

# Diagnosis of Cirrhosis and Evaluation of Hepatic Encephalopathy: Common Errors and Their Significance for the PCP

Steven L. Flamm, MD

## CONTINUING MEDICAL EDUCATION

### LEARNING OBJECTIVES

1. Identify strategies to improve early detection of liver cirrhosis and its complications
2. Describe the evidence linking alterations in the human microbiome with liver disease and complications such as hepatic encephalopathy
3. Describe results of preliminary investigations showing improved health outcomes in patients with liver cirrhosis managed with treatments intended to restore the gut microbiome

### FACULTY DISCLOSURE STATEMENT

The Illinois Academy of Family Physicians adheres to the conflict of interest policy of the ACCME and the AMA. It is the policy of Illinois AFP to ensure balance, independence, objectivity, and scientific rigor in all its educational activities. All individuals in a position to control the content in our programs are expected to disclose any relationships they may have with commercial companies whose products or Services may be mentioned so that participants may evaluate the objectivity of the presentations. In addition, any discussion of off-label, experimental, or investigational use of drugs or devices will be disclosed

by the faculty. Only those participants who have no conflict of interest or who agree to an identified resolution process prior to their participation were involved in the CME activity.

### FACULTY DISCLOSURES

Dr. Flamm discloses that he is on the advisory board and speakers' bureau for Salix Pharmaceuticals.

Gregory Scott, PharmD, RPh, editorial support and Michael Hanak, MD, CME reviewer disclosed no relevant financial relationship or interest with a proprietary entity producing, marketing, reselling or distributing health care goods or services.

This program does not include any discussion or demonstration of any pharmaceuticals or medical devices that are not approved by the Food and Drug Administration (FDA) or that are considered "off-label."

### SPONSORSHIP

This educational activity is sponsored by the Illinois Academy of Family Physicians and Primary Care Education Consortium.

### SUPPORTER

This activity is supported by an educational grant from Valeant Pharmaceuticals

### ACCREDITATION

The Illinois Academy of Family Physicians (IAFP)/Family Practice Education Network (FPEN) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

### CREDIT DESIGNATION

AMA PRA Category 1 - The Illinois Academy of Family Physicians/Family Practice Education Network designates this enduring material for a maximum of 1.00 AMA PRA Category 1 credit™.

### METHOD OF PARTICIPATION

To receive CME credit, please read the journal article and on completion, **go to [www.pceconsortium.org/liver](http://www.pceconsortium.org/liver) to complete the online evaluation and receive your certificate of completion.**

Release Date: 1 April 2017  
Expiration Date: 31 March 2018

**Steven L. Flamm, MD**, Chief, Liver Transplantation Program, Professor of Medicine, Northwestern Feinberg School of Medicine, Chicago, IL

### DISCLOSURES

Dr. Flamm discloses that he is on the advisory board and speakers' bureau for Salix Pharmaceuticals, Inc.

### SUPPORT

This educational activity is sponsored by the Illinois Academy of Family Physicians and Primary Care Education Consortium and supported by an educational grant from Valeant Pharmaceuticals.

## CIRRHOSIS – EPIDEMIOLOGY AND UNDERRECOGNITION

Cirrhosis has become the focus of greater attention in recent years largely because of the increasing prevalence of 2 of its most common causes: chronic viral hepatitis and steatohepatitis (a subset of nonalcoholic fatty liver disease [NAFLD]).<sup>1</sup> Cirrhosis is the result of progressive destruction and regeneration of the liver parenchyma due to chronic liver disease (CLD). Cirrhosis may be more common than previously thought, with an estimated prevalence of 0.27% in adults in the United States, according to data from the National Health

and Nutrition Examination Survey (NHANES).<sup>2</sup> The 2-year mortality rate is estimated to be 26.4%.<sup>2</sup> Surprisingly, 69% of adults with cirrhosis assessed in NHANES reported they were unaware of having liver disease, highlighting the possibility of many undiagnosed cases of cirrhosis.

