Project ID: 11-0063

# Clinical Judgments in the Management of HE & HCV

## Objectives

Upon completion of this activity, the participant will be better able to:

- Review current testing options for minimal hepatic encephalopathy (MHE) in patients with hepatic cirrhosis; compare the efficacy of lactulose and rifaximin in those who test positive for MHE and describe benefits of treatment

- Recognize the benefits of prophylactic treatment following an episode of overt hepatic encephalopathy (OHE) in patients with advanced liver disease; compare the efficacy of lactulose and rifaximin when used as prophylactic therapy following an OHE episode

- Assess use of ribavirin (RBV) dose reduction, administration of an erythropoietic stimulating agent, or a combination of RBV dose reduction and an erythropoietic stimulating agent in treating anemia secondary to the treatment of HCV with boceprevir or telaprevir in combination with pegylated interferon (PegIFN) and RBV; explain rationale for current treatment guidelines for anemia associated with treatment of HCV with direct acting antiviral agents/PegIFN/RBV

## Introduction

Clinical drug trials utilize rigorous study protocols that define patient selection, the study regimen, efficacy assessment, and the management of adverse reactions; they are performed under highly controlled conditions. Clinical studies, however, cannot address all situations encountered by the medical community once a drug is approved for a particular indication. Thus, clinical judgment by the community-based physician is required for determining whether or not to prescribe a drug for a particular patient, for choosing which drug to use, and for managing adverse events. A recent symposium, held in conjunction with *ACG 2011, The American College of Gastroenterology's Annual Scientific Meeting and Postgraduate Course*, dealt with the pros and cons underlying controversies regarding the use of rifaximin in the treatment of hepatic encephalopathy and the management of anemia associated with the treatment of hepatitis C with peginterferon/ribavirin in combination with boceprevir or telaprevir. The symposium was presented in the form of a mock trial with Eugene R. Schiff, MD, serving as judge and Bruce R. Bacon, MD; Kimberly A. Brown, MD; Luis A. Balart, MD; and Vinod Rustgi, MD serving as expert witnesses. The audience served as the jury.

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## Overview of hepatic encephalopathy

Hepatic encephalopathy (HE) is characterized by varying degrees of neuropsychiatric impairment in patients with advanced liver disease after exclusion of other known brain disease.[1] Two forms of HE are recognized based on the nature and severity of clinical manifestations: Minimal HE (MHE) and overt HE (OHE).[2] MHE is thought to affect up to 60% of those with liver disease, while up to 45% of patients with cirrhosis and 50% of those with transjugular intrahepatic portosystemic shunts (TIPS) develop OHE.[3] A diagnosis of MHE has prognostic importance for the development of OHE, is associated with impaired driving skills, may affect employability due to cognitive and locomotive defects, and significantly diminishes quality of life (QOL).[4, 5, 6] The development of OHE portends a poor prognosis. A retrospective review of 111 patients followed for 12–17 months following the first episode of OHE found that 74% died during the follow-up period; the survival probability was 42% at 1 year and 23% at 3 years.[4] OHE can be diagnosed by clinical recognition of its distinctive neurologic features, by a knowledge that underlying cirrhosis is present, by exclusion of all other etiologies of neurologic and/or metabolic abnormalities, and by identification of precipitating factors.[7] The initial management of OHE involves recognition and treatment of the precipitating events and the initiation of measures to lower blood ammonia concentrations.[2] Controversy exists, however, as to whether initiating prophylactic therapy following an OHE episode will prolong the time to a recurrent episode. No consensus on diagnostic criteria or diagnostic testing has been established for MHE.[8] Controversy also exists as to whether patients with advanced liver disease should be tested for MHE and if therapy should be initiated in those with cognitive impairment.

While the etiology of HE is undoubtedly multifactorial, cerebral edema is a major contributing factor. The swelling is the result of an uptake of ammonia into astrocytes. Portal ammonia, derived from urease activity of colonic bacteria and the deamination of glutamine in the small bowel, is largely metabolized by the normal liver. Metabolism is compromised in the diseased liver, and increased arterial concentrations of ammonia result.[9] Drugs approved for the treatment of HE act by lowering blood ammonia concentration and include a nonabsorbable dissacharide (lactulose) and antibiotics (rifaximin and neomycin) (Table 1).[10] Metabolism of lactulose by the bacterial flora in the colon to lactic acid lowers the colonic pH and creates a hostile environment for bacteria involved in the production of $NH_3$. The reduction in colonic pH also favors the formation of the nonabsorbable $NH_4^+$ from $NH_3$, thus trapping $NH_3$ in the colon and effectively reducing plasma concentrations.[2] Rifaximin and neomycin reduce ammonia-producing enteric bacteria. Rifaximin, a minimally absorbed

oral antimicrobial agent, has broad-spectrum activity and a low risk of inducing bacterial resistance.[11] Neomycin is no longer considered a first-line therapy for HE because of its potential for adverse effects.[2]

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

**Table 1. Products currently marketed in the United States with an indication for the treatment of hepatic encephalopathy.[10]**

