Clinical Roundtable Monograph

The Treatment of Hepatic Encephalopathy in the Cirrhotic Patient

Discussants

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Abstract

Cirrhosis of the liver is a rising epidemic in the United States, affecting 2 out of every 1,000 adults. It is responsible for the deaths of more than 27,000 people each year. The primary diseases that underlie cirrhosis include viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease. Monitoring the extent of fibrosis and aggressively treating the underlying disease is essential for maintaining quality of life and preventing the complications of cirrhosis. As patients progress toward end-stage liver disease, the most common complications include portal hypertension, the development of esophageal varices, and hepatic encephalopathy. Esophageal varices can lead to hemorrhaging, a dangerous complication that is fatal in 30–50% of patients during the first occurrence. Hepatic encephalopathy is another serious complication of end-stage liver disease, as it significantly reduces patient quality of life and places heavy economic and caregiving burdens upon the patient's family. In this clinical roundtable monograph, the latest advances in the monitoring of liver disease and the management of portal hypertension and hepatic encephalopathy are discussed.

Target Audience: This activity has been designed to meet the educational needs of gastroenterologists involved in the management of patients with cirrhosis of the liver.

Statement of Need/Program Overview: About 2 of every 1,000 adults in the United States have cirrhosis of the liver. The primary diseases that underlie cirrhosis include viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease. As patients progress toward end-stage liver disease, the most common complications include portal hypertension, esophageal varices, and hepatic encephalopathy (HE), which is characterized by personality changes, intellectual impairment, and a depressed level of consciousness. Subtle signs of HE are observed in nearly 70% of patients with cirrhosis. Debilitating symptoms are observed in 24–53% of patients who undergo portosystemic shunt surgery. Approximately 30% of patients dying of end-stage liver disease experience significant HE, approaching coma. New pharmacokinetic data may illuminate strategies for management of this life-threatening condition. This clinical roundtable monograph will examine the latest advances in the monitoring of liver disease and discuss the management of portal hypertension and HE.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Outline challenges in the detection and treatment of cirrhosis.
2. Discuss the potential complications of cirrhosis, including hepatic encephalopathy (HE), esophageal varices, and hepatocellular carcinoma.
3. Summarize the best options for long-term maintenance of patients with end-stage liver disease.
4. Review the latest data on the use of rifaximin, lactulose, benzodiazepine receptor antagonists, and L-ornithine-L-aspartate as treatment options in patients with HE.

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Arun J. Sanyal, MD—Grant/Research Support: Salix, Gilead, Roche. Consultant/Advisory Board: Takeda.
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Current Issues in the Epidemic of Liver Disease

Arun J. Sanyal, MD

Cirrhosis of the liver affects about 2 out of every 1,000 adults in North America.[1] It is the twelfth leading cause of mortality in the United States and is responsible for more than 27,000 deaths each year.[2] The principle diseases that lead to the development of cirrhosis include viral hepatitis, alcoholic liver disease, and nonalcoholic fatty liver disease (NAFLD).

Chronic viral hepatitis B and C are very common in the United States. About 1.2 million Americans are living with chronic hepatitis B, and 3.2 million are living with chronic hepatitis C.[3] Most of these individuals are unaware of their underlying liver disease because the disease is clinically silent and remains so until it becomes fairly advanced.

NAFLD encompasses a spectrum of disease states ranging from simple steatosis to nonalcoholic steatohepatitis to cirrhosis. About 15% of patients with nonalcoholic steatohepatitis will progress to cirrhosis within 15–20 years.[4] NAFLD is closely linked to obesity, insulin resistance, hypertension, coronary artery disease, diabetes, and hypertriglyceridemia.[5] Population studies have estimated that the prevalence of NAFLD in Europe, Japan, and the United States is approximately 14–25%.[6-8]

Alcoholic liver disease mirrors NAFLD but occurs as the result of excessive alcohol consumption over time. Nearly all long-term heavy drinkers develop steatosis. Of these, about 10–35% will develop steatohepatitis, and about 8–20% will progress to cirrhosis.[9] Alcohol is also a cofactor in the progression of liver disease related to viral hepatitis.[10,11]

The Importance of Maximizing Liver Function in End-stage Liver Disease

There is a tremendous impetus to identify chronic liver disease long before it becomes cirrhosis. Indeed, the quality of life for patients with end-stage liver disease is quite poor. In the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatment (SUPPORT), one-third of the 575 patients with end-stage liver disease with cirrhosis reported that their pain was at least moderately severe most of the time.[12] This high burden of pain is comparable to that seen in patients with lung and colon cancer. Beyond poor quality of life, there is a tremendous economic burden associated with end-stage liver disease. A 1997 study found that mean inpatient hospital charges for patients admitted for complications from end-stage liver disease varied from about $31,000 for patients receiving treatment for esophageal varices to $110,000 for patients who died from various complications of end-stage liver disease.[13]