One of the largest risk groups for CLD are people with NAFLD, which afflicts approximately 30% to 40% of the population and is projected to become the single most common indication for liver transplantation in the United States over the next 2 decades.<sup>3,4</sup> However, the results of a 2013 survey suggest that the importance of NAFLD appears to be under-recognized among primary care providers (PCPs).<sup>3</sup> The survey results showed that less than half of PCPs screened patients with diabetes and obesity for NAFLD and only one-quarter of PCPs referred patients with NAFLD to a hepatologist for evaluation.

This underdiagnosis of cirrhosis may be compounded by the use of liver function enzyme blood tests as the basis for current strategies to identify liver disease in the general population, even though they are nonspecific markers of liver injury and may be normal in patients with significant liver disease.<sup>5</sup> One study of 504 patients with risk factors for cirrhosis showed that 72% of patients with elevated liver stiffness (ie, diminished elastic property of liver tissue), 60% (12 of 20) with liver fibrosis on biopsy, and 91% (10 of 11) diagnosed with cirrhosis had a normal alanine aminotransferase (ALT).<sup>5</sup>

In addition, the general absence of symptoms in early stages of liver disease often delays diagnosis.<sup>5</sup> Compensated cirrhosis is defined by the development of clinically evident complications of liver disease (eg, esophageal varices, ascites, jaundice, spontaneous bacterial peritonitis, hepatic encephalopathy, portal hypertension, hepatocellular carcinoma). Patients with compensated cirrhosis do not have symptoms related to their cirrhosis and are often not recognized until these complications manifest. At that point, median survival for decompensated cirrhosis is reduced drastically (<2 years vs >12 years for compensated cirrhosis).<sup>6,7</sup>

Because PCPs are the first medical contact for the majority of patients, they can play a key role in identifying patients who are at risk for, or who have symptoms due to, CLD. They can also collaborate with the specialist in managing and preventing cirrhosis-related complications, such as screening for hepatocellular carcinoma, which is vital, as early detection is associated with a high rate of cure.

### CLINICAL PEARLS FOR DETECTING CIRRHOSIS

The clinical presentation of patients with cirrhosis, even those with severe disease, is often asymptomatic, with a completely normal or only mildly abnormal liver panel. Moreover, patients can have cirrhosis and feel well early in the course of the disease, although their quality of life may be affected.

When patients become symptomatic, it is often too late to reverse the clinical course. For these reasons and to facilitate early intervention, PCPs are encouraged to identify patients at risk for cirrhosis and to be vigilant for subtle signs and symptoms so that a diagnosis can be made before the development of serious complications, such as hepatocellular carcinoma or esophageal and gastric varices.<sup>1</sup> Subtle signs and symptoms include abdominal swelling, elevated ALT or aspartate aminotransferase (AST)/ALT ratio, platelet count <150,000/L, elevated alkaline phosphatase, bilirubin >1.1 mg/dL, serum albumin <2.5 g/dL, and prothrombin time <100%.

Risk factors for cirrhosis in the patient's medical history merit attention. These include body mass index (BMI), presence of diabetes mellitus or hyperlipidemia, other autoimmune disease, family history of liver disease, sexual orientation, history of intravenous drug abuse (even in the remote past), history of blood transfusion in the remote past, and history of significant alcohol use (even in the past).

Measurement of the serum ammonia level is generally to be avoided, since it is rarely helpful for diagnosis or assessment of treatment response. Thrombocytopenia (platelet count <150 x 10<sup>9</sup>/L) is often an incidental finding on routine laboratory testing, but it is often indicative of portal hypertension and cirrhosis, even in the absence of an abnormal liver panel.<sup>8</sup> In a study of 223 patients with low platelets, liver disease was the cause in 92 (42%), including 19 with no or mild abnormalities in the liver panel.<sup>8</sup> Elevation of serum prothrombin time or International Normalized Ratio (INR) may indicate hypoalbuminemia or a decreased ability of the liver to synthesize clotting factors. However, these are uncommon findings in compensated cirrhosis.

Given the high disease burden of NAFLD in patients with metabolic syndrome or diabetes, obtaining a random ALT and AST in these patients may be reasonable, since up to 80% of patients with nonalcoholic steatohepatitis (NASH; the subset of NAFLD patients most likely to develop cirrhosis or hepatocellular carcinoma) may be identified based on elevated transaminases.<sup>4</sup> Alkaline phosphatase and/or gamma-glutamyltransferase may be mildly elevated, but bilirubin typically remains normal unless advanced disease is present. It is important to keep in mind that normal liver function tests (LFTs) do not rule out cirrhosis.