## Arguments in support of testing for and treating patients with MHE

Increasing evidence supports the argument that patients with cirrhosis should be tested for MHE and those with MHE should receive treatment. The goals of therapy include delaying progression to OHE, improving QOL, maintaining employment status, and preserving driving privileges.[12] The impact of MHE on health-related QOL (HRQOL) as determined by the Sickness Impact Profile (SIP) is illustrated in Figure 1.[13] The SIP questionnaire consists of 136 items grouped into 12 scales: sleep and rest, eating, work, home management, recreation and pastimes, ambulation, mobility, body care and movement, social interaction, alertness, emotional behavior, and communication. Scores (0 best to 100 worst) are computed based on patient responses. Both lactulose and rifaximin have been used to treat MHE. In a study of 61 patients diagnosed with MHE utilizing neuropsychometric (NP) testing (number and figure connection tests parts A and B, picture completion, and block design tests), the effect of lactulose (30–60 mL in 2 or 3 divided doses so that patient passed 2–3 semisoft stools/day; n=31) was compared with no treatment (n=30). The study duration was 3 months. Study results are summarized in Table 2. The mean number of abnormal NP tests decreased significantly in patients receiving lactulose (baseline, 2.74; after 3 months, 0.75; $P$=.0001) compared with no significant change in untreated patients (baseline, 2.47; after 3 months, 2.55; $P$=NS). Only 5 of 25 patients (20%) still met the criteria for a diagnosis of MHE following 3 months of lactulose therapy compared with 18 of 20 patients (90%) in the untreated group. One patient in the lactulose treatment group developed OHE; 2 patients in the untreated group developed OHE. The total SIP score improved in the lactulose-treated group, changing from 10.39 at baseline to 3.77 at the end of treatment. The total SIP score was unchanged in the untreated group over the 3-month interval (10.36 at baseline vs 10.39 at the end of 3 months). The difference at the end of

treatment in the total SIP score between the lactulose treated group and the untreated group was significant ($P$=.002). The authors concluded that both cognitive function and HRQOL improve in patients with MHE treated with lactulose therapy.[13]
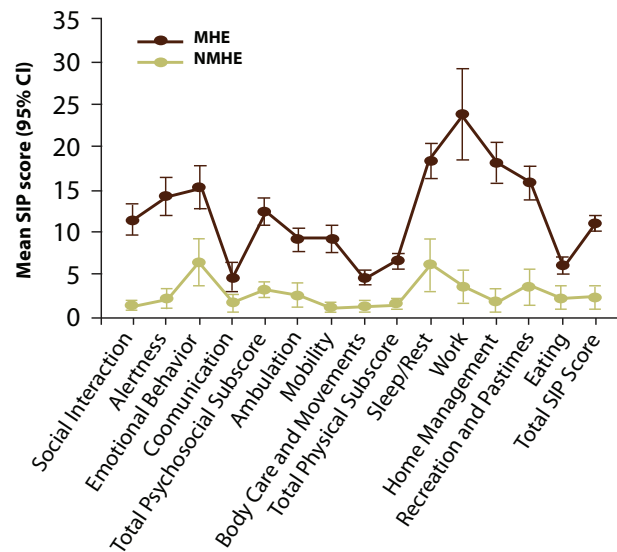


**Figure 1. Mean (95% Confidence Interval [CI]) Sickness Impact Profile (SIP) scores in cirrhotic patients with (MHE, n=61) and without (NMHE, n=29) MHE at baseline as determined by quantitative neuropsychometric testing. Differences were significant (P<.0001) for all scores except communication.[13]**

| | No Treatment | | Lactulose | |
|---|---|---|---|---|
| | Baseline (n=30) | 3 Months (n=20) | Baseline (n=31) | 3 Months (n=25) |
| Mean abnormal NP test results (no.) | 2.47 | 2.55 | 2.74 | 0.75 |
| Patients with MHE (no.) | 30 | 18 | 31 | 5 |
| Development of OHE | | 2 | | 1 |
| Mean total SIP score | 10.36 | 10.39 | 10.39 | 3.77 |

**Table 2. Effect of lactulose administered for 3 months compared with no treatment in patients diagnosed with MHE at baseline on NP test results, resolution of MHE, the development of OHE, and mean total SIP score.[13] NP, neuropsychometric; SIP, Sickness Impact Profile.**

Sidhu and colleagues studied the effect of treatment of MHE with rifaximin (1200 mg/day; n=49) compared with placebo (n=45) on NP test performance and HRQOL in cirrhotic patients. MHE was diagnosed utilizing NP tests (number and figure connection tests, picture completion, digit symbol, and block design tests) and HRQOL was assessed utilizing the SIP questionnaire. The results of the study are summarized in Table 3. A significant reduction in the mean number of abnormal NP tests occurred in the rifaximin group (2.35 at baseline vs 1.29 at the end of 2 weeks [$P$=.002] and 0.81 at the end of 8 weeks [$P$<.001]); no significant changes

