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A Step-by-Step Approach to the Diagnosis and Management of Hepatic Encephalopathy in the United States

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Primary Biliary Cholangitis: Diagnosis and Management

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Target Audience

This CME Supplement will target gastroenterologists, hepatologists, physician assistants, and nurse practitioners.

Learning Objectives

After completing this activity, participants should be better able to:

- Describe evolving patient management strategies for hepatic encephalopathy (HE) and primary biliary cholangitis (PBC)
- Discuss the latest treatment algorithms for HE and PBC and apply them to clinical practice

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A Step-by-Step Approach to the Diagnosis and Management of Hepatic Encephalopathy in the United States

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Abstract: Hepatic encephalopathy (HE) is an important manifestation of decompensated cirrhosis. HE is characterized by signs of altered consciousness, notably, personality changes, impaired intellectual function, and neuromuscular dysfunction. Survival rates for patients hospitalized with HE are 50% at 1 year and 25% at 3 years. Early recognition of HE can facilitate appropriate management, mitigate clinical consequences, and enable preventive strategies. Overt HE occurs in at least 30% to 45% of patients with cirrhosis. It is important to recognize covert HE because its presence can predict the development of overt HE and is associated with poor health-related quality of life. Diagnosis of HE requires a combination of high clinical suspicion, exclusion of alternative etiologies, and a favorable response to therapy. This article provides a detailed algorithm for the diagnosis and management of overt HE. It also discusses how to recognize and treat covert HE.

Introduction

Cirrhosis encompasses a wide spectrum of pathology, ranging from no symptoms to devastating manifestations of end-stage liver disease. Patients with compensated, or asymptomatic, cirrhosis have an excellent prognosis. Once symptoms of decompensation occur, which include hepatic encephalopathy (HE), variceal bleeding, ascites, and jaundice, there is a significant adverse impact on health-related quality of life (HRQoL), morbidity, and mortality.

HE is a common and important manifestation of decompensation, yet can be difficult to recognize in its earliest stages. The consequences of HE can be dire, as HE episodes often require inpatient hospitalization and can occur without warning. Development of HE also has a prognostic impact. One- and 3-year survival rates for patients hospitalized with HE are less than 50% and 25%, respectively.[1]

HE is characterized by signs of altered consciousness, notably, personality changes, impaired intellectual function, and neuromuscular dysfunction. These deficits can impact patients' HRQoL by disrupting their sense of well-being, and by leading to frequent falls, impaired cognition, depression, and poor sleep patterns. HE can also impact employment and limit personal autonomy, especially driving capacity.

Despite the rising incidence and prevalence of HE, its diagnosis and management remain controversial. Guidelines have been published recently, yet HE management often remains inadequate. Early recognition of HE can facilitate appropriate management, mitigate clinical

Table 1. Conditions That Either Increase Ammonia Production or Decrease its Elimination

Conditions That Increase Ammonia Production
• Multiple myeloma
• Chemotherapy
• Bone marrow transplant: idiopathic hyperammonemia
• Urea-producing bacteria: *Proteus mirabilis, Escherichia coli, Klebsiella* species, *Providencia rettgeri, Helicobacter pylori*
• Increased protein metabolism: seizures, exercise, starvation, total parenteral nutrition, gastrointestinal bleeding

Conditions That Decrease Ammonia Elimination
• Organic acidurias
• Urea-cycle disorders
• Dibasic aminoaciduria
• Impaired fatty acid oxidation
• Pyruvate metabolism errors
• Congenital portosystemic shunts
• Medications: valproic acid, glycine, ribavirin, carbamazepine, 5-fluorouracil, cyclophosphamide, salicylates
• Portosystemic shunts (eg, vascular malformations in Osler-Weber-Rendu disease)

Adapted from Laish I, Ben Ari Z. *Liver Int.* 2011;31(9):1259-1270.[21]

Adapted from Laish I, Ben Ari Z. *Liver Int.* 2011;31(9):1259-1270.[21]

consequences, and enable preventive strategies. The purpose of this article is to offer a simple, evidence-based approach to the evaluation and management of HE. Furthermore, the step-by-step approach afforded by an algorithm may be more conducive to use in the clinical setting.

Terminology

Common terminology is vital to both diagnosis and management. Care of an individual with HE is generally shared among several clinicians and, without a common vernacular, transitions in management can lead to poor patient care. Integral to this is a classification scheme that will effectively communicate the status of the patient so that multiple providers can easily identify improvement or decline in functional status.

Encephalopathy: A syndrome of global brain dysfunction caused by various etiologies rather than a single disease.

Hepatic encephalopathy (HE): Brain dysfunction directly due to liver dysfunction or portosystemic shunting, most often recognized in advanced liver disease. HE may cause disturbances of consciousness and progress to coma. There are 2 classifications of HE:

- *Overt HE (OHE)*: Consists of clinically evident HE (West Haven Criteria grade II or higher).
- *Covert HE (CHE)*: Includes the older terms "minimal hepatic encephalopathy (MHE)" and "subclinical encephalopathy." This includes West Haven Criteria grades 0 and I.

Portosystemic shunt: A shunt that bypasses the liver and allows portal venous blood to directly enter the systemic venous circulation. It can be congenital, acquired spontaneously, or iatrogenic.

Transvenous intrahepatic portosystemic shunt (TIPS): A minimally invasive technique for creating a portosystemic shunt by placing a stent connecting the portal and systemic venous circulation to decompress the portal circulation. The most common etiologies leading to TIPS placement are refractory variceal bleeding and refractory ascites.

Decompensated cirrhosis: Cirrhosis with complications of advanced liver disease including but not limited to jaundice, ascites, variceal bleeding, and encephalopathy.

Compensated cirrhosis: Histologic cirrhosis with or without portal hypertension (nonbleeding varices, splenomegaly, low platelets), but without any of the complications of cirrhosis listed above.

Nonhepatic hyperammonemia: This term refers to hyperammonemia from nonhepatic etiologies.[2] Although encephalopathy may be present, it is not required. Table 1 lists conditions that either increase ammonia production or decrease its elimination.

Causes of increased ammonia levels can include congenital defects in metabolism (eg, inborn errors in the urea cycle or disorders in fatty acid oxidation, occasionally presenting only in adulthood), drug-associated hyperammonemia (eg, valproate, 5-fluorouracil, cyclophosphamide, and salicylates), portosystemic shunts (eg, vascular malformations in Osler-Weber-Rendu disease), and urinary tract infection with urease-producing bacteria in an anatomically abnormal urinary system. As an example of the limitations of the test, exercise-induced hyperammonemia[3,4] may lead to misinterpretation of biochemical testing.