Other patients in whom CLD should be suspected despite a normal liver panel are those with "CLD stigmata" (ie, vascular spiders, palmar erythema, and muscle wasting).<sup>7</sup> A palpable left liver lobe, hepatomegaly, and splenomegaly may also be suggestive of cirrhosis.

Liver biopsy is the gold standard for diagnosing and staging liver fibrosis but has several limitations: invasiveness, cost, poor patient acceptance, and risk of complications.<sup>7</sup>

**TABLE Clinical description of hepatic encephalopathy based on West Haven Criteria<sup>13</sup>**

WHC including MHE	ISHEN	Description
Unimpaired		No encephalopathy at all, no history of hepatic encephalopathy
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change
Grade I		Trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction, altered sleep rhythm
Grade II	Overt	Lethargy or apathy, disorientation for time, obvious personality change, inappropriate behavior, dyspraxia, asterixis
Grade III		Somnolence to semi-stupor, responsiveness to stimuli, confusion, gross disorientation, bizarre behavior
Grade IV		Coma

**Abbreviations:** ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; MHE, minimal hepatic encephalopathy; WHC, West Haven Criteria.

**Adapted from:** Vilstrup H, Amodio P, Bajaj J, et al. *Hepatology*. 2014;60(2):715-735, p. 719, Table 2.

Several noninvasive imaging and laboratory-based tests for diagnosis and staging of fibrosis have been developed, including elastography techniques, which measure mechanical property (stiffness) of liver. Ultrasound, computed tomography, and magnetic resonance imaging have been applied with varying degrees of success.<sup>7</sup> Fibrosis can also be detected using noninvasive scoring systems that utilize different combination of serum surrogate markers for liver disease, eg, Fibrosis-4 (FIB-4) index, AST-to-platelet ratio index (APRI), and the BMI, AST/ALT ratio, diabetes (BARD) score.<sup>9</sup>

Patients diagnosed with cirrhosis should undergo liver cancer screening semiannually with liver imaging using ultrasound.<sup>10</sup> In addition, endoscopy should be performed. If moderate to large varices are present, a non-cardioselective beta-blocker is indicated to prevent variceal bleeding; the patient also should be instructed to avoid aspirin and non-steroidal anti-inflammatory drugs.<sup>11</sup> Protein intake generally is limited to 1 g/kg of body weight.

### DETECTING HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is a common and major complication of cirrhosis that impacts quality of life, increases the risk of accidents, and is associated with significant morbidity and mortality.<sup>12</sup> Hepatic encephalopathy encompasses a spectrum of cognitive and motor abnormalities that range from minimal deficits, detected only with psychometric or neuropsychological tests and possibly subtle personality changes reported by caregivers (covert HE [CHE]), to progressively greater disturbances in cognition and motor dysfunction (overt HE [OHE]), to coma (**TABLE**).<sup>13</sup>

The neuronal dysfunction of HE is due to hyperammonemia, which is a consequence of impaired metabolic

capacity of the urea cycle in the liver and intra- and extra-hepatic portosystemic shunting of blood related to portal hypertension.<sup>14,15</sup>

The number of hospitalizations associated with a diagnosis of HE has increased approximately 10% annually, with more than 610,000 hospital discharges for patients with HE in 2014.<sup>16</sup> In one study, an estimated 50% of cirrhotic patients had underlying CHE, and 30% developed an episode of OHE over 13 months.<sup>17</sup> Once OHE occurs, patients have a 40% risk for recurrence within 1 year despite standard treatment with lactulose.<sup>13</sup> OHE is associated with diminished survival (40%-50% at 1 year and approximately 20% at 3 years).<sup>14,18,19</sup>