Liver transplantation is, of course, the only treatment for end-stage liver disease that has any effect on patient survival. Yet, the total number of liver transplants in the United States has remained relatively flat over the last several years at about 6,000 annually, despite the fact that the demand for transplant continues to grow.[14] While prioritizing patients via the Model for End-stage Liver Disease (MELD) score has improved the process of providing organs to those who are most sick, there is still a great lack of organs. One way to fill the gap has been living donor liver transplantation, but a more effective option would probably be to change the legislation such that the default would be consent for organ donation, unless the deceased person had specified that he or she did not wish to be a donor.

Monitoring Liver Fibrosis and Function

A high priority must be placed on monitoring the extent of liver fibrosis and function in patients with a chronic liver disease. The gold standard for this purpose has historically been percutaneous liver biopsy.[15] Unfortunately, liver biopsies are associated with a considerable amount of sampling variability. For example, Skripenova and colleagues obtained paired liver biopsy specimens from the right and left hepatic lobes of 60 patients with chronic hepatitis C.[16] When scored, there was a difference of 1 grade or 1 stage in 30% of the paired samples. These data are not unexpected considering that an assessment of the entire liver is made based upon a sample that is typically between 1–2 cm in length.

Because of these inaccuracies and because liver biopsy is an invasive procedure, there has been great interest in the development of noninvasive methods to evaluate liver fibrosis and to stage liver disease. These indirect methods attempt to utilize readily available clinical serum test results, such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, platelet count, and international normalized ratio. In 2001, Pohl and colleagues[17] demonstrated that in patients with chronic hepatitis C virus without a history of alcohol abuse, an AST/ALT ratio of at least 1 in combination with a platelet count of less than 150,000/mm^{3} identified severe fibrosis or cirrhosis with a positive predictive value (PPV) of 93.1% and a negative predictive value (NPV) of 85.0%. These laboratory parameters did not predict liver fibrosis stage in patients with an AST/ALT ratio of less than 1 or platelet counts greater than 150,000/mm^{3}, or in alcoholic patients.

Several algorithms were later developed in order to increase the predictive value of the laboratory values. These

include the AST/ALT ratio,[18] age-platelet index,[19] cirrhosis discriminant score,[20] Pohl score,[21] and AST-to-platelet ratio index (APRI).[22] Of these indirect tests, APRI has the strongest track record. In one study by Lackner and colleagues, an APRI of 1.5 or greater had a PPV of 83% to 91% for significant fibrosis, whereas an APRI of less than 2.0 had an NPV of 91% for cirrhosis.[23]

Recently, several noninvasive tests have been developed that combine traditional serum markers with novel biomarkers. One of these is FibroSURE (known as *FibroTest* outside of the United States). The FibroSURE fibrosis index includes α2-macroglobulin (A2M), apolipoprotein A1, haptoglobin, total bilirubin, and γ-glutamyl transpeptidase; the necrotico-inflammatory activity index combines the same 5 markers, plus ALT. FibroSURE has been validated for alcoholic liver disease, non–alcoholic liver disease, hepatitis C, and hepatitis B, with NPV of about 85–90% and a PPV of about 60–70% for significant fibrosis.[24-27] A second test is FibroIndex, a calculation based upon platelet count, AST, and gamma globulin levels. In patients with chronic hepatitis C, FibroIndex is reported to have a PPV of 87% and a specificity of 94% at the 1.25 threshold, and a PPV of 94% and a specificity of 97% at the 2.25 threshold.[28] Other reports, however, have found FibroIndex to have less diagnostic power than FibroSURE or aspartate aminotransferase to platelet ratio index (APRI).[29] The FibroMeter algorithm incorporates platelets, prothrombin index, AST, alpha-2-macroglobulin, hyaluronate, urea, and age; it has been shown to have similar diagnostic power as the FibroIndex.[30]

The use of hyaluronic acid as a biomarker is another recent and promising addition to the armamentarium of noninvasive predictive tests. Zhang and colleagues[31] analyzed laboratory data and liver biopsy results from 137 patients with chronic hepatitis B and found that an APRI of at least 1.5 in combination with a hyaluronic acid level of greater than 300 ng/mL could detect moderate to severe fibrosis with a PPV of 93.7% and a specificity of 98.9%. Mild fibrosis, however, could not be detected by an APRI of less than 1.5 in combination with any hyaluronic acid cutoff level. Similarly, McHutchison and colleagues evaluated hyaluronic acid serum concentrations in 486 hepatitis C virus–infected patients, of whom 78 (16%) had cirrhosis.[32] In this cohort, hyaluronic acid levels of less than 60 µ/L excluded cirrhosis and extensive fibrosis, with NPVs of 99% and 93%, respectively, whereas values greater than 110 µ/L had a PPV of 44% for cirrhosis.