over the same time periods occurred in the placebo group (2.31 at baseline vs 2.03 at the end of 2 weeks and 1.97 at the end of 8 weeks). MHE resolved in 57% of patients treated with rifaximin at the end of 2 weeks of therapy and in 75.5% at the end of 8 weeks of therapy; resolution of MHE was observed in only 18% of placebo patients at 2 weeks into the trial and in only 20% following 8 weeks of placebo. A significant improvement in HRQOL, as assessed by the SIP score, was observed in the rifaximin group at the end of 8 weeks (11.67 at baseline vs 6.45 at the end of 8 weeks; $P<.001$); the change in the SIP score in the placebo group was not significant (9.86 at baseline vs 8.51 at the end of 8 weeks; $P=.82$). The authors concluded that rifaximin is a safe and effective treatment for improving cognitive function and HRQOL in patients with MHE.[14]

| | Placebo (n=45) | Rifaximin (n=49) |
|---|---|---|
| **Mean abnormal NP tests (no.)** | | |
| Baseline | 2.31 | 2.35 |
| At 2 weeks | 2.03 | 1.29 ($P=0.002$) |
| At 8 weeks | 1.97 ($P>.05$) | 0.81 ($P<.001$) |
| **Reversal of MHE** | | |
| At 2 weeks | 18% | 57% |
| At 8 weeks | 20% | 75.5% |
| **Mean total SIP score** | | |
| Baseline | 9.86 | 11.67 |
| At 8 weeks | 8.51 ($P=.82$) | 6.45 ($P<.001$) |

**Table 3. Effect of rifaximin administered for 8 weeks compared with placebo in patients diagnosed with MHE on NP test results, reversal of MHE, and SIP Score.[14] NP, neuropsychometric; SIP, Sickness Impact Profile.**

A recent study by Bajaj et al utilized a driving simulator to evaluate the effect of rifaximin therapy vs placebo on driving performance in cirrhotic patients with MHE.[15] Patients who were current drivers were randomly assigned to placebo (n=21) or rifaximin (550 mg twice a day; n=21) and followed for 8 weeks. MHE was diagnosed utilizing NP testing (i.e., number connection tests A and B, digit symbol and block design test) as well as the computerized Inhibitory Control Test (ICT). Compared with the placebo group, the rifaximin group experienced a significantly greater decrease in total driving errors (rifaximin 76% vs placebo 33%; $P=.013$), a significantly greater decrease in speeding tickets (rifaximin 81% vs placebo 33%; $P=.005$), and a significantly greater decrease in illegal turns (rifaximin 62% vs placebo 19%; $P=.012$) at the end of the 8-week study. Although the reduction in collisions was greater in the rifaximin group (43%) than in the placebo group (33%), the difference was not statistically significant. The authors concluded that clinically relevant outcomes such as driving performance can

be observed with therapy for MHE using rifaximin.[15]
In summary, it was suggested that the evidence supports both testing patients with cirrhosis for MHE and treating those with MHE with lactulose and/or a nonabsorbable antibiotic such as rifaximin.

## Arguments against testing for and treating patients with MHE

The principal argument for not testing for and not treating patients with MHE is that no consensus on diagnostic criteria or diagnostic testing has been established for MHE.[8] Table 4 lists methods that have been utilized for detecting MHE as well as advantages and limitations for each method.[2] The original tests recommended for testing were the number connection tests A and B, the block design test, and the digit symbol test. Copies of the tests may be difficult to obtain, copyright issues may apply, and administering and interpreting the tests is time consuming. If possible, it may be advisable to have testing done in a psychology testing laboratory where the staff is experienced in administering the tests and interpreting the results.[7]
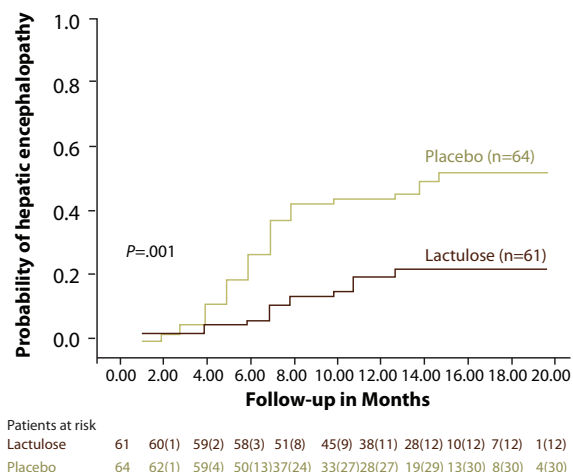
| Methods | Advantages | Limitations |
|---|---|---|
| Formal neuropsychological assessment | • Established and well-recognized clinical significance | • Expensive<br>• Time-consuming |
| Short neuropsychological batteries | • Easy to administer in office setting<br>• Inexpensive<br>• Rapid results<br>• High sensitivity for discerning MHE from other encephalopathies | • Test often copyrighted<br>• Limited access |
| Computerized tests (CFF, ICT, reaction times, etc) | • Easy to apply | • Limited data on diagnostic significance<br>• Require standardization |
| Neurophysiologic tests (EEG, spectral EEG, P300) | • Allows for objective repeat testing | • Equipment<br>• Limited data on diagnostic significance |

**Table 4. Advantages and limitations of diagnostic methods for detecting MHE. CFF, critical flicker frequency; ICT, inhibitory control test; P300, auditory event-related evoked potential; EEG, electroencephalography.[2]**

## Arguments in support of prophylactic therapy following an episode of OHE to prevent recurrent episodes

Drug therapy for MHE to prevent development of a first overt episode can be referred to as primary prophylaxis of HE while preventing recurrence of overt HE in patients who have had a previous episode of overt HE can be referred to as secondary prophylaxis.[16] Both lactulose and rifaximin have been utilized in the outpatient management of patients following an episode of OHE. The goals of therapy in this situation include prolonging the time until a recurrent episode of OHE and improving the daily functioning of patients with advanced cirrhosis.[17] Secondary prophylactic therapy is continued for an indefinite period of time or until liver transplant.