Prevalence

The prevalence of cirrhosis in the United States—as ascertained by an aspartate aminotransferase-to-platelet ratio of greater than 2 and abnormal liver function tests—is 0.27%, or 633,323 adults based on the 2010 census.[5] Cirrhosis and its associated complications are increasing, driven primarily by the increasing obesity epidemic and a large cohort of individuals who have been chronically infected with HCV for more than 20 years.[6] In the United States alone, over 64 million people are projected to have nonalcoholic fatty liver disease (NAFLD), with annual direct medical costs of approximately $103 billion ($1613 per patient).[7-9] As prevalence is expected to continue to increase, it is imperative that clinicians are aware of the manifestations and management of cirrhosis-related complications.

HE is a life-altering manifestation of hepatic decompensation. OHE occurs in at least 30% to 45%

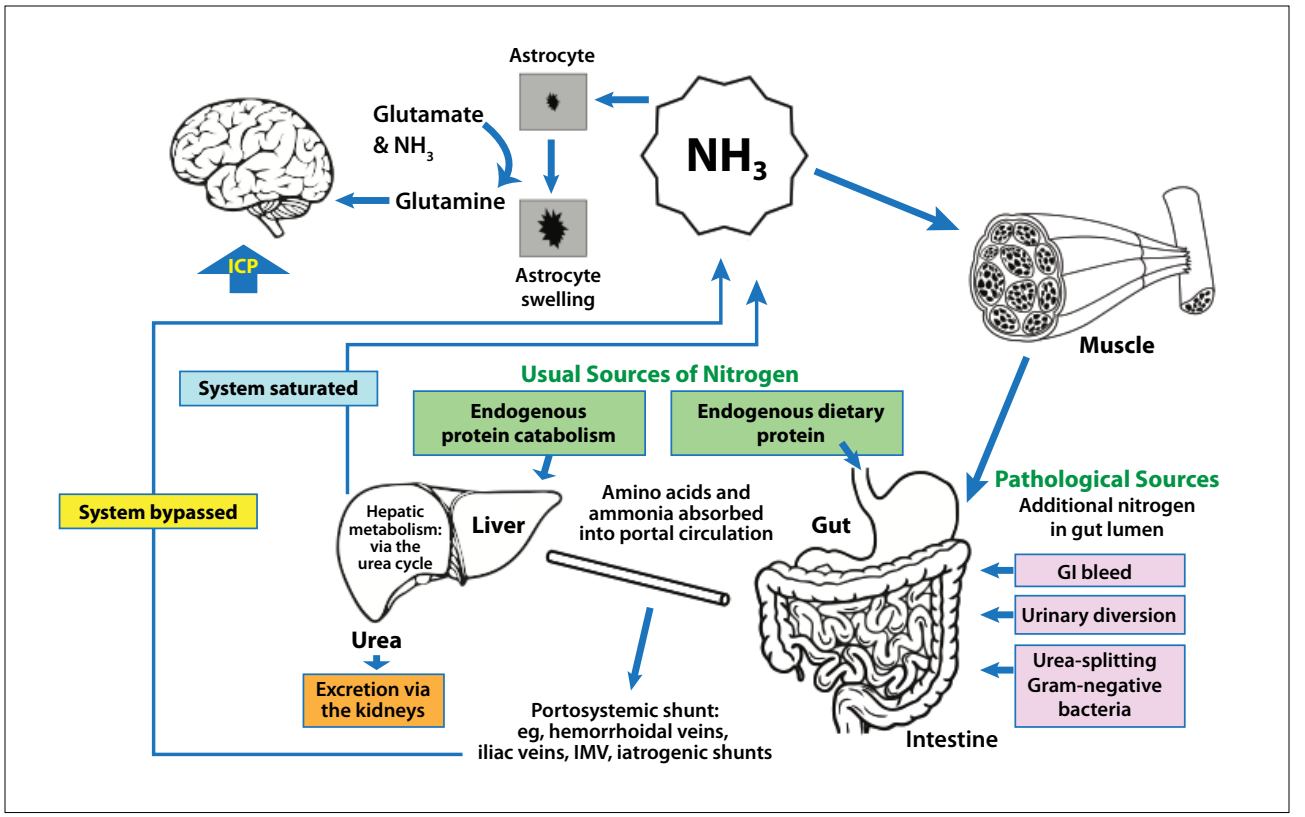

Figure 1. Multifactorial etiology of hepatic encephalopathy. GI, gastrointestinal; ICP, intracranial pressure; IMV, inferior mesenteric vein.

of patients with cirrhosis.[10] The prevalence of OHE at the time of diagnosis of cirrhosis is 10% to 14%.[10-12] HE is a formidable burden on the health care system, as it represents a common and increasing diagnosis in both initial hospitalization and rehospitalization for patients with cirrhosis.[13,14] Thirty-day readmission rates of between 20% and 37% have been reported in patients with cirrhosis and are driven primarily by HE and volume management.[15,16]

Pathophysiology

Despite more than half a century of investigation, the pathogenesis of HE is not completely understood, which is reflective of the complexity of this multifactorial process. Portosystemic shunting in combination with excess ammonia, cerebral edema, oxidative stress, and inflammatory mediators are among the factors identified in a complex picture of multiple contributing mechanisms and toxins.[17-20] Understanding the various factors that contribute to this relationship helps clarify both the diagnosis and management of HE (Figure 1).

TIPS and HE

The TIPS technique involves placement of a minimally invasive shunt that functions like a side-to-side portacaval shunt and is used to control complications of portal hypertension, including refractory ascites and variceal bleeding. Unfortunately, from 30% to 55% of patients who undergo TIPS shunt placement will develop HE.[21] Risk factors for post-TIPS HE include older age (>65 years), previous episodes of HE, and a Child-Pugh score of 10 or higher.[22] Even in patients without these risk factors, the risk of OHE post-TIPS is still nearly 30%. Decreasing the portosystemic gradient to 5 mmHg or lower may increase the risk of complications, including refractory HE.[23] The presence of CHE may also predict post-TIPS OHE.[24] Prophylactic therapy post-TIPS does not prevent HE occurrence.[25]

Diagnosis

Recognize Patients at Risk of HE

The diagnosis of HE is clinical, meaning that no test is completely able to confirm or exclude the diagnosis. Therefore, diagnosis requires a combination of high clinical suspicion, exclusion of alternative etiologies, and a favorable response to therapy. In the authors' opinion, a patient with cirrhosis or portosystemic shunting and a presentation consistent with OHE does not need additional confirmatory studies; however, exacerbating events must be excluded (Table 2; Figure 2).