Symptoms of HE, graded by the West Haven Criteria (WHC), are relatively nonspecific (**TABLE**), making a definitive diagnosis of HE challenging. Consequently, HE remains a diagnosis of exclusion.<sup>20</sup> The patient history should focus on changes in cognition, behavior, sleep patterns, work performance, and driving performance. A caregiver may be able to provide history to assist a PCP in detecting changes. A physical examination should evaluate patients for the presence of stigmata of cirrhosis and asterixis. Other causes of encephalopathy should be excluded (eg, electrolyte disturbances, hypoglycemia, uremia, sepsis, thyroid dysfunction). Obtaining ammonia levels is generally not recommended, given the limited utility of a single value in the diagnosis of HE and the nonspecificity of elevated ammonia levels for HE.<sup>14</sup>

PCPs play an important role in identifying the condition because they will often see the patients when HE is in its early stages, and its neuropsychiatric manifestations are subtle. As PCPs are also likely to see patients more frequently and over a longer span of time than specialists, they are more likely to recognize these subtle changes.<sup>21</sup>

Given the poor prognosis associated with the development of OHE, prompt detection, workup, and referral are vital to allow for early initiation of appropriate management (FIGURE).<sup>18</sup> The most important step in the management of HE is identification and treatment of precipitating factors (eg, infections, gastrointestinal [GI] bleeding, overdiuresis, vomiting/diarrhea, electrolyte disorder, constipation).<sup>20</sup> Medications used to treat HE are primarily directed at reducing serum ammonia levels.

## GUT MICROBIOME IMPLICATIONS FOR THE TREATMENT OF HEPATIC ENCEPHALOPATHY

The pharmacologic basis for some of the treatments for HE is supported by a growing body of evidence regarding the interactions between the gut microbiome and its human host. The human microbiome is the collective genome (ie, genetic material) of the more than a thousand microorganisms living in association with the human body, the vast majority of which reside in the distal gut.<sup>22,23</sup> This ecological system interacts with internal and external factors to help maintain overall health of the individual.<sup>24</sup> Much of our current knowledge in this area comes from the Human Microbiome Project and Human Gut Microbiome Initiative—programs focused on identifying and characterizing gut microorganisms found in healthy and diseased humans.<sup>22,23</sup>

In selected conditions, including inflammatory bowel diseases, NAFLD, obesity, type 2 diabetes mellitus, and cirrhosis, changes in the composition of the gut microbiota and proinflammatory activities are thought to contribute to disease pathophysiology.<sup>22</sup> The altered gut microbiota (dysbiosis) associated with cirrhosis contributes to hyperammonemia and a systemic pro-inflammatory milieu that can potentiate neuroinflammation, brain edema, and neuronal dysfunction.<sup>25</sup> With the progression of cirrhosis, it is hypothesized that the hyperammonemia and the pro-inflammatory potentiation occur via the relative reduction in autochthonous (indigenous) commensal organisms and the increase in microbes such as *Enterobacteriaceae* and *Streptococaceae*, which can produce endotoxin and ammonia through their urease activity, respectively.<sup>25</sup> While knowledge is evolving regarding various other mechanisms that may contribute to dysbiosis and its functional consequences for liver disease, our current understanding helps inform treatment approaches for hepatic encephalopathy.<sup>26</sup>

## TREATMENT OPTIONS FOR HEPATIC ENCEPHALOPATHY

### Probiotics

Probiotics are live, nonpathogenic microbiologic dietary supplements that alter the intestinal microflora environment. A

2016 meta-analysis of probiotics for management of CHE or OHE included 14 trials and 1152 patients.<sup>27</sup> Probiotics had no impact on the overall mortality compared to either lactulose or no treatment/placebo. When probiotics were compared to no treatment/placebo, they were associated with significant improvement in minimal HE (MHE) (odds ratio [OR], 3.91; 95% confidence interval [CI], 2.25-6.80;  $P<.00001$ ), decreased hospitalization rates (OR, 0.53; 95% CI, 0.33-0.86;  $P=.01$ ) and decreased progression to OHE (OR, 0.40; 95% CI, 0.26-0.60;  $P<.0001$ ). Compared to lactulose, however, probiotics did not show a significant difference in any of these outcomes.