On the imaging side, transient elastography has been validated as a good marker of fibrosis in patients with viral hepatitis. In one study, Ziol and colleagues compared the fibrosis scores determined via liver biopsy with those predicted by transient elastography in 327 patients with chronic hepatitis C.[33] A FibroScan score cutoff of 8.80 kPa had a PPV of 88% and an NPV of 56% for a Metavir fibrosis score of 2 or greater; a score cutoff of 9.60 kPA had a PPV of 71% and an NPV of 93% for a fibrosis score of 3 or greater; and a score cutoff of 14.60 kPa had a PPV of 78% and an NPV of 97% for a fibrosis score of 4.

The value of transient elastography for patients with nonalcoholic steatohepatitis has been more controversial. One Japanese study of 97 patients with NAFLD reported excellent results with FibroScan in the nonalcoholic steatohepatitis population, finding that the area under the receiver operating characteristic curve of FibroScan was 0.927 for a fibrosis score of 1 or greater; 0.865 for a fibrosis score of 2 or greater; 0.904 for a fibrosis score of 3 or greater; and 0.991 for a fibrosis score of 4 or greater.[34] Yet, a large study by Castéra and colleagues of 13,369 transient elastography patient examinations concluded that unreliable examinations (<10 valid shots) and examination failure (no valid shots) occur about 19% of the time.[35] Examination failure and unreliable examinations were most strongly associated with body mass index greater than 30 kg/m^2 and operator experience of fewer than 500 examinations. These results emphasize the need for adequate operator training and for technological improvements to be made for use in the obese patient population.

All of these noninvasive markers share some common problems. They are all generally good at identifying patients who have no or minimal fibrosis as well as those who have advanced fibrosis; however, they are less useful for predicting the intermediate stages of fibrosis or for monitoring changes in fibrosis. The bottom line is that because these tests have not been robustly validated for monitoring changes in patients' degree of fibrosis, liver biopsy is still relied upon as the gold standard at this time. It is my belief that with the increasing interest in and development of noninvasive tests for liver fibrosis, we can be very optimistic about their standalone value in the future.

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Managing Portal Hypertension

Kevin D. Mullen, MD

Esophageal varices are seen in 40% and 60% of compensated and decompensated cirrhotic patients, respectively, when cirrhosis is diagnosed. In cirrhotic patients without varices, the incidence of new varices is about 5% per year.[1] Regular monitoring of patients with cirrhosis for the development of varices is critical, because the prognosis is extremely poor for patients who experience a variceal hemorrhage, with 30–50% of patients dying within 6 weeks of the first major bleed. Among those who survive the first hemorrhage, 47–84% show recurrent bleeding, and 70% die within the first year.[2]

Varices and ascites are likely to develop when the hepatic venous pressure gradient increases above 10 mm Hg, and variceal bleeding may occur when it rises above 12 mm Hg.[3] Earlier this decade, it was thought that ß-blockers would be useful for the prevention of the development of varices in cirrhotic patients; however, a large 2005 study showed that ß-blockers offered no benefit over placebo and were associated with significantly more serious adverse events.[4] ß-Blocker therapy also did not produce any significant differences in the rates of ascites, encephalopathy,

liver transplantation, or death between the treatment and placebo groups. It was concluded that ß-blockers are ineffective in preventing varices in patients with cirrhosis and portal hypertension and should be avoided for this purpose. The only true preventive strategy that we currently have is to prevent the progression of cirrhosis, through abstinence from alcohol for patients with alcoholic liver disease, antiviral therapy for patients with viral cirrhosis, and weight loss for patients with NAFLD.