In adults, most hyperammonemia is linked to liver disease. However, approximately 10% of cases are caused by either increased ammonia production or decreased elimination. Patients with noncirrhotic portal hypertension are also at risk for HE.[26] These etiolo-

Table 2. Conditions That Can Mimic or Precipitate OHE

Conditions That Can Mimic OHE
• Delirium
• CVA/hemorrhage
• Uremia
Precipitating Factors of OHE
• Gastrointestinal bleeding
• Infection: UTI, SBP, bacteremia
• Medications: sedatives, pain medications
• Electrolyte abnormalities: hypernatremia, hyperglycemia
• Renal failure
• Constipation
• Dehydration
• Dietary
• Medication noncompliance

CVA, cerebrovascular accident; OHE, overt hepatic encephalopathy; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infection.

gies should be considered in the differential diagnosis of any individual with elevated ammonia (Table 1).

Although all patients with cirrhosis are at risk of developing HE, some factors increase the risk (Table 3).[27]

Obtain a Detailed History and Physical Examination

The patient history should be elicited from the patient if possible, or from close contacts. It is imperative to have information regarding symptoms of infection and medication adherence, and to review use of prescribed and over-the-counter therapies and illicit drugs. Clinical evaluation requires a physical examination, including neurologic and psychiatric evaluation, as well as assessment of exacerbating factors, such as spontaneous bacterial peritonitis and other infections. Confusion and asterixis are the most commonly observed diagnostic parameters; however, many other presentations are recognized (Table 4).

Grade Encephalopathy

Once the diagnosis of HE is suspected, the severity should be graded. This serves to enable different caregivers to gauge the response to interventions. The West Haven Criteria[28] is one of the most commonly used scales to grade HE (Table 5). Some clinicians further classify HE based on the cause, using the criteria established at the 1998 World Congress of Gastroenterology, or the Glasgow Coma Scale, which can be implemented in cases of significantly altered consciousness.[29] The authors recommend the West Haven Criteria, as these offer the most clinical utility and allow the use of standardized nomenclature that reflect deterioration and improvement, which is vital for circumstances where clinical management is shared among providers.

Obtain Biochemical Studies

There is no specific biochemical diagnostic test for OHE. Therefore, OHE is a diagnosis based on the exclusion of other etiologies by laboratory and radiological assessments.[30] Such confounding issues include alcohol abuse, narcotics use, benzodiazepine use, dementia, and electrolyte abnormalities.[30]

Serum Ammonia Levels

Measurement of serum ammonia levels is insufficient for a diagnosis of OHE, as ammonia levels can be normal in approximately 10% of patients with significant encephalopathy[31] and can be elevated in nearly 70% of patients without signs and symptoms of clinically apparent encephalopathy,[32] including those with noncirrhotic explanations for high ammonia (Table 1). Overreliance on this test can be misleading. Therefore, serial monitoring of serum ammonia levels is not as useful as clinical assessment in diagnosing OHE or in gauging the effectiveness of an intervention. Measurement of serum ammonia levels can be an important confirmatory test when there is concern regarding the etiology of confusion. It is important to note that accurate assessment is highly dependent on processing.[33]

Consider Cerebral Imaging

Patients with HE are at increased risk of falling. Coagulopathy and thrombocytopenia associated with liver disease may also increase the risk of bleeding. For individuals with new-onset HE, assessment for subarachnoid, intracranial hemorrhage or a cerebral vascular event should be considered. Repeat

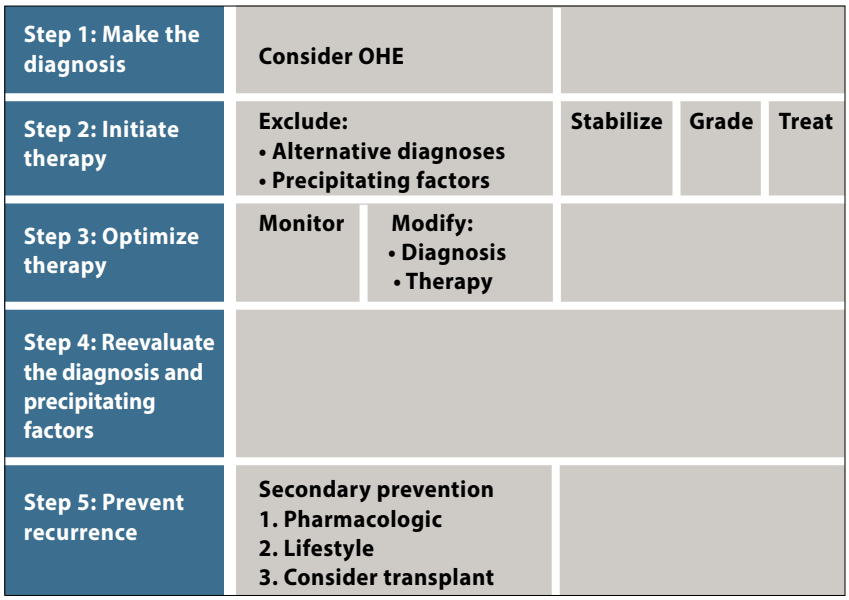

Figure 2. Algorithm for the diagnosis and management of overt hepatic encephalopathy.

Table 3. Patients With Cirrhosis and One of the Following Conditions Are at Higher Risk of Developing Hepatic Encephalopathy

• Portal hypertension
• TIPS placement
• Sarcopenia
• Renal failure
• Hyponatremia/retractable ascites
• Diabetes mellitus

TIPS, transvenous intrahepatic portosystemic shunt.

Adapted from Butt Z et al. *J Diabetes.* 2013;5(4):449-455.[27]

assessment is not necessary for exacerbation of HE, unless physical examination raises concern for an injury or a focal neurologic deficit.

Consider Neurocognitive Testing

Several modalities (Table 6) have demonstrated abnormalities in patients with HE; however, most are reserved for research rather than routine clinical use at the current time.[34] If the presentation of OHE is unusual or fails to respond to standard therapy, neurologic consultation is advised.

Diagnosis of Covert Hepatic Encephalopathy (CHE)

Because CHE is subclinical, testing is necessary for diagnosis. It is important to recognize CHE because its presence can predict the development of OHE and is also associated with poor HRQoL. Although up to 50% of patients with cirrhosis have CHE, there are no clear-cut guidelines on whom to test and when. It is practical to test patients who are experiencing a decline in HRQoL or functional status.

