapy (*P*=0.000), while the change in the placebo group was not significant (9.86 [95% CI 8.66-11.06] vs. 8.51 [7.35-9.67]). One patient in the rifaximin and 2 patients in the placebo group developed OHE during the study. Two patients in the rifaximin arm reported epigastric discomfort and vomiting; therapy was stopped in one patient for 3 days and symptoms improved in the other patient after taking antacids.[16]

Cirrhotic patients have a higher self-reported occurrence of traffic violations and motor vehicle accidents compared to age and educational status-matched controls, and cirrhotic patients with MHE have higher rates than those without MHE.[18] Baja et al compared driving simulator performance of MHE patients before and after treatment with either rifaximin (550 mg BID) or placebo for 8 weeks. MHE was diagnosed by psychometric testing (number-connection tests A and B, digit-symbol, and block-design test) and the computerized inhibitory control test. Twenty-one patients received rifaximin and 21 patients received placebo.There was a significant improvement in mean total errors and in the number of speeding tickets and illegal turns in the rifaximin group; the reduction in the number of collisions was not statistically significant (Table 3).

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| | Rifaximin | | | Placebo | | |
|---|---|---|---|---|---|---|
| | Baseline | End | *P* value | Baseline | End | *P* value |
| Total errors | 10.3±6.2 | 5.5±3.8 | 0.0001 | 7.2±4.8 | 7.6±3.9 | .77 |
| Speeding tickets | 4.4±4.1 | 2.0±2.0 | 0.006 | 2.6±2.8 | 2.9±3.1 | .70 |
| Illegal turns | 2.6±3.4 | 0.9±1.2 | 0.03 | 1.9±2.7 | 1.5±1.3 | .50 |
| Collisions | 3.2±2.2 | 2.6±1.9 | 0.27 | 2.7±1.3 | 3.0±1.9 | .50 |

**Table 3. Driving simulator outcomes compared with baseline in MHE patients treated for 8 weeks with rifaximin or placebo. Adapted from Bajaj JS et al. *Gastroenterology* 2011;140:478-487.**

Although not statistically significant, there were slight increases in total errors and in speeding tickets and collisions in the placebo group; there was a small reduction in illegal turns. The authors concluded that treatment of MHE with rifaximin significantly improves driving simulator performance, compared with placebo. It is possible that lactulose therapy for MHE could have a similar effect on actual driving performance.[19]

## Summary

HE is a serious complication that develops in up to 60% of those with liver cirrhosis. HE consists of a spectrum of neuropsychiatric disorders thought to be associated with elevated ammonia levels in the systemic circulation that result in cerebral edema and increased intracranial pressure. MHE can only be diagnosed using psychometric testing. OHE is diagnosed by symptoms ranging from a trivial lack of awareness to loss of consciousness. MHE has a negative effect on QOL, daily functioning, employment capability and driving ability and presages the development of OHE. Patients who have an episode of OHE have a survival probability of only 42% at 1 year without liver transplantation.

Drugs currently approved for the treatment of HE include lactulose and rifaximin, and both decrease production of ammonia by colonic bacteria. Identifying and correcting a precipitating factor while simultaneously utilizing agents to reduce intestinal ammonia production is the recommended therapy for OHE. Following an episode of OHE, long-term prophylactic therapy with lactulose, rifaximin, or a combination of the two can improve patients' quality of life and decrease the probability of a recurrent OHE episode. Recent studies also suggest that identifying those cirrhotic patients with MHE and initiating long-term treatment with either lactulose or rifaximin can improve QOL, decrease the probability of progression to OHE, and improve driving skills as measured by driving simulation.



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

**1. Minimal hepatic encephalopathy:**

***a***. Is usually assessed using the West-Haven grading system

***b***. Is diagnosed by psychometric testing

***c***. Affects approximately 10% of patients with liver cirrhosis

***d***. Seldom progresses to overt hepatic encephalopathy

**2. Which of the following antibiotics is considered a first-line therapy for the treatment of hepatic encephalopathy?**

***a***. Neomycin

***b.*** Metronidazole

***c.*** Rifaximin

***d.*** Vancomycin

**3. Following an episode of OHE:**

***a***. A recurrent episode of OHE is unlikely

***b.*** Lactulose prophylactic therapy is ineffective in preventing a recurrent episode of OHE

***c.*** Rifaximin prophylactic therapy is ineffective in preventing a recurrent episode

***d.*** Either lactulose or rifaximin prophylactic therapy is effective in preventing a recurrent episode of OHE

**4. Treatment of minimal hepatic encephalopathy with either lactulose or rifaximin results in:**

***a***. Reversal of MHE and improvement in quality of life in a significant number of patients

***b.*** Reversal of MHE in a significant number of patients, but no improvement in quality of life

***c.*** No reversal of MHE, but a significant improvement in quality of life in most patients

***d.*** No reversal in MHE and no improvement in quality of life

**5. A problematic side effect impacting long-term prophylactic therapy with lactulose is:**

***a***. Constipation

***b***. Renal toxicity

***c***. Diarrhea

***d***. Ototoxicity



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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 manifestations seen in cirrhotic patients with hepatic encephalopathy | ***Knowledge*** | ❑ | ❑ | ❑ | ❑ |
| | ***Competence*** | ❑ | ❑ | ❑ | ❑ |
| | ***Performance*** | ❑ | ❑ | ❑ | ❑ |
| | ***Patient Outcomes*** | ❑ | ❑ | ❑ | ❑ |
| • 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 | ***Knowledge*** | ❑ | ❑ | ❑ | ❑ |
| | ***Competence*** | ❑ | ❑ | ❑ | ❑ |
| | ***Performance*** | ❑ | ❑ | ❑ | ❑ |
| | ***Patient Outcomes*** | ❑ | ❑ | ❑ | ❑ |
| • To assess the importance of diagnosing minimal hepatic encephalopathy in cirrhotic patients and to describe the benefits of treatment of minimal hepatic encephalopathy | ***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.*

| | *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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- 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

CLDF Chronic Liver Disease Foundation

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## 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.*

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

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

Full Name *(please print clearly)*
Last Name: First Name: Middle Initial:

Street Address:

City: State or Province: Postal Code:

Phone: – – Ext. Fax: – –

Specialty:

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**Signature is required to receive statement of credit**

Signature: _____ Date: _____

### Attestation to time spent on activity is required

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