Sharma et al studied the effect of administration of lactulose (30–60 mL in 2 or 3 divided doses per day so that patients passed 2–3 semisoft stools per day; n=70) vs placebo (n=70) in patients after recovery from OHE.[16] Patients were randomized to either group within 1 week following recovery. Therapy with lactulose or placebo continued until the development of recurrent OHE or a minimum follow-up of 6 months. The median follow-up was 14 months (range, 1–20 months). Figure 2 illustrates graphically the probability of recurrent OHE over time in patients receiving lactulose compared with patients receiving placebo. Twelve (19.6%) of 61 patients in the lactulose group developed an episode of OHE; 30 (46.8%) of 64 patients in the placebo group developed OHE. Table 5 summarizes the precipitating factors of recurrent episodes of OHE and death in each group. Patients in the lactulose group remained adherent to therapy. Of 61 patients, 14 (23%) had diarrhea, 6 (10%) had abdominal bloating, and 8 (13%) disliked the taste of lactulose; the dose of lactulose was reduced but not stopped in these patients. Constipation was reported in 10 (16%) of the patients in the placebo group. The authors concluded that lactulose is effective for prevention of recurrence of OHE in patients with cirrhosis.[16]

Rifaximin has also been studied for the prevention of recurrent episodes of OHE in patients with hepatic cirrhosis who were in remission following a previous episode of OHE. In a randomized, double-blind, placebo-controlled trial, cirrhotic patients who were in remission from recurrent HE received either rifaximin (550 mg twice daily; 140 patients) or placebo (159 patients) for 6 months. The primary efficacy endpoint was the time to the first breakthrough episode of OHE; a secondary endpoint was the time to the first HE-related hospitalization. Lactulose therapy was permitted in both the placebo group and the rifaximin group, both prior to and during the study. In the placebo group, 91.2% were receiving lactulose at baseline, and in the rifaximin group, 91.4% were receiving lactulose at baseline. In the placebo group, 91.2% received lactulose during the study, and in the rifaximin group, 91.4% received lactulose during the study. Rifaximin significantly reduced the risk of an episode of OHE compared with placebo during the 6-month period (hazard ratio [HR] with rifaximin, 0.42; 95% CI, 0.38–0.64; $P<.001$); the risk of HE-related hospitalization compared with placebo was also reduced (HR with rifaximin, 0.50; 95% CI, 0.29–0.87; $P=.01$) (Figure 3, A and B). A breakthrough episode of HE occurred in 22.1% of rifaximin-treated patients compared with 45.9% of patients in the placebo group; 13.6% of rifaximin-treated patients had an HE-related hospitalization compared with 22.6% in the placebo group. Rifaximin treatment resulted in a 58% relative reduction in risk of a breakthrough episode of OHE compared with placebo and a 50% reduction in the risk of HE-related hospitalization compared with placebo over the 6-month study period.[18] The effect of treatment with rifaximin on HRQOL was assessed using the Chronic Liver Disease Questionnaire (CLDQ), which was administered every 4 weeks. Time-weighted averages for the overall CLDQ score and the scores for each domain were significantly higher in the rifaximin group than in the placebo group; time-weighted averages for patients who remained in remission were significantly higher than in patients who experienced HE breakthrough ($P$-values were <.0001). Differences in least square means of time-weighted average values for subjects in the rifaximin vs placebo groups are presented in Figure 4.[19] The incidence of adverse events during the study was similar for the rifaximin and placebo groups as was the incidence of serious adverse events. The authors concluded rifaximin maintained remission from HE more effectively than did placebo and reduced the risk of hospitalization. Rifaximin significantly improved HRQOL in patients with cirrhosis and recurrent HE.[18,19]