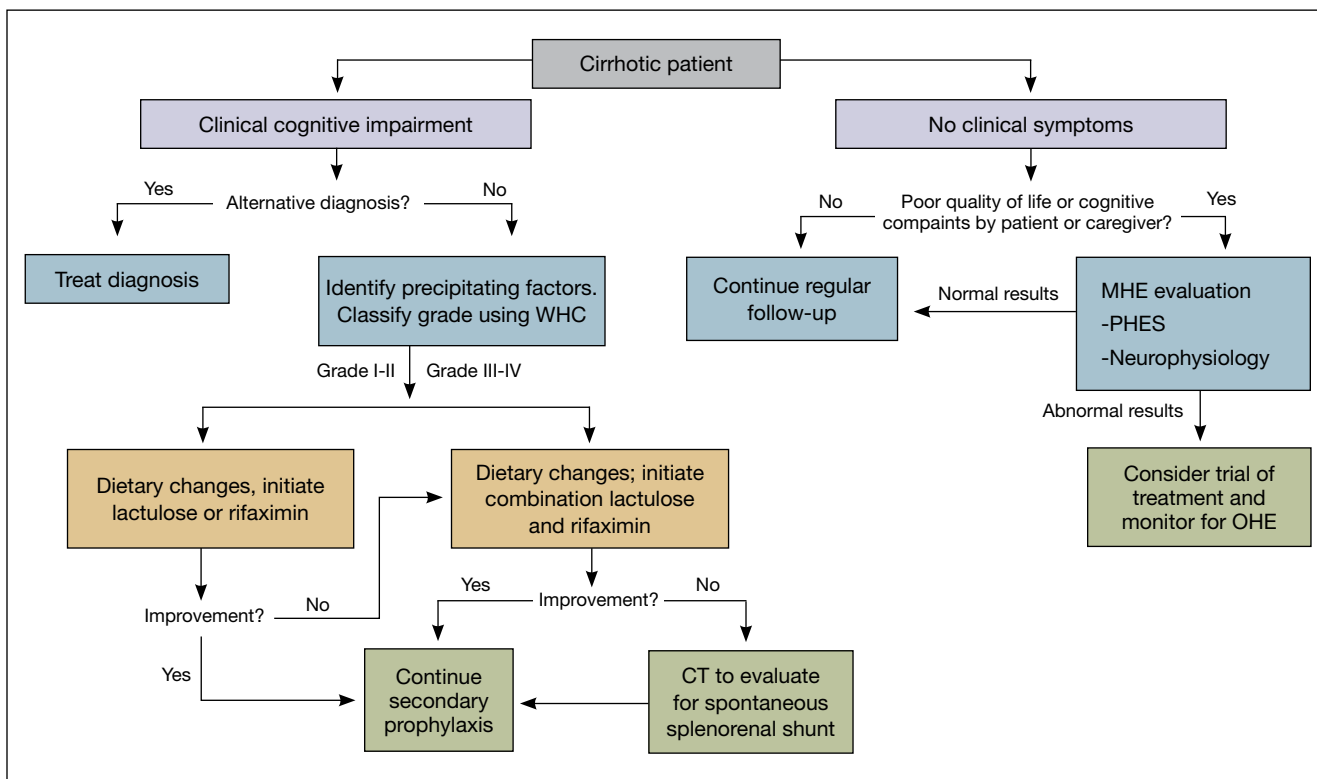
Although the mechanisms of HE improvement remain somewhat uncertain, probiotics may act by decreasing colonization by pathogenic bacteria, blocking epithelial attachment, decreasing the production and absorption of ammonia, and altering gut permeability.<sup>28</sup>

A 2011 Cochrane review of probiotics for patients with HE included 7 trials and 550 patients.<sup>29</sup> Compared to no treatment, probiotics were associated with reduced plasma ammonia levels but no significant differences in all-cause mortality, recovery from HE, adverse events, quality of life, or change of/withdrawal from treatment. Compared to lactulose, probiotics were associated with no differences in lack of recovery, adverse events, change of/withdrawal from treatment, plasma ammonia concentration, or change in plasma ammonia concentration.<sup>29</sup> For these reasons and because of the wide variability in the content of probiotics, probiotics are not currently recommended as treatment for HE.