Prevention of Primary Variceal Hemorrhage

ß-Blocker therapy does have value for the prevention of primary variceal hemorrhage in patients with cirrhosis who already have varices. A pivotal study by Merkel and colleagues showed that patients with small varices treated with nadolol had a significantly slower progression to large varices (11% at 3 years) than patients who were randomized to placebo (37% at 3 years).[5] Of note, although progression was slowed in the treatment group, there was no significant difference in survival between the groups. Based on these data, the cur-

rent American Association for the Study of Liver Diseases (AASLD) and the American College of Gastroenterology (ACG) practice guidelines recommend that cirrhotic patients with small varices that have not bled but who have the risk factors of either a Child-Pugh classification of B/C or the presence of red wale marks should be treated with nonselective ß-blockers.[6] For patients with compensated cirrhosis and small varices but no risk factors for bleeding, the recommendation is that they can be treated with ß-blockers, with the knowledge that the long-term benefit has not been demonstrated. If the physician or patient refuses treatment with ß-blockers, then upper endoscopy should be performed every 2 years to monitor the progression of the varices. If the patient's cirrhosis becomes decompensated, the upper endoscopy should be performed annually.[6]

ß-Blocker therapy for the prevention of first variceal bleed in patients with medium or large varices is also supported by a strong body of evidence. Chen and colleagues conducted a meta-analysis of 11 trials evaluating nonselective ß-blockers versus non-active treatment or placebo in the prevention of first variceal hemorrhage.[7] Among the 1,189 patients with large- or medium-sized varices, the risk of first variceal bleeding was significantly lower in the ß-blocker group when compared with controls (14% vs 30%; $P<.05$), as was mortality. The authors noted that 1 bleeding episode was avoided for every 10 patients treated with ß-blockers.

A second option for patients with medium or large varices is endoscopic variceal ligation (EVL), also known as *endoscopic band ligation*. A meta-analysis of 8 trials comprising 596 patients with large varices demonstrated that EVL reduced the rate of first variceal bleed by 43% when compared with ß-blocker therapy (relative risk [RR], 0.57; 95% confidence interval [CI], 0.38–0.85; $P=.0067$).[8] In contrast, a more recent trial not included in the above meta-analysis concluded that prophylactic EVL and propranolol were similarly effective for primary prophylaxis of variceal bleeding (22% vs 24%; $P=.68$), with similar overall mortality (28% vs 24%; $P=.49$).[9] Based on these data, the AASLD/ACG guidelines recommend that patients with medium or large varices that have not bled but have a high risk of hemorrhage be treated either with nonselective ß-blockers or EVL. Patients with medium or large varices that have not bled and are not at the highest risk of hemorrhage should be treated with ß-blockers as a first-line approach. Patients with contraindications, intolerance, or non-compliance to ß-blocker therapy should then be treated with EVL.[6]

Prevention of Secondary Variceal Hemorrhage

Patients who survive an episode of acute variceal hemorrhage have a very high risk of a secondary hemorrhage. The median rebleeding rate in untreated individuals is about 60% within 2 years of the primary hemorrhage, with a mor-

tality rate of 33%.[10] Therefore, patients should be started on therapy as soon as possible after recovering from the primary hemorrhage in order to prevent recurrence. A certain percentage of patients will have required shunt surgery or transjugular intrahepatic portosystemic shunt (TIPS) to control the acute episode, and these patients do not require further preventive measures. For the remainder of patients, the current treatment guidelines recommend a combination of EVL plus ß-blocker therapy. A very recent meta-analysis from Ravipati and colleagues further confirms this recommendation.[11] The investigators analyzed data from 25 clinical trials comprising 2,159 patients in which EVL, ß-blocker therapy, or a combination of both were compared for the prevention of secondary variceal hemorrhage. Combination therapy was found to significantly reduce the incidence of all rebleeding (RR, 0.623; 95% CI, 0.523–0.741; $P<.001$) and variceal rebleeding (RR, 0.601; 95% CI, 0.440–0.820; $P<.001$) when compared with either treatment alone. However, combination therapy did not reduce all-cause mortality or mortality caused by rebleeding more than monotherapy.

Sclerotherapy is no longer recommended for use in the secondary prophylaxis of variceal hemorrhage, as meta-analysis data indicate that EVL is superior in terms of reducing the risk of rebleeding and is associated with significantly fewer adverse events.[12]

Portosystemic Shunting in the Management of Portal Hypertension

Although TIPS is not used as a first-line treatment option in the management of portal hypertension, it does have proven clinical efficacy as salvage therapy during an acute variceal hemorrhage. In one study, 52 patients admitted to the hospital for an acute variceal hemorrhage who had an hepatic venous pressure gradient of at least 20 mm Hg were randomized to receive either TIPS within the first 24 hours of admission or standard care.[13] Those patients who did not receive TIPS had more treatment failures (50% vs 12%; $P=.0001$), greater transfusional requirements ($P=.002$), higher need for intensive care (16% vs 3%; $P<.05$), and worse actuarial probability of survival than did those who received TIPS. Because confirmation of these data is needed in larger, more comprehensive clinical trials, the current recommendation is to perform TIPS only in patients whose acute bleeding cannot be controlled by standard treatments, but future studies will shed more light on the issue.