Most accurate tests for CHE require formal psychometric or neurophysiological evaluations, many of which are impractical and time-consuming (Table 6). The Stroop test is available as a mobile app and requires minimal time for administration, as does the number connection test. It is important to recognize that cognitive function has several facets, and not all tests may be able to discern abnormalities. In the authors' opinion, if there is a high index of suspicion, results from several modalities should be considered before accepting a negative diagnosis.

Table 4. Neurologic Manifestations of Overt Hepatic Encephalopathy

Common
• Confusion or coma
• Asterixis
• Loss of fine motor skills
• Hyperreflexia
Less Common
• Cognitive deficits detected by spacial testing
• Babinski sign
• Slow, monotonous speech
• Extrapyramidal-type movement disorders
• Clonus
• Decerebrate posturing
• Decorticate posturing
• Hyperventilation
• Seizures

Adapted from Mullen KD et al. *Semin Liver Dis.* 2007;27(suppl 2):32-47.[49]

Therapies

Most therapies target the increased levels of nitrogenous substances produced in the gut, but may have additional mechanisms of action. Using agents with complementary mechanisms of action is likely to improve efficacy, especially when one agent is not achieving the desired result. Using several agents that have the same mechanism of action is unlikely to increase efficacy over a single agent (eg, using 2 antibiotics for gut decontamination).

Treatments for OHE approved by the US Food and Drug Administration (FDA), as well as some unapproved treatments, are available for use (Table 7). It is important to remember that in patients with cirrhosis and portosystemic shunting, skeletal muscle mass and renal clearance are vital to neurotoxin clearance. Measures to avoid and reverse malnutrition are integral to successful therapy.

First-Line Therapies

Nonabsorbable disaccharides (NADs) (lactulose and lactitol): These agents reduce serum ammonia levels through several mechanisms, but efficacy is attributed primarily to the following process. Metabolism of these sugars by colonic bacteria produces an acidic environment, which converts ammonia to the positively charged ammonium, thus preventing absorption into the portal venous circulation in the colon. The colonic composition of the microbiota therefore changes, producing a cathartic effect. This decreases transit time and toxin absorption.

The systematic Cochrane Review of 2016 found that NADs were beneficial for both covert and overt HE. NADs had a beneficial effect on liver-related morbidity and all-cause mortality, and provided effective prophylaxis against the development of HE.[35]

Antibiotics for colonic decontamination (rifaximin, neomycin, metronidazole, vancomycin): Poorly absorbed antibiotics decrease ammonia-producing gut bacteria and, as a result, serum ammonia levels. Other mechanisms of action have been suggested, such as decreasing inflammation and endotoxemia.[36] Serious potential side effects limit the use of all the listed agents except rifaximin. Although neomycin is FDA-approved for hepatic coma (portal-systemic encephalopathy), hepatic and renal dysfunction increases systemic exposure and potential toxicity (intestinal malabsorption, nephrotoxicity, and ototoxicity) in the patient population most likely to require neomycin therapy. Additionally, the potential toxicities associated with metroni-

Table 5. West Haven Criteria for Grading Mental State in Patients With Cirrhosis

	Grade	Neurologic Findings
Covert HE	0	• No abnormalities detected
	I	• Trivial lack of awareness, euphoria or anxiety, shortened attention span, impairment of addition or subtraction
Overt HE	II	• Lethargy or apathy, disorientation concerning time, obvious personality change, inappropriate behavior
	III	• Somnolence to semistupor, responsive to stimuli, confused, gross disorientation, bizarre behavior
	IV	• Coma, unable to test mental state

HE, hepatic encephalopathy.

Adapted from Conn HO. Quantifying the severity of hepatic encephalopathy. In: Conn HO, Bircher J, eds. *Hepatic Encephalopathy: Syndromes and Therapies*. Bloomington, IL: Medi-Ed Press; 1994:13-26.[28]

dazole include irreversible peripheral neurotoxicity, and those associated with vancomycin include vancomycin-resistant enterococci. Rifaximin is the FDA-approved treatment of choice among nonabsorbable antibiotics.

Second-Line Therapies

Probiotics: The stool microbiome is altered in patients with cirrhosis. Probiotics have been viewed as complementary to intestinal decontamination. Few studies have shown benefit for their use in treating HE, but they are generally considered safe.[37,38] Two recent systematic reviews of probiotics to treat HE have not shown substantiated efficacy[39,40]; however, efficacy similar to lactulose in secondary prophylaxis has been reported.[41]

Polyethylene glycol 3350–electrolyte solution (PEG): PEG is regarded as safe, and is a commonly used and highly effective purgative. Its potential therapeutic efficacy in HE was assessed in the HELP study (Hepatic Encephalopathy: Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution).[42] This randomized, controlled trial compared PEG (4 L over 4 hours administered orally or via a nasogastric tube at the discretion of the treating physician) with lactulose treatments in patients with cirrhosis admitted to the hospital for HE. The findings suggested that PEG produced HE resolution more rapidly than standard therapy. It is especially useful in patients with severe HE when oral intake is impaired.

Ammonia scavengers: Several agents are thought to activate nonurea cycle pathways for ammonia removal and have been used in the management of inborn errors of the urea cycle. Sodium benzoate is commonly used off-label for refractory HE, as it is readily available as a food preservative. In combination with sodium phenylacetate, it is also FDA-approved for patients with urea cycle disorders and hyperammonemia. Sodium phenylbutyrate is available as an oral supplement. Sodium phenylbutyrate, ornithine phenylacetate, and glyceryl phenylbutyrate (a prodrug of sodium phenylbutyrate) have all been studied in HE, although none is FDA-approved for use in HE.

Branched-chain amino acids (BCAA): BCAA products supply glutamate, used for skeletal muscle ammonia metabolism. The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends BCAA supplementation in patients with grade III or higher HE, but many of these supplements are expensive and/or unpalatable. Increasing vegetable protein intake will increase BCAA as a proportion of total protein intake.

Protein restriction: The role of nutrition in the management of HE has been the focus of renewed attention. An expert panel commissioned by the International Society for Hepatic Encephalopathy and Nitrogen Metabolism[43] recommended that all patients with cirrhosis and HE should undergo baseline nutritional assessment and interval reassessments as part of management planning. Protein restriction should never be recommended in patients with cirrhosis (with or without HE).