**Figure 2. Probability of recurrent OHE over time following an episode of OHE in cirrhotic patients receiving either lactulose or placebo.[16]**
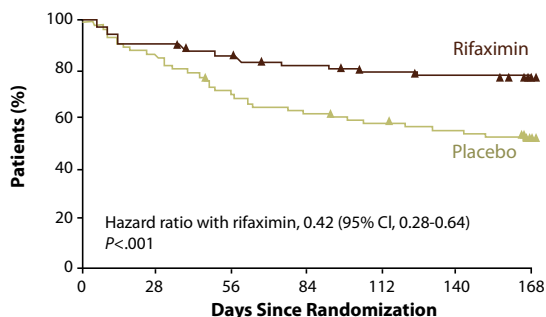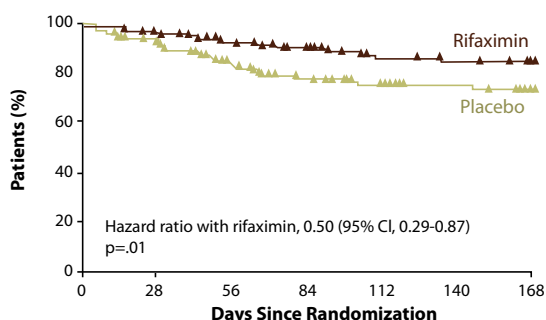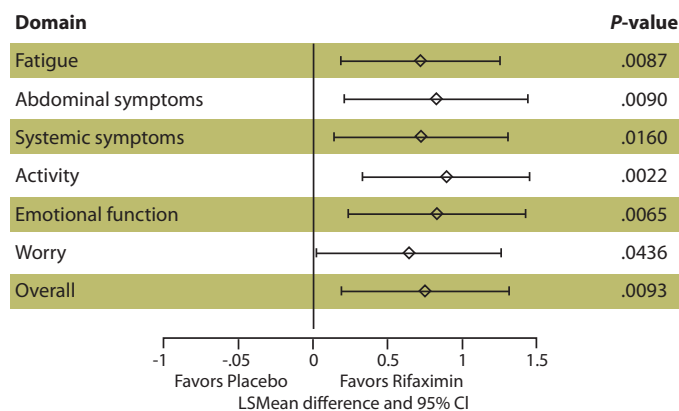
| | Lactulose | | Placebo | |
|---|---|---|---|---|
| **Precipitating Factors** | **Patients (no.)** | **Death** | **Patients (no.)** | **Death** |
| Variceal bleed | 3 | 1 | 4 | 2 |
| Spontaneous bacterial peritonitis | 3 | 1 | 9 | 3 |
| Urinary tract infection with sepsis | 2 | 2 | 3 | 1 |
| Constipation | 0 | 0 | 4 | 1 |
| Pneumonia with sepsis | 0 | 0 | 4 | 2 |
| Unknown | 4 | 1 | 6 | 2 |

**Table 5. Precipitating factors of OHE and mortality in patients with a prior episode of OHE receiving either lactulose of placebo. Median follow-up of 14 months (range, 1–20 months).[16]**

**A  Time to First Breakthrough HE Episode (Primary Endpoint)**



Hazard ratio with rifaximin, 0.42 (95% CI, 0.28-0.64)
$P<.001$

**B  Time to First HE-Related Hospitalization (Key Secondary Endpoint)**



Hazard ratio with rifaximin, 0.50 (95% CI, 0.29-0.87)
p=.01

**Figure 3. Kaplan-Meier estimates of the primary (time to a recurrent episode of OHE) and secondary (time to an HE-related hospitalization) endpoints for cirrhotic patients with recurrent HE treated with either rifaximin or placebo.**[18]

| Domain | | *P*-value |
|---|---|---|
| Fatigue | | .0087 |
| Abdominal symptoms | | .0090 |
| Systemic symptoms | | .0160 |
| Activity | | .0022 |
| Emotional function | | .0065 |
| Worry | | .0436 |
| Overall | | .0093 |

Favors Placebo    Favors Rifaximin
LSMean difference and 95% CI

**Figure 4. Chronic Liver Disease Questionnaire domain scores for rifaximin vs placebo. Differences in least square means of time weighted average scores and corresponding 95% Confidence Intervals for patients in the rifaximin vs placebo groups. *P*-values were calculated using an analysis of variance model.**[19]

In summary, it was suggested the evidence supports the use of combination therapy with lactulose and the nonabsorbable antibiotic rifaximin to prolong the time to recurrence of OHE. It was noted that ~90% of patients in the rifaximin study were receiving lactulose at baseline and during the study, and the improvement noted can be considered to be the beneficial effect of combination lactulose/rifaximin.

## Arguments supporting lactulose as the agent of choice for prophylactic therapy following an episode of OHE to prevent recurrent episodes

Lactulose is currently the mainstay of therapy for HE. In clinical studies, 70% to 80% of patients with HE have improved on lactulose treatment, and lactulose alone can prevent recurrent HE in selected patients.[2,20] The cost differential, with rifaximin being considerably more expensive than lactulose, also favors the use of lactulose monotherapy.[20] Data for rifaximin in the treatment of HE are limited. As noted previously, ~90% of patients in the registration trial in both the rifaximin and placebo arms were also receiving lactulose. Additional studies with rifaximin are needed to better evaluate rifaximin monotherapy, to further evaluate the possible development of resistance, and to evaluate long-term safety.[20] For patients with an inadequate response to lactulose, switching to rifaximin rather than adding rifaximin to lactulose may be preferable for a number of reasons. The concomitant use of 2 drugs increases cost and may increase the incidence of adverse effects. The registration trial for rifaximin, however, demonstrated that adding rifaximin to lactulose seems to maintain HE remission in a larger number of patients compared with lactulose monotherapy.[18]