Two meta-analyses have found that although rebleeding was significantly less frequent with TIPS than it was with EVL or ß-blocker therapy, post-treatment encephalopathy occurred significantly more often after TIPS, and there was no difference in mortality between the groups.[14-15] Therefore, TIPS should not be used as a preventive treatment, but as a rescue therapy for patients who have failed pharmacological plus endoscopic treatment.[6]

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Managing Hepatic Encephalopathy

Nathan M. Bass, MD, PhD

Hepatic encephalopathy (HE) is a neuropsychiatric disorder seen in patients with chronic liver disease that results from the accumulation of toxins in the bloodstream. HE can vary in its clinical presentation. Patients with cirrhosis can present in an acute confusional state that can evolve into coma, which is known as *acute encephalopathy*. Acute encephalopathy in patients with liver disease is most commonly associated with a precipitating factor that triggers the change in mental state. Other presentations may include recurrent episodes of an altered mental state that may occur in the absence of precipitating factors, called *recurrent encephalopathy*. In some cases, neurological deficits may not completely reverse between episodes, which is known as *persistent encephalopathy*. The most frequent neurological disturbance—minimal or subclinical encephalopathy—is not evident on clinical examination; these mild cognitive abnormalities are only recognizable with psychometric or neurophysiologic tests. It has been estimated that about 80% of patients with cirrhosis have minimal HE.[1] It should be noted that the definition and clinical implications of a diagnosis of minimal encephalopathy are still the subjects of much debate.

The severity of HE or an HE episode is often staged using the West Haven criteria of altered mental state.[2] Screening for mental changes in early HE can be somewhat difficult. Mathematical calculations are one way for the physician to evaluate the patient's mental ability, such as asking the patient to serially subtract 7 from 100 (100, 93, 86, etc). Asterixis can also be detected at stage 1. Yet, it is often family members who first alert the physician to changes in the patient's mental state. These changes may manifest as mild confusion, depression, anxiety, or euphoria. A very typical manifestation of early HE is sleep inversion, whereby patients have difficulty sleeping during the night but are able to take naps during the daytime. Another important but often overlooked area in which patients with minimal HE are affected is their ability to drive safely. There is recent evidence that about 50–60% of patients with either minimal HE or stage 1 HE are not fit to drive, which is raising many important questions.[3] Clinicians should be aware of this issue.

As HE progresses, particularly in the transition from stage 1 to stage 2, patients lose insight into their own HE episodes. At stage 2, patients are often brought to the emergency department or are hospitalized. Upon examination, the patient is noticeably confused and disoriented, and asterixis is obvious. Measurement of venous ammonia blood levels may be helpful in the initial evaluation when there is doubt about the presence of significant liver disease. Automated electroencephalogram analysis and critical flicker frequency testing are very promising diagnostic modalities, although they have not yet been validated or brought into widespread clinical use.

Medical Treatment of HE

The first therapeutic intervention for patients experiencing an acute episode of HE is to identify any reversible

precipitating causes and treat them. Common precipitating factors include constipation, infection, hypokalemia, gastrointestinal bleeding, increased protein intake, sedatives, and tranquilizers. HE is caused by reversible factors in more than 80% of patients.[4]

Lactulose and rifaximin are the usual treatments for HE. The use of antibiotics such as neomycin, metronidazole, and nitazoxanide is less common.