In addition, ESPEN strongly advises against protein restriction, instead advising intake of 1.2 g/kg/day of protein for patients with compensated cirrhosis and 1.5 g/kg/day in patients with decompensated cirrhosis.[44,45] Consuming a mostly whole-food, plant-rich diet provides fiber and antioxidants, and is recommended. Although not universally agreed upon, some clinicians advocate that plant rather than animal protein should be the major source of protein, and that processed red meats should be restricted or eliminated.[46]

Zinc: Zinc deficiency is common in patients with cirrhosis, with prevalence as high as 96%.[47] Pathways essential for ammonia metabolism require zinc as a cofactor. Few studies have investigated the role of zinc replacement in HE, and a replacement has not always been shown to reduce serum ammonia levels or to improve HE. Zinc replacement therapy (225 mg/day) is relatively benign, although it does impact copper absorption. Side effects include dyspepsia.

Fecal microbiota transplant (FMT): Standard treatments in HE target the gut microbiota; however, other unconventional approaches may be able to perform the same function. A recently reported case study described the use of FMT, commonly used to reverse intestinal dysbiosis, as a potential therapy in HE.[48] Based on the case study results, it may be possible to use serial FMT treatments to improve cognition in CHE. Confirmation of the beneficial effect of FMT in this setting would require additional

Table 6. Psychometric and Neurophysiological Testing Options for Covert Hepatic Encephalopathy

	Description	Availability
Stroop Test	Test of mental speed and flexibility. Stroop tests show a combination of ink colors and words to evaluate a person's cognitive abilities. Cannot be performed on color-blind individuals.	EncephalApp Stroop is available for smartphones
Number Connection Test (NCT) (Halstead-Reitan)	Timed connect-the-numbers test. Test traditionally has 2 parts, but often only the first part of the test is used.	Paper-pencil test
Psychometric Hepatic Encephalopathy Score (PHES)	Composed of 5 tests: number connection test-A (NCT-A), number connection test-B (NCT-B), serial dotting test (SDT), line tracing test (LTT), and digital symbol test (DST). Can be used to assess motor speed, motor accuracy, concentration, attention, visual perception, visual-spatial orientation, visual construction, and memory.	Paper-pencil test battery
Inhibitor Control Test (ICT)	Patients are shown a series of letters and are asked to respond by pressing a mouse key when an X is followed by a Y, or a Y is followed by an X (alternating presentation, termed "targets"). Patients are instructed not to respond to X following X or Y following Y (nonalternating presentation, termed "lures"). Measures reaction time, response inhibition, attention, and working memory.	Computer-based
Cognitive Drug Research (CDR) Battery	Computerized testing that measures neurocognitive functions and does not rely as heavily on motor function of the patient.	Computer-based
Critical Flicker Frequency (CFF)	Computer-assisted test that measures the frequency at which the patient perceives that a fused/single light becomes a flickering light.	Can be carried out by clinical personnel using a portable device

larger studies. Additionally, its potential for use in OHE remains unknown.

Algorithm for the Diagnosis and Management of OHE

Clinical Scenario: New Onset or Acute Exacerbation of OHE

An individual with known or suspected liver disease presents with lethargy or mental status changes, and the physical examination is consistent with HE. Suspicion of encephalopathy is the initial step in the OHE diagnosis and management algorithm.

Steps 1 and 2: Diagnose, Exclude Alternative Etiologies and Precipitating Factors, Grade the Severity, and Initiate Therapy

The first step is not a tiered approach, but rather a simultaneous, multipronged treatment regimen (Figure 2). The clinician must begin an evaluation to exclude alternative etiologies and exacerbating conditions (Table 1). Diagnosing OHE requires both the exclusion of other conditions that can mimic OHE and the identification of potential precipitating factors, such as sepsis, gastrointestinal bleeding, drugs, electrolyte abnormalities, and constipation.[30,49,50] Several precipitating factors and concurrent causes of encephalopathy in patients with cirrhosis and suspected OHE can be identified through a clinical evaluation, central nervous system imaging, and laboratory tests (Tables 2 and 3).[51] Detection of precipitating factors or exacerbating conditions should prompt administration of corrective treatments or procedures.

Steps must also be taken to provide supportive care for the patient in an appropriate location and may include transfer to an intensive care setting (Figure 2). General supportive care should include fall and aspiration precautions and nutritional support. Intensive care unit monitoring is required for grade III or IV HE.[30,52,53] Furthermore, prevention of infections may be accomplished by changing intravenous lines, instituting aspiration precautions, and patient isolation. The fluid status of patients should also be assessed, monitored, and corrected as needed. Patients should be monitored in order to maintain correct levels of glucose and electrolytes and to correct alkalosis. Because hyponatremia can alter brain function both directly and by interacting with the mechanisms causing HE, sodium monitoring is essential. If present, hyponatremia should be corrected slowly because of the risk of developing central pontine myelinolysis, now referred to as "osmotic demyelinating syndrome."[43] Equally important is grading the condition so that interventions can be assessed for effectiveness (Table 5).

Treatment (Table 7; Figure 3) should be initiated concurrently with

Table 7. Treatment Options for Hepatic Encephalopathy

Drug Name	Description	Availability	Dose	FDA Approval/ Status for Use in HE
First-line				
Lactulose	Poorly absorbed disaccharide	• Decreases blood ammonia concentration • Promotes elimination of NH_3 • Fermentation by bacteria acidifies the colon and prevents absorption • Reduces urease-producing bacteria	20-30 g orally 3-4 times per day Maintenance dose adjusted to achieve 2-3 soft stools per day	Approved
Rifaximin	Nonaminoglycoside semisynthetic, nonsystemic antibiotic	• Decreases blood ammonia concentration • Broad-spectrum antibiotic; results in a change in bowel flora • May cause downregulation of intestinal glutaminase activity	550 mg BID	Approved
Second-line				
Lactobacillus, Bifidobacterium	Probiotic	• Modulates fecal flora • Reduces generation of ammonia	9 billion CFU	Not approved
Metronidazole	Synthetic antiprotozoal/ antibacterial agent	• Modulates fecal flora • Reduces generation of ammonia • Associated with neurotoxicity	250 mg BID	Not approved
Neomycin	Aminoglycoside antibiotic	• Decreases blood ammonia concentration • Inhibits intestinal glutaminase • Association with ototoxicity and nephrotoxicity • Should not be used in clinical practice	4-12 g orally per day in divided doses	Approved
Polyethylene glycol 3350 (PEG)	Cathartic	• Increases excretion of ammonia in the stool	4 L orally or via nasogastric tube	Not approved
Sodium benzoate and/or sodium phenylacetate	Nitrogen-binding agents	• Promotes renal excretion	5 g BID	Not approved
Valine, leucine, isoleucine	Branched-chain amino acids (BCAAs)	• Correct plasma ratio of BCAAs to aromatic amino acids • May reduce catabolism and muscle breakdown and prevent synthesis of false neurotransmitters	1.2-1.5 g/kg/day	Not approved