### DIETARY MODIFICATION

Protein calorie malnutrition is a common occurrence in patients with HE and is associated with poor prognosis.<sup>18</sup> Contributors include frequent body fluid removal via paracentesis, anemia from GI bleeding, and low-protein diets (previously recommended based on the presumption that they led to reduced ammonia production).<sup>14,18</sup>

Maintaining adequate protein intake is essential to prevent muscle wasting, as skeletal muscle is the next largest site of ammonia metabolism after the liver.<sup>18</sup> For patients with HE, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) recommends that the daily energy intake should be 35 to 40 kcal/kg ideal body weight with daily protein intake of 1.2 to 1.5 g/kg ideal body weight.<sup>30</sup> Meals should be small and evenly distributed during the day, with a late-night snack of complex carbohydrates to help minimize protein utilization. Patients should be encouraged to adhere to diets rich in vegetable and dairy protein. Branched-chain amino acid supplements may be of value in patients intolerant of dairy protein. Increasing dietary fiber may also be beneficial.<sup>30</sup>

**FIGURE** Evaluation and management of hepatic encephalopathy<sup>18</sup>

**Abbreviations:** CT, computed tomography; MHE, minimal hepatic encephalopathy; OHE, overt hepatic encephalopathy; PHES, Psychometric Hepatic Encephalopathy Score; WHC, West Haven Criteria.

**Adapted from:** Suraweera D, Sundaram V, Saab S. *Gut Liver*. 2016;10(4):509-519 under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>).

## LACTULOSE

Nonabsorbable disaccharides, primarily lactulose, have been the mainstay of treatment for HE.<sup>13</sup> Lactulose is degraded by microbiota in the colon to short-chain organic acids, resulting in an acidic environment and an osmotic gradient in the intestinal lumen.<sup>17</sup> The acidic environment is thought to reduce ammonia-producing bacteria and to convert ammonia to nonabsorbable ammonium. The laxative effect results in intestinal cleansing via removal of excess fecal nitrogen.<sup>17</sup>

Lactulose is usually initiated with an oral dose of 30 mL to 45 mL every 1 to 2 hours to produce at least 2 soft bowel movements per day; it is then titrated to a goal of 2 to 3 soft bowel movements a day.<sup>31</sup> Common adverse events of lactulose include flatulence, abdominal discomfort, and diarrhea.<sup>17</sup>

Lactulose has demonstrated variable efficacy in trials (mostly small and underpowered) of patients with HE, but a recent Cochrane review including 38 trials and 1828 patients determined that nonabsorbable disaccharides may be associated with beneficial effects on clinically relevant outcomes compared to placebo/no intervention.<sup>32</sup> These effects

included mortality (relative risk [RR], 0.59; 95% CI 0.40-0.87) and reduction of serious complications associated with the underlying liver disease (liver failure, hepatorenal syndrome, and variceal bleeding; RR, 0.47; 95% CI, 0.36-0.60).<sup>32</sup>

## ANTIBIOTICS

The rationale for using antibiotics for cirrhosis is to diminish deaminating enteric bacteria, thus decreasing the production and absorption of ammonia and endotoxins.<sup>33</sup> Neomycin and metronidazole have been used for the treatment of OHE, but limited efficacy and adverse events limit their use.<sup>13</sup> Rifaximin is another antibiotic approved by the US Food and Drug Administration for reducing the risk of OHE recurrence in adults. Rifaximin is a poorly absorbed oral antibiotic with a broad spectrum of activity against Gram-positive and Gram-negative bacteria and anaerobic enteric bacteria that inhibits bacterial protein synthesis.<sup>33</sup> The 2014 guidelines issued by the American Association for the Study of Liver Diseases/European Association for the Study of the Liver recommend the addition of rifaximin for



prevention of OHE recurrence in patients who have experienced  $\geq 1$  bouts of OHE while on lactulose treatment.<sup>13</sup>

In a phase 3 trial to assess the efficacy of rifaximin for prevention of HE in high-risk patients, 299 patients in remission from recurrent HE were randomized to receive placebo or rifaximin 550 mg twice daily for 6 months.<sup>34</sup> Rifaximin significantly reduced the risk of another HE episode (hazard ratio [HR], 0.42; 95% CI, 0.28-0.64;  $P < .001$ ), and of hospitalization involving HE (HR, 0.50; 95% CI, 0.29-0.87;  $P = .01$ ).<sup>34</sup> More than 90% of patients in each treatment group received concomitant lactulose therapy, and the adverse event rate was similar between placebo and rifaximin groups.