Lactulose

The nondigestible disaccharide lactulose is the first-line pharmacologic treatment for HE. It acts to reduce the level of nitrogen-containing compounds in the gut. The most recent ACG guidelines for the treatment of HE acknowledge that current standards of evidence-based medicine are not met by the published clinical studies in favor of lactulose treatment.[2] Als-Nielsen and colleagues conducted a systemic review of the available studies of lactulose in 2004.[5] Compared with placebo or no intervention, lactulose reduced the risk of no improvement of hepatic encephalopathy (RR, 0.62; 95% CI, 0.46–0.84 [6 trials]) but had no statistically significant effect on mortality (RR, 0.41; 95% CI, 0.02–8.68 [4 trials]). However, when only the 2 trials of high methodological quality were analyzed, there was no significant effect of lactulose on the risk of no improvement (RR, 0.92; 95% CI, 0.42–2.04). A 2007 study by Prasad and colleagues showed that lactulose does improve cognitive function and health-related quality of life among patients with cirrhosis who have minimal HE.[6] A recent study by Sharma and colleagues reported that lactulose is effective for the prevention of HE recurrence.[7] In their study, 140 cirrhotic patients who recovered from an acute episode of HE were randomized to receive lactulose or placebo and were followed for a median time of 14 months. An overt episode of HE developed during follow-up in 20% of the lactulose group and 47% of the placebo group (P=.001), but it should be kept in mind that the study was open label. Based on these data, lactulose remains a front-line therapy for patients with HE, although further studies of high methodological quality would be desirable.

Rifaximin

Rifaximin, an oral nonsystemic antibiotic with less than 0.4% absorption, is another pharmacological option for the treatment of HE. In March 2010, the US Food and Drug Administration (FDA) approved the use of rifaximin 550 mg tablets for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients 18 years of age or older. (The use of the 200-mg dose had previously been approved for the treatment of traveler's diarrhea caused by non-invasive strains of *Escherichia coli*.) Rifaximin has been used as a single-agent and in combination with lactulose to treat HE, and data suggest it may fulfill a therapeutic gap for patients who do not respond to lactulose alone.

My colleagues and I recently published the results of a large, randomized, placebo-controlled trial of rifaximin for the prevention of recurrent episodes of overt HE.[8] The study enrolled 299 patients with cirrhosis and a history of at least 2 episodes of HE (Conn score of at least 2) during the 6 months preceding enrollment. Patients were randomized to receive either rifaximin 550 mg twice daily (n=140) or placebo (n=159). Lactulose use was permitted in this trial; 91% of patients were taking lactulose at baseline and continued to do so during the trial. The primary endpoint was a breakthrough overt HE episode, and the secondary endpoint was HE-related hospitalization. The risk of breakthrough was reduced by 58% in the rifaximin group compared with the placebo group. The risk of HE-related hospitalization was reduced by 50% in the rifaximin group compared with the placebo group. Rifaximin was well-tolerated in this study, with no greater incidence of serious adverse events when compared with placebo. We then conducted an open-label maintenance study that enrolled 70 patients from the rifaximin group, 82 patients from the placebo group, and 115 new cirrhotic patients with a history of at least 1 episode of HE (Conn score of ≥2) within 12 months of screening.[9] Patients received rifaximin 550 mg twice daily; 75% of the patients were taking concomitant lactulose and continued to do so during the study. After 6 months, patients who crossed over to rifaximin or continued with rifaximin after the original randomized study had a significantly reduced risk of HE breakthrough when compared with patients who had received placebo in the original randomized study but did not continue on to rifaximin maintenance treatment (crossover hazard ratio [HR], 0.30; 95% CI, 0.17–0.55; P<.0001; continuing HR, 0.08; 95% CI, 0.04–0.15; P<.0001).

In a 2008 study by Mantry and colleagues, rifaximin added to lactulose significantly reduced the number of hospitalizations and reduced the length of hospital stay.[10] Study subjects received rifaximin 400 to 1,200 mg/day plus lactulose for a mean of 14 months after receiving lactulose monotherapy for a mean of 21 months (n=65) or received lactulose monotherapy for a mean of 24 months (n=58). In the rifaximin plus lactulose cohort, mean hospitalizations per patient were 0.26 versus 0.95 among the patients who received lactulose alone (odds ratio, 0.13; P<.001).

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Question and Answer Forum

How can the quality of liver biopsy samples be improved in order to increase the accuracy of the results?

Dr. Arun Sanyal At our center, we use a biopsy gun with a tri-axial cannula needle system, which we have found gives us a 3-cm sample to work with. One other advantage of this system is that trainees find it much easier to use.

Dr. Kevin Mullen A difficulty can arise when the only option is to conduct a transjugular biopsy, which we often use because of coagulopathies, massive ascites, or, in some cases, morbid obesity. The samples obtained in this way are often small, which can increase the error rate in the fibrosis score. Also, the extent of scar tissue in the liver can be overestimated easily from a biopsy obtained through the transjugular route because of fibrous septa located in the region of the hepatic vein. These disadvantages can be overcome in many cases by using 18-gauge or larger Tru-Cut biopsy needles and by obtaining more than 1 core.

Do you prefer to treat cirrhotic patients with medium or large esophageal varices that have not bled but have a high risk of hemorrhage with ß-blockers or EVL?