BID, twice daily; CFU, colony-forming units; HE, hepatic encephalopathy; FDA, US Food and Drug Administration.

correction of precipitating factors of OHE. However, it is important to be mindful of the dangers of excessive lactulose, as induction of dehydration may exacerbate electrolyte abnormalities or renal insufficiency.[49]

Initial treatment for OHE consists of lactulose solution USP (15 mL containing 10 g lactulose) administered either orally, through a nasogastric tube, or by enema.[53,54] For oral and nasogastric tube administration, 30 to 45 mL (20-30 g) should be initially administered 3 to 4 times daily, and the amount should be titrated to produce 2 to 3 soft stools per day. For those receiving lactulose via enema, 300 mL (200 g) in 1 L of water should be administered to patients in the Trendelenburg position, to increase access to the right colon. If aspiration is a concern, administration of lactulose through a nasogastric tube or rectally is advised.

The addition of one 550-mg rifaximin tablet taken orally twice a day, with or without food, is recommended. Studies in acute OHE comparing lactulose plus placebo with combination lactulose and rifaximin demonstrated faster reversal of HE and shorter hospital stays in the combination arm.[55]

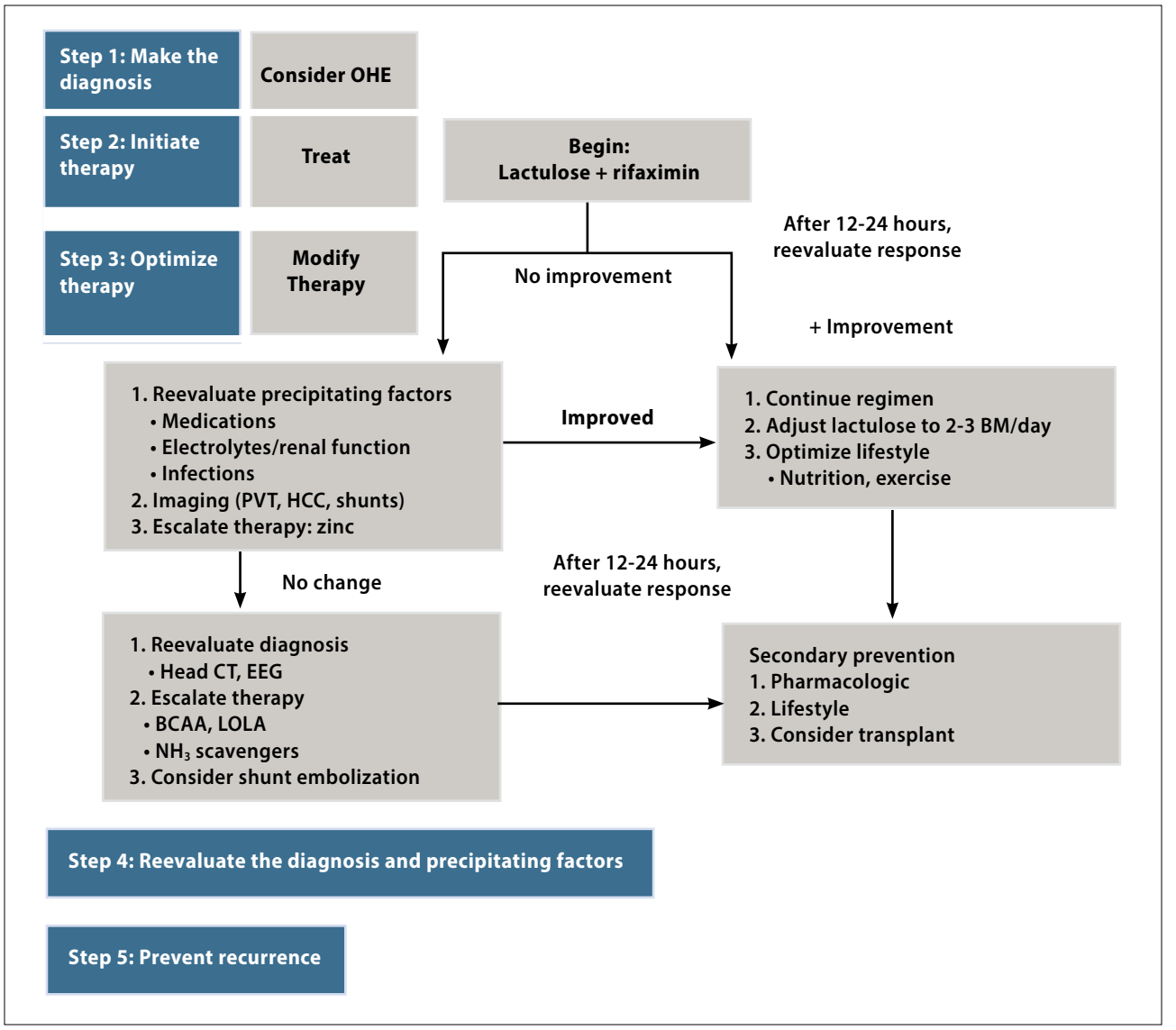

Figure 3. Optimizing therapy for overt hepatic encephalopathy (OHE). BCAA, branched-chain amino acids; BM, bowel movements; CT, computed tomography; EEG, electroencephalogram; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; LOLA, L-ornithine-L-aspartate; PVT, portal vein thrombosis.

Step 3: Optimize Therapy

Patients with OHE require close monitoring (Figures 2 and 3). Reassessment should occur at a minimum of 4- to 6-hour intervals to ensure response, but medication modifications can be delayed for 12 to 24 hours before being deemed inadequate. The grade of encephalopathy should be documented when reevaluated.

Step 4: Reevaluate the Diagnosis and Precipitating Factors

Response to medical therapy is integral to the management of OHE. In patients who are refractory to first-line treatment, an alternative diagnosis should be sought aggressively. This includes a careful review of medications that have psychoactive effects. Patients hospitalized for OHE are frequently agitated and may be given sedating medications, especially at night. This often occurs in models of comanagement, where several individuals contribute to patient care. Additionally, abdominal and central nervous system imaging may be helpful in the reevaluation of precipitating factors and diagnosis, respectively.