Although rifaximin is not currently approved for treatment of OHE, 14 of 19 trials included in a 2014 meta-analysis compared rifaximin to either placebo or active treatment (primarily lactulose or lactitol).<sup>35</sup> Rifaximin increased the proportion of patients who recovered from OHE (RR, 0.59; 95% CI, 0.46-0.76), reduced mortality (RR, 0.68; 95% CI, 0.48-0.97), and had a beneficial effect on secondary prevention of OHE (RR, 1.32; 95% CI, 1.06-1.65). This latter benefit is important since readmission for HE is common. A study that assessed the combination of rifaximin plus lactulose vs lactulose alone for the treatment of OHE showed the combination to be superior in terms of complete reversal of HE (76% vs 50.8% of patients;  $P < .004$ ), decreased mortality (primarily due to sepsis) (23.8% vs 49.1%;  $P < .05$ ), and shorter hospital stay ( $5.8 \pm 3.4$  vs  $8.2 \pm 4.6$  days;  $P = .001$ ).<sup>36</sup>

## CONCLUSION

Cirrhosis is more common than previously thought. Because the liver panel is often normal and the clinical presentation is often asymptomatic, detection of cirrhosis at its earliest stages is often missed in the primary care setting. Consequently, PCPs are encouraged to identify patients at risk for cirrhosis and to be vigilant for subtle signs and symptoms before the development of serious complications, such as hepatic encephalopathy. Treatment has typically been directed at reducing serum ammonia levels. Our evolving knowledge about the pathophysiologic role of gut microbiota disturbances in liver disease, and specifically hepatic encephalopathy, has prompted the development and use of treatments aimed at manipulation of the gut microbiota. ●