## Overview of management of anemia associated with the treatment of hepatitis C

Anemia is a well-recognized adverse effect associated with peginterferon (PegIFN)/ribavirin (RBV) combination therapy for chronic hepatitis C. Anemia is, in part, the result of hemolysis secondary to RBV combined with the bone marrow suppressive effects of interferon. The median decline in hemoglobin during treatment with PegIFN/RBV is 2.5 g/dL; approximately 20% of patients have a decline of 4 g/dL or more. Especially problematic when treating hepatitis C virus (HCV) genotype 1 patients who develop anemia secondary to PegIFN/RBV therapy is that decreases in the dosage of either PegIFN or RBV are associated with decreases in the sustained viral response (SVR) rates. SVR rates are particularly sensitive to reductions in the dose of RBV. As a result, the use of the hematologic growth factor epoetin alfa became commonplace as a method of controlling anemia secondary to PegIFN/RBV therapy and decreased the need for RBV dose reduction.[21] The *2009 AASLD Practice Guidelines: Diagnosis, Management, and Treatment of Hepatitis C* concluded that, while epoetin alfa can improve a patient's sense of well-being and decrease the need for ribavirin dose reduction, its use has not been shown to improve SVR rates. In addition, while not specifically advising against the use of epoetin alfa, the guidelines

note that its use increases the cost of treatment and may be associated with serious side effects, including cardiovascular and thromboembolic events, pure red cell aplasia, progression of certain cancers, and death.[22]

Anemia is also a common adverse effect associated with the use of the oral HCV-protease inhibitors, boceprevir and telaprevir, both of which were recently introduced for use in combination with PegIFN/RBV for the treatment of genotype 1 HCV.[23,24] The addition of either boceprevir or telaprevir to PegIFN/RBV is associated with an additional decrease in hemoglobin concentrations over that seen with PegIFN/RBV. In boceprevir registration clinical trials, anemia occurred in 49% of patients treated with boceprevir/PegIFN/RBV compared with 29% of patients in the control PegIFN/RBV study arms.[25] With telaprevir registration clinical trials, anemia occurred in 36% of telaprevir/PegIFN/RBV-treated patients compared with 17% of patients in the control PegIFN/RBV arms of the studies.[26] Interestingly, in the boceprevir registration trials, dose modifications of PegIFN/RBV and/or erythropoiesis stimulating agents were permitted for the management of anemia. Among patients in boceprevir containing arms, 43% received erythropoiesis stimulating agents compared with 24% in the PegIFN/RBV study arms.[25] In contrast, the use of erythropoietin or other hematopoietic growth factors was prohibited in the telaprevir registration trials, and anemia was managed by RBV dose modification (i.e., reduction, interruption, or discontinuation). Among patients in telaprevir containing study arms, 32% underwent RBV dose modification compared with 12% in the PegIFN/RBV control arms.[26]

The most recent *2011 AASLD Practice Guideline–An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection: 2011 Practice Guideline by the American Association for the Study of Liver Diseases* recommends that patients who develop anemia on protease inhibitor/PegIFN/RBV therapy be managed by reducing the RBV dose. The Guideline concludes that the potential benefits of erythropoietin must be weighed against the fact that its use in HCV therapy is not approved, its potential side effects, and its cost.[28]
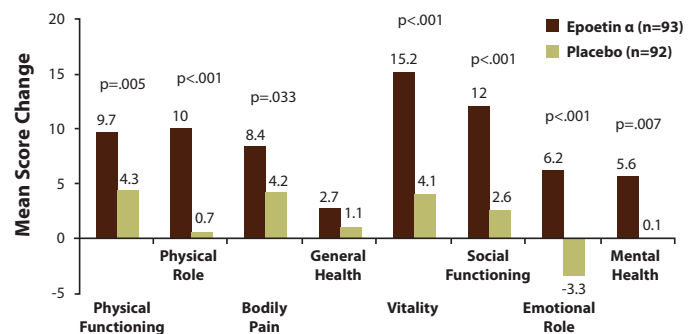
## Arguments in support of the use of epoetin alfa for treating anemia associated with the protease inhibitor/PegIFN/RBV therapy for HCV

A review of data presented in Table 6 suggests that the use of either RBV dosage modification or the administration of erythropoietin (boceprevir/PegIFN/RBV clinical trials) had several benefits not seen with RBV dosage modification alone (telaprevir/PegIFN/RBV clinical trials) for managing anemia. Hemoglobin levels fell below 8.5 g/dL in a greater percentage of

patients in the telaprevir trials (14%) than in the boceprevir trials (7%); a higher percentage of patients required blood transfusions in the telaprevir trials (6%) than in the boceprevir trials (3%).[25,26,27] It should be noted, however, that the trials were not head to head. Epoetin alfa has been used extensively for treating anemia associated with PegIFN/RBV combination therapy for hepatitis C. For example, a retrospective cohort study of data from 5706 patients from the National VA Hepatitis C Clinical Case Registry found that 1722 treated patients (30%) were at risk for RBV dosage reduction (i.e., hemoglobin concentration below 10 g/dL during treatment, or they received epoetin or darbepoetin during therapy); 1381 patients (24%) received erythrocyte growth factor for managing anemia during PegIFN/RBV treatment. Patients who received growth factors during treatment had higher mean adherence to antiviral therapy.[29] Most importantly, management of anemia with epoetin alfa improved HRQOL during treatment with PegIFN/RBV combination therapy. In a study by Afdhal and colleagues, significant improvements in HRQOL were demonstrated in all domains of the Medical Outcomes Survey Short Form-36 version 2 tool except the 'general health' domain (Figure 5).[30] RBV doses were maintained in 88% of the patients who received epoetin alfa vs 60% of those who received placebo (*P*<.001).[30]