Large portosystemic shunts can contribute to refractory HE. Retrospective series have suggested that embolization of these shunts may improve control of HE.[56] Screening for hepatocellular carcinoma (HCC) should also be considered. A retrospective analysis of 276 patients with HCC concluded that encephalopathy was present in approximately 18% of patients at the time of diagnosis.[57] Because HE occurs frequently with primary HCC, and because intractable encephalopathy occurs almost invariably in most patients at the end stages of HCC,

screening for HCC is warranted in patients with new-onset OHE.

Regardless of response, lactulose therapy should be titrated to produce 2 to 3 loose bowel movements daily. Aggressive lactulose administration can increase the risk of complications, including dehydration, acidosis, malnutrition, and aspiration.

In patients who do not respond to lactulose and rifaximin, second-line therapy includes zinc supplementation, based on the findings of a randomized, open-label trial that showed potential benefits in patients with OHE.[47] More recently, a randomized, controlled trial became the first to indicate that zinc supplementation over a 3-month duration was effective and safe for treating hyperammonemia in cirrhosis.[58] The addition of BCAAs, such as valine, leucine, and isoleucine, has been recommended, and the elimination of wheat and milk proteins may also benefit patients.[53] Other therapies may offer benefit for individuals who continue to have refractory OHE (Table 7).

Step 5: Prevent Recurrence (Secondary Prophylaxis)

The risk for recurrent episodes of OHE is high, and it increases as liver function worsens. After an episode of OHE has been resolved, patients with cirrhosis should remain on therapy for an indefinite period or until they undergo liver transplant.[51] The goals of secondary prophylactic therapy are to prevent recurrent episodes of HE and to ensure a reasonable HRQoL.[59] In support of this recommendation, studies have demonstrated that continuing treatment after resolution of HE decreases the probability of recurrence.[60] Nutrition counseling and therapy to maintain muscle mass are also important. A recently published study concluded that use of proton pump inhibitors may be a risk factor for HE in patients with cirrhosis.[61]

When a precipitating factor (eg, lactulose noncompliance, constipation, opioid and benzodiazepine use, dehydration, infections, acute renal failure, hypokalemia [potassium <3.5 mmol/L], gastrointestinal bleeding, large-volume paracentesis, TIPS, hyponatremia [sodium <130 mmol/L], high-protein diet)[62] can be identified and eliminated, the decision to continue secondary prophylaxis should be individualized. For patients with preserved liver function and adequate muscle mass, the risk for recurrent OHE is lower than for patients without these characteristics.

Continue therapy: Once OHE is controlled, the regimen used to stabilize the patient is continued to prevent recurrence (Figure 2). If lactulose is part of the regimen, it is important to adjust the dose to achieve 2 to 3 soft stools per day, avoiding diarrhea, which can lead to electrolyte abnormalities, dehydration, malnutrition, and, paradoxically, exacerbation of HE. Lactulose noncompliance is the leading cause for readmission or recurrence of OHE. It is important to put strategies in place to limit lactulose therapy in patients who are poorly tolerant. The addition of rifaximin to lactulose treatment in lactulose responders is also recommended, based on the results of several studies.[60,63-65] Reduced rates of OHE-related hospitalizations are observed with combination therapy with no significant adverse events following long-term (≥2 years) exposure to rifaximin.[66] Rifaximin monotherapy is also an option,[66,67] especially in patients who are poorly tolerant of lactulose.[68]

The use of probiotics (*Lactobacillus* and *Bifidobacterium*) as secondary prophylaxis is supported by an open-label study in which lactulose, probiotics, or no therapy was administered to patients with cirrhosis who recovered from HE.[41] Compared with placebo, fewer episodes of HE were found in both the lactulose and probiotic arms, and there was no difference between interventions. Unfortunately, there was no difference in the readmission rates among the study arms.[41]

Optimize nutrition and muscle mass: Exercise is not contraindicated, but it should be carefully monitored. An established relationship between exercise intensity and plasma ammonia concentration is well established. However, few patients with cirrhosis are able to exercise to a degree that exacerbates OHE.[3,4] Physical therapy should be encouraged for those unable to engage in activity safely.

Nutrition is an important component of secondary prophylaxis. Avoidance of fasting, intake of small meals evenly distributed throughout the day, and a late-night snack[69] should be encouraged.[30,43]

Consider liver transplant: Evaluation for liver transplant should be undertaken in all patients with HE who do not have obvious contraindications to transplant.

Management of Covert Hepatic Encephalopathy (CHE)

CHE is characterized by deficits in attention, reaction time, working memory, visuoconstructive abilities, and fine motor performance. CHE occurs in 20% to 80% of patients with cirrhosis[70-75] and it adversely impacts employability,[72,74] driving capacity,[76,77] and many domains of HRQoL.[70,78,79] Additionally, once CHE is identified, more than 50% of patients will go on to develop OHE within 30 months.[80]

Exclude Exacerbating Effects and Initiate Preventive Measures (Primary Prophylaxis)

If CHE is identified (Table 6), efforts to identify potential precipitating factors (Table 2) should be addressed during regular clinic visits. Such efforts must include reviewing medication dosing and adverse effects, and emphasizing abstinence from alcohol and other toxic substances.[81]

Treating patients with CHE to prevent the development of a first episode of OHE is referred to as "primary prophylaxis of OHE."[60] Ideally, the goals of primary prophylactic therapy in patients with CHE are to delay progression to OHE, improve quality of life, maintain employment status, and

preserve driving privileges.[51] Routine treatment for CHE is currently not recommended, but can be considered when symptoms appear to be impacting a patient's quality of life.[30]

Clinicians who diagnose CHE may initiate therapy with lactulose[78,82] or rifaximin,[79,83,84] and should schedule frequent follow-up visits to assess and manage potential OHE-precipitating factors.[81] Additionally, the results of a recent report from India have provided support for nutritional interventions.[85] This randomized, controlled trial showed that nutritional therapy consisting of 30 to 35 kcal/kg/day (1.0 to 1.5 g) vegetable protein/kg/day for 6 months, was significantly more effective in the treatment of CHE than the absence of nutritional intervention, and was associated with improvement in HRQoL, too. Primary prophylactic therapy to prevent TIPS-associated HE is not indicated, as neither lactulose nor rifaximin pharmacologic therapy appeared to prevent HE more effectively than placebo.[25] If post-TIPS OHE occurs, treatment with lactulose and rifaximin should be initiated. Reducing the diameter of the shunt can be considered if HE is refractory to medical therapy.