KM When I see very high-risk varices on a screening upper endoscopy, I nearly always will go ahead and treat with EVL rather than wait for the first bleed. I think some of the concern about doing pre-bleeding EVL is that the ligation process itself can cause a certain amount of bleeding, but I have rarely seen that.

AS We usually go with ß-blockers, but we do go straight to EVL when the varices are very large, particularly if they have red wale markings on them. Another case in which I would prefer EVL over ß-blockers is for the patient with severe liver failure who already has borderline-low blood pressure. This patient is less likely to be able to tolerate ß-blockers and would benefit more from EVL.

Dr. Nathan Bass The clinical literature is very clear that EVL and ß-blockers produce equal outcomes in this patient population. One argument in favor of ß-blockers may be their cost-effectiveness, but overall, the outcomes with EVL and ß-blockers are quite comparable, and therefore, it is quite reasonable in a high-risk patient to go ahead and do EVL right off the bat.

Do you see a future role for rifaximin in the treatment of patients with milder forms of encephalopathy who were enrolled in the randomized, placebo-controlled trial?

NB That is a key question. The FDA has now approved the use of rifaximin 550 mg tablets for reduction in risk of overt hepatic encephalopathy (HE) recurrence in patients 18 years of age or older. Should rifaximin be administered to patients who have persistent stage 1 HE, for example, or even minimal HE? I do believe that studies will eventually be done in these patient populations, mainly because of the lack of adverse events seen with rifaximin in the large, placebo-controlled trial we conducted. Lactulose is associated with a number of moderate adverse events that many patients are unable to tolerate over the long-term, such as flatulence, abdominal pain and cramping, and diarrhea. Rifaximin, on the other hand, was well-tolerated in the study. Interestingly, in a study by Leevy and colleagues in which patients with a history of HE were treated with lactulose for 6 months and then switched to rifaximin for 6 months, the authors found that patients were far more compliant with rifaximin than they were with lactulose.[1] Whether because of increased compliance, or whether because of truly superior efficacy, the patients had significantly fewer hospitalizations, and hospitalizations of shorter duration, during the rifaximin phase than they did during the lactulose phase. Thus, when rifaximin gets into clinical use, there will likely be a strong push for efficacy and safety studies to be conducted to address the question of treating or preventing the milder forms of encephalopathy.

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Slide Library

Principle Diseases That Lead to the Development of Cirrhosis

- Viral hepatitis
- Alcoholic liver disease
- Nonalcoholic fatty liver disease

Noninvasive Methods to Evaluate Liver Fibrosis and to Stage Liver Disease

- AST
- ALT
- Platelet count
- International normalized ratio

AST=aspartate aminotransferase; ALT=alanine aminotransferase.

Algorithms to Increase the Predictive Value of Laboratory Tests

- AST/ALT ratio
- Age-platelet index
- Cirrhosis discriminant score
- Pohl score
- APRI

APRI=aspartate aminotransferase-to-platelet ratio index.

Strategies to Prevent the Progression of Cirrhosis

- Abstinence from alcohol for patients with alcoholic liver disease
- Antiviral therapy for patients with viral cirrhosis
- Weight loss for patients with nonalcoholic fatty liver disease

West Haven Criteria of Altered Mental State

Stage 0	Lack of detectable changes in personality or behavior. Asterixis absent.
Stage 1	Trivial lack of awareness. Shortened attention span. Impaired addition or subtraction. Hypersomnia, insomnia, or inversion of sleep pattern. Euphoria or depression. Asterixis can be detected.
Stage 2	Lethargy or apathy. Disorientation. Inappropriate behavior. Slurred speech. Obvious asterixis.
Stage 3	Gross disorientation. Bizarre behavior. Semistupor to stupor. Asterixis generally absent.
Stage 4	Coma.

Data from Ferenci P, et al. Hepatology 2002;35:716-721.