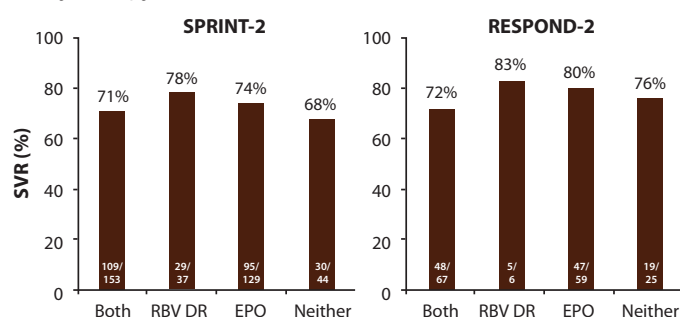| | Boceprevir/PegIFN/RBV (N=1548) | Telaprevir/PegIFN/RBV (N=1797) |
|---|---|---|
| Hemoglobin <10 g/dL | 49% | 36% |
| Hemoglobin <8.5 g/dL | 7% | 14% |
| RBV dose modification (reduction, interruption, or discontinuation) | 26% | 32% |
| Use of erythropoiesis stimulating agents | 43% | 1%* |
| Blood transfusion | 3% | 6% |

**Table 6. Observed hemoglobin values during therapy in boceprevir/PegIFN/RBV and telaprevir/PegIFN/RBV registration trials and management techniques utilized. Studies were not head to head. *According to study protocols, the use of erythropoietin or other hematopoietic growth factors was prohibited in the telaprevir registration trials.[25,26,27]**



**Figure 5. Health Related Quality of Life effect of treatment with epoetin alpha compared to placebo for management of anemia secondary to PegIFN/RBV therapy for HCV.[30]**

## Arguments against the use of epoetin alfa for treating anemia associated with the protease inhibitor/PegIFN/RBV therapy for HCV

While dose reduction of RBV was found to decrease SVR rates in patients treated with PegIFN/RBV combination therapy, an analysis of boceprevir/PegIFN/RBV registration trials found that SVR rates were similar regardless of how anemia was managed during treatment; the highest SVR rates were obtained when RBV dose reduction was the only management technique used (Figure 6).[31] As described above, anemia in boceprevir registration trials was managed by dose modifications of PegIFN/RBV and/or by erythropoiesis stimulating agents. Only dose modifications of PegIFN/RBV were used to manage anemia in telaprevir trials, so similar data do not exist for telaprevir registration trials. An additional concern with the use of epoetin alfa for the management of anemia secondary to treatment of HCV patients with protease inhibitor/PegIFN/RBV therapy is that epoetin has a black-box warning that it can increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis or vascular access, and tumor progression or recurrence.[32] Lastly, epoetin adds significant cost to an already costly therapy.[28]



Figure 6. SVR rates in patients with hemoglobin <10 g/dL during treatment with boceprevir/PegIFN/RBV according to management intervention.[31] Both, RBV dose reduction and epoetin alfa; RBV DR; RBV dose reduction only; EPO, epoetin only; neither, no intervention.

## Summary: Judge Schiff's rulings based on evidence from the expert witnesses and input from the jury (the audience)

Should patients with cirrhosis be tested for MHE, and should those with MHE receive treatment? The evidence suggests the following:

- We have no consensus on how best to diagnose MHE.
- Both lactulose and rifaximin are effective treatments once MHE is diagnosed.
- Treatment of MHE improves QOL and prolongs time to development of OHE.

Can we prolong the time to recurrence after recovery from an occurrence of OHE? Which prophylactic therapy is best? The evidence suggests the following:

- Prophylactic therapy prolongs the time to recurrence.
- Historically, lactulose has been used as a first-line therapy.
- Addition of rifaximin to lactulose is more effective than lactulose monotherapy (i.e., longer time to another occurrence of OHE and/or until hospitalization).
- Rifaximin monotherapy is most likely effective in those who cannot tolerate or who fail lactulose therapy.

Should RBV dose reduction be used to manage anemia with direct-acting antiviral (boceprevir or telaprevir) and PegIFN/RBV therapy? The evidence suggests the following:

- RBV dose reduction is an effective management technique.
- Boceprevir clinical studies found SVR rates were similar when anemia was treated with either dose reduction, epoetin alfa, or a combination of the two.
- Telaprevir clinical studies utilized only RBV dose reduction for managing anemia.
- Quality of life and adherence studies are needed.