## REFERENCES

- Grattagliano I, Ubaldi E, Portincasa P, Palasciano G. Liver disease: early signs you may be missing. *J Fam Pract.* 2009;58(10):514-521.
- Scaglione S, Kliethermes S, Cao G, et al. The epidemiology of cirrhosis in the United States: A population-based study. *J Clin Gastroenterol.* 2015;49(8):690-696.
- Said A, Gagovic V, Malecki K, Givens ML, Nieto FJ. Primary care practitioners survey of non-alcoholic fatty liver disease. *Ann Hepatol.* 2013;12(5):758-765.
- Spengler EK, Loomba R. Recommendations for diagnosis, referral for liver biopsy, and treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Mayo Clin Proc.* 2015;90(9):1233-1246.
- Harman DJ, Ryder SD, James MW, et al. Direct targeting of risk factors significantly increases the detection of liver cirrhosis in primary care: a cross-sectional diagnostic study utilising transient elastography. *BMJ Open.* 2015;5(4):e007516.
- Walker M, El-Serag HB, Sada Y, et al. Cirrhosis is under-recognised in patients subsequently diagnosed with hepatocellular cancer. *Aliment Pharmacol Ther.* 2016;43(5):621-630.
- Muir AJ. Understanding the complexities of cirrhosis. *Clin Ther.* 2015;37(8):1822-1836.
- Hancox SH, Smith BC. Liver disease as a cause of thrombocytopenia. *QJM.* 2013;106(5):425-431.
- Sun W, Cui H, Li N, et al. Comparison of FIB-4 index, NAFLD fibrosis score and BARD score for prediction of advanced fibrosis in adult patients with non-alcoholic fatty liver disease: A meta-analysis study. *Hepatol Res.* 2016;46(9):862-870.
- Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology.* 2011;53(3):1020-1022.
- Garcia-Tsao G, Sanyal AJ, Grace ND, Carey W. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology.* 2007;46(3):922-938.
- Ditisheim S, Giostra E, Burkhard PR, et al. A capillary blood ammonia bedside test following glutamine load to improve the diagnosis of hepatic encephalopathy in cirrhosis. *BMC Gastroenterol.* 2011;11:134.
- Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology.* 2014;60(2):715-735.
- NeSmith M, Ahn J, Flamm SL. Contemporary understanding and management of overt and covert hepatic encephalopathy. *Gastroenterol Hepatol (N Y).* 2016;12(2):91-100.
- Wijdticks EF. Hepatic encephalopathy. *N Engl J Med.* 2016;375(17):1660-1670.
- Agency for Healthcare Research and Quality. 2014 National statistics - all listed. <https://hcupnet.ahrq.gov/#setup>. Accessed January 17, 2017.
- Pañdar KR, Bajaj JS. Covert and overt hepatic encephalopathy: diagnosis and management. *Clin Gastroenterol Hepatol.* 2015;13(12):2048-2061.
- Suraweera D, Sundaram V, Saab S. Evaluation and management of hepatic encephalopathy: current status and future directions. *Gut Liver.* 2016;10(4):509-519.
- Saab S. Evaluation of the impact of rehospitalization in the management of hepatic encephalopathy. *Int J Gen Med.* 2015;8:165-173.
- Shawcross DL, Dunk AA, Jalan R, et al. How to diagnose and manage hepatic encephalopathy: a consensus statement on roles and responsibilities beyond the liver specialist. *Eur J Gastroenterol Hepatol.* 2016;28(2):146-152.
- Wakim-Fleming J. Hepatic encephalopathy: suspect it early in patients with cirrhosis. *Cleve Clin J Med.* 2011;78(9):597-605.
- US National Institutes of Health. NIH human microbiome project. About the HMP. <http://hmpdacc.org/overview/about.php>. Published 2016. Accessed February 14, 2017.
- Gordon JI, Ley RE, Wilson R, et al. Washington University. Extending our view of self: the Human Gut Microbiome Initiative (HGMI). <https://www.genome.gov/pages/research/sequencing/seqproposals/hgmiseq.pdf>. Published 2015. Accessed February 14, 2017.
- Moraes-Filho JP, Quigley EM. The intestinal microbiota and the role of probiotics in irritable bowel syndrome: a review. *Arg Gastroenterol.* 2015;52(4):331-338.
- Ahluwalia V, Betrapally NS, Hylemon PB, et al. Impaired gut-liver-brain axis in patients with cirrhosis. *Sci Rep.* 2016;6:26800.
- Llorente C, Schnabl B. The gut microbiota and liver disease. *Cell Mol Gastroenterol Hepatol.* 2015;1(3):275-284.
- Saab S, Suraweera D, Au J, Saab EG, Alper TS, Tong MJ. Probiotics are helpful in hepatic encephalopathy: a meta-analysis of randomized trials. *Liver Int.* 2016;36(7):986-993.
- Sharma BC, Singh J. Probiotics in management of hepatic encephalopathy. *Metab Brain Dis.* 2016;31(6):1295-1301.
- McGee RG, Bakens A, Wiley K, Riordan SM, Webster AC. Probiotics for patients with hepatic encephalopathy. *Cochrane Database Syst Rev.* 2011;11:CD008716.
- Amodio P, Bemeur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. *Hepatology.* 2013;58(1):325-336.
- Enulose [package insert]. Baltimore, MD: Actavis Mid Atlantic LLC; 2007.
- Glud LL, Vilstrup H, Morgan MY. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. *Cochrane Database Syst Rev.* 2016;4:CD003044.
- Flamm SL. Rifaximin treatment for reduction of risk of overt hepatic encephalopathy recurrence. *Therap Adv Gastroenterol.* 2011;4(3):199-206.
- Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362(12):1071-1081.
- Kimer N, Krag A, Møller S, Bendtsen F, Glud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. *Aliment Pharmacol Ther.* 2014;40(2):123-132.
- Sharma BC, Sharma P, Lunia MK, Srivastava S, Goyal R, Sarin SK. A randomized, double-blind, controlled trial comparing rifaximin plus lactulose with lactulose alone in treatment of overt hepatic encephalopathy. *Am J Gastroenterol.* 2013;108(9):1458-1463.