Common Precipitating Factors of Hepatic Encephalopathy

- Constipation
- Infection
- Hypokalemia
- Gastrointestinal bleeding
- Increased protein intake
- Sedatives
- Tranquilizers

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The Treatment of Hepatic Encephalopathy in the Cirrhotic Patient

CME Post-Test: *Circle the correct answer for each question below.*

1. In the study by Skripenova and colleagues in which paired liver biopsy specimens were scored and compared, there was a difference of 1 grade or 1 stage in __ of the paired samples.

   a. 10%
   b. 20%
   c. 30%
   d. 40%

2. Which of the following noninvasive tests demonstrated the best diagnostic accuracy for significant fibrosis in the study by Lackner and colleagues?

   a. APRI
   b. AST/ALT ratio
   c. cirrhosis discriminant score
   d. Pohl score

3. Which of the following is associated with unreliable transient elastography examinations?

   a. patient fibrosis score of 3 or greater
   b. patient body mass index of 30 kg/m^2 or higher
   c. patient fibrosis score of less than 3
   d. type of clinic (teaching hospital, community hospital, etc)

4. What is the only measure currently available to prevent patients with cirrhosis and no esophageal varices from developing varices?

   a. ß-blocker therapy
   b. transjugular intrahepatic portosystemic shunting (TIPS)
   c. endoscopic variceal ligation (EVL)
   d. slow the progression of underlying liver disease

5. The long-term benefits of ß-blocker therapy for the prevention of variceal hemorrhage have been demonstrated by clinical trial data in which of the following patient populations?

   a. cirrhotic patients with small varices with red wale markings
   b. cirrhotic patients with medium to large varices
   c. cirrhotic patients with a Child-Pugh classification of B/C and small varices
   d. all of the above

6. At which of the following West Haven criteria stages for HE is asterixis first present?

   a. stage 0
   b. stage 1
   c. stage 2
   d. stage 3

7. TIPS should be avoided for the prophylaxis of secondary variceal hemorrhage because:

   a. rebleeding is more frequent with TIPS than with EVL or ß-blocker therapy
   b. mortality is more frequent with TIPS than with EVL or ß-blocker therapy
   c. post-treatment encephalopathy occurs significantly more often after TIPS than after EVL or ß-blocker therapy
   d. all of the above

8. In a recent open-label study by Sharma and colleagues of lactulose for the prevention of HE recurrence, __ of the lactulose group and __ of the placebo group (P=.001) experienced HE breakthrough over the 14-month follow-up.

   a. 20%, 47%
   b. 27%, 40%
   c. 30%, 47%
   d. 47%, 53%

9. In the large, placebo-controlled trial of rifaximin for the prevention of HE recurrence, the risk of breakthrough was reduced by __ in the rifaximin group compared with the placebo group (P<.0001).

   a. 33%
   b. 45%
   c. 58%
   d. 72%

10. True or False? A recent randomized study by Strauss and colleagues showed that neomycin was not superior to placebo for the treatment of acute HE.

    a. True
    b. False

Evaluation Form The Treatment of Hepatic Encephalopathy in the Cirrhotic Patient

PIM is committed to excellence in continuing education, and your opinions are critical to us in this effort. 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. **You must complete this evaluation form to receive acknowledgment for completing this activity.**

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree

Learning Objectives
After participating in this activity, I am now better able to:

1. Outline challenges in the detection and treatment of cirrhosis. — 1 2 3 4 5
2. Discuss the potential complications of cirrhosis, including hepatic encephalopathy (HE), esophageal varices, and hepatocellular carcinoma. — 1 2 3 4 5
3. Summarize the best options for long-term maintenance of patients with end-stage liver disease. — 1 2 3 4 5
4. Review the latest data on the use of rifaximin, lactulose, benzodiazepine receptor antagonists, and L-ornithine-L-aspartate as treatment options in patients with HE. — 1 2 3 4 5

Based upon your participation in this activity, choose the statement(s) that apply:
❒ I gained new strategies/skills/information that I can apply to my area of practice.
❒ I plan to implement new strategies/skills/information into my practice.

What strategies/changes do you plan to implement into your practice? _____
_____

What barriers do you see to making a change in your practice? _____
_____

Which of the following best describes the impact of this activity on your performance?
❒ I will implement the information in my area of practice.
❒ I need more information before I can change my practice behavior.
❒ This activity will not change my practice, as my current practice is consistent with the information presented.
❒ This activity will not change my practice, as I do not agree with the information presented.

Please rate your level of agreement by circling the appropriate rating:
1 = Strongly Disagree   2 = Disagree   3 = Neutral   4 = Agree   5 = Strongly Agree
The content presented:
Enhanced my current knowledge base — 1 2 3 4 5
Addressed my most pressing questions — 1 2 3 4 5
Promoted improvements or quality in health care — 1 2 3 4 5
Was scientifically rigorous and evidence-based — 1 2 3 4 5
Avoided commercial bias or influence — 1 2 3 4 5

Would you be willing to participate in a post-activity follow-up survey?   ❒ Yes   ❒ No

Please list any topics you would like to see addressed in future educational activities: _____
_____

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Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

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