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

1. **The principal argument that many use for *not* testing and treating patients with minimal hepatic encephalopathy (MHE) is:**
   *a*. No consensus on diagnostic criteria or diagnostic testing for MHE has been established
   *b*. It is best to wait for an episode of overt hepatic encephalopathy (OHE) before initiating therapy
   *c*. Treatment with lactulose of rifaximin has little effect on quality of life or cognitive function
   *d*. Side effects of current treatment options outweigh any treatment benefits

2. **A review of current agents used for the treatment of patients with MHE found:**
   *a*. Lactulose to be more effective than rifaximin in head-to-head studies
   *b*. Rifaximin to be more effective than lactulose in head-to-head studies
   *c*. Evidence supporting the treatment of those with MHE with either lactulose and/or rifaximin
   *d*. Neither lactulose nor rifaximin can be recommended for the treatment of MHE

3. **Arguments in support of the use of lactulose over rifaximin as the agent of choice for prophylactic therapy following an episode of OHE to prevent recurrence include all of the following *except*:**
   *a*. Lactulose is currently considered the mainstay of therapy for HE
   *b*. 70% to 80% of patients in clinical studies have improved on lactulose treatment
   *c*. Lactulose is less expensive than rifaximin
   *d*. Lactulose therapy is free of side effects

4. **Patients in the rifaximin registration trial for prophylactic therapy following an episode of OHE to prevent recurrence also received lactulose under which of the following conditions:**
   *a*. ~90% received lactulose prior to the trial and ~90% received lactulose during the trial
   *b*. ~90% received lactulose prior to the trial; none received lactulose during the trial
   *c*. None received lactulose prior to the trial; ~90% received lactulose during the trial
   *d*. None received lactulose prior to the trial; lactulose was permitted only in patients who developed an episode of OHE during the trial

5. **Anemia associated with treatment of HCV with boceprevir or telaprevir in combination with PegIFN/RBV:**
   *a*. Is due to hemolysis caused by PegIFN
   *b*. Is due to the bone marrow suppressive effect of RBV
   *c*. Occurs with a higher incidence when either boceprevir or telaprevir is added to PegIFN/RBV than the incidence seen with PegIFN/RBV combination therapy
   *d*. Is seldom problematic and seldom requires intervention

6. **For patients who develop anemia when treated with either boceprevir or telaprevir in combination with PegIFN/RBV, the *2011 AASLD Practice Guideline--an Update on Treatment of Genotype 1 Chronic Hepatitis C virus Infection: 2011 Practice Guideline* by the American Association for the Study of Liver Diseases recommends which of the following as the preferred intervention:**
   *a*. Dose reduction of the direct acting antiviral (boceprevir or telaprevir)
   *b*. Dose reduction of RBV
   *c*. Dose reduction of PegIFN
   *d*. Treatment of anemia with an erythropoietic stimulating agent (erythropoietin)

# Clinical Judgments in the Management of HE & HCV

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 |
|---|---|---|---|---|
| **Review current testing options for minimal hepatic encephalopathy (MHE) in patients with hepatic cirrhosis; compare the efficacy of lactulose and rifaximin in those who test positive for MHE and describe benefits of treatment** | | | | |
| *Knowledge* | ❑ | ❑ | ❑ | ❑ |
| *Competence* | ❑ | ❑ | ❑ | ❑ |
| *Performance* | ❑ | ❑ | ❑ | ❑ |
| *Patient Outcomes* | ❑ | ❑ | ❑ | ❑ |
| **Recognize the benefits of prophylactic treatment following an episode of overt hepatic encephalopathy (OHE) in patients with advanced liver disease; compare the efficacy of lactulose and rifaximin when used as prophylactic therapy following an OHE episode** | | | | |
| *Knowledge* | ❑ | ❑ | ❑ | ❑ |
| *Competence* | ❑ | ❑ | ❑ | ❑ |
| *Performance* | ❑ | ❑ | ❑ | ❑ |
| *Patient Outcomes* | ❑ | ❑ | ❑ | ❑ |
| **Assess use of ribavirin (RBV) dose reduction, administration of an erythropoietic stimulating agent, or a combination of RBV dose reduction and an erythropoietic stimulating agent in treating anemia secondary to the treatment of HCV with boceprevir or telaprevir in combination with pegylated interferon (PegIFN) and RBV; explain rationale for current treatment guidelines for anemia associated with treatment of HCV with direct acting antiviral agents/PegIFN/RBV** | | | | |
| *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  ❑ Interdisciplinary teams  ❑ System-based practice

  ❑ Practice-based learning and improvement  ❑ Professionalism  ❑ Utilize informatics

  ❑ Interpersonal and communication skills  ❑ Quality improvement  ❑ None of the above

  ❑ Employ evidence-based practice  ❑ Medical knowledge

- 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.

# Clinical Judgments in the Management of HE & HCV

|  | 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 ....... | ❑ | ❑ | ❑ | ❑ | ❑ |

• 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
_____
_____

# Clinical Judgments in the Management of HE & HCV

**If you wish to receive acknowledgement of participation for this activity please complete this posttest, evaluation form, and request for credit (pages 9-12) and fax to 973-867-3684**

*Please do not use abbreviations.*
*We need current and <u>complete</u> 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:                –          –

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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 *1.0 AMA PRA Category 1 Credit(s)*™.
Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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

☐ I participated in only part of the activity and claim _____ credits