Reduce Other Risks

Fitness to drive is compromised in cirrhotic patients diagnosed with HE.[86,87] Requirements as to whether or when health care providers must refer potentially unsafe drivers to state motor vehicle authorities vary by state. No state vehicle codes specifically address HE. As of 2011, there were no lawsuits completed against physicians or patients with HE concerning motor vehicle accidents.[86] In the absence of definitive laws, physicians should carefully evaluate cirrhotic patients for any degree of HE and, if present, recommend they undergo a professional driving evaluation conducted by the state's department of transportation.[87] If practicing in a state with mandatory requirements for reporting, health care providers should abide by their state rules.

Summary and Conclusions

HE is a common and clinically important manifestation of decompensated liver disease. Early recognition and a simultaneous, multipronged approach to exclude alternative etiologies and exacerbating conditions while initiating therapy offers the most efficient strategy to improve symptoms. Secondary prophylaxis to prevent recurrent symptoms and address exacerbating conditions is also imperative for optimizing quality of life and preventing readmission.

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Primary Biliary Cholangitis: Diagnosis and Management

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Abstract: Primary biliary cholangitis (PBC) is the most common chronic cholestatic liver disease in adults in the United States. PBC is characterized by progressive immune-mediated inflammatory destruction of septal and interlobular bile ductules. Clinical features are nonspecific and include fatigue, pruritus, right upper quadrant abdominal pain, dyslipidemia, bone mineral density loss, xanthelasmas, and, rarely, xanthomas. Without pharmacological treatment, PBC will lead to progressive fibrosis. Ursodeoxycholic acid (UDCA) was the first pharmacologic agent approved by the US Food and Drug Administration (FDA) for treatment of PBC. UDCA reduces fibrosis progression, diminishes the need for liver transplant, and improves liver transplant–free survival. Up to 40% of PBC patients who are treated with UDCA for at least a year have an inadequate biochemical response and experience decreased benefits. In May 2016, the FDA approved obeticholic acid (OCA) for treating PBC. OCA is approved in combination with UDCA in adults with an inadequate biochemical response to UDCA for at least 12 months, and as monotherapy in adults who cannot tolerate UDCA.

Primary biliary cholangitis (PBC), formerly known as "primary biliary cirrhosis," is the most common chronic cholestatic liver disease in adults in the United States. The disease disproportionately affects middle-aged women (with a 9:1 female-to-male ratio). In September 2015, a multisocietal position paper established the change in the disease's nomenclature, while maintaining the commonly used acronym "PBC."[1]

Characterized by progressive immune-mediated inflammatory destruction of septal and interlobular bile ductules, the fundamental pathophysiological mechanism for PBC is likely related to a complex interaction between unidentified environmental triggers and genetically susceptible individuals. Molecular mimicry, loss of tolerance, and dysregulated immune attacks directed against the E2 subunit of pyruvate dehydrogenase complex (PDC-E2) appear to be the cornerstone of PBC pathogenesis.[2] The result, at least microscopically, reflects the new terminology and can be identified by nonsuppurative cholangitis manifesting biochemically as cholestasis. Without pharmacological treatment, progressive fibrosis characterizes the natural history of PBC. Clinical features are nonspecific and include fatigue, pruritus, right upper quadrant abdominal pain, dyslipidemia, bone mineral density loss, xanthelasmas and, rarely, xanthomas.

PBC diagnosis may be established by 2 of the following 3 criteria in the absence of a cholestatic drug reaction or biliary obstruction: a) biochemical evidence of cholestasis (an otherwise unexplained elevation of serum alkaline phosphatase); b) presence of autoantibodies, typically antimitochondrial antibodies (AMA); and c) histological findings of nonsuppurative destructive cholangitis.[3] Characteristic histological features, previously thought to be necessary for establishing a PBC diagnosis, are not mandatory if the other 2 diagnostic criteria are satisfied. Furthermore, the pathognomonic "florid duct lesion" is only present in a minority of PBC patients, particularly during the early stages.[4] It is important to recognize that AMA, the hallmark autoantibody of PBC, may not be detectable in approximately 5% to 10% of patients with the disease (the so-called AMA-negative PBC), in which histology is mandatory to establish the diagnosis. In this scenario, PBC-specific autoantibodies, such as Sp100 and/or gp210, may be obtained to corroborate the diagnosis.[5]

Ursodeoxycholic acid (UDCA), the first pharmacologic agent licensed for PBC treatment, has proven to alter the natural history of the disease significantly when administered orally at

Table 1. Recommended Doses for UDCA and OCA for Treating PBC

	No Cirrhosis and Compensated Cirrhosis	Decompensated Cirrhosis
UDCA	13-15 mg/kg/day	13-15 mg/kg/day
OCA	5 mg/day, titrate up to 10 mg/day after 3 months if tolerated	5 mg/week, titrate up to 5 mg twice weekly after 3 months and subsequently to 10 mg twice weekly if tolerated

OCA, obeticholic acid; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

Table 2. General Recommendations for the Management of Patients With PBC

Complication	Recommendation
Pruritus	*First-line:* bile acid sequestrants (cholestyramine or colestipol) *Second-line:* rifampicin, naltrexone, sertraline
Fatigue	Evaluate for potential causes including comorbidities, medications, depression, itching. May use modafinil (off-label)
Dyslipidemia	Statins if needed, based on individual risk factors for cardiovascular disease
Sicca syndrome	*First-line:* artificial tears/artificial saliva *Second-line:* pilocarpine or cevimeline for dry eyes/mouth, cyclosporine ophthalmic for dry eyes
Osteopenia/osteoporosis	Baseline and regular screening every 2-3 years with bone mineral density scan Calcium 1500 mg/day and vitamin D 1000 IU/day supplementation for peri- and postmenopausal women Bisphosphonates for patients with osteoporosis
Gastroesophageal varices	Initiate screening with upper endoscopy once cirrhosis is diagnosed or Mayo risk score >4.1 or platelets <140,000
Hepatocellular carcinoma	Screening with liver ultrasonography every 6-12 months for individuals with cirrhosis or Mayo risk score >4.1. Men and UDCA-nonresponders appear to be at increased risk

PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

Adapted from Lindor KD et al. Primary biliary cirrhosis. *Hepatology* 2009;50:291-308.[3]

a dose of 13 to 15 mg/kg/day.[6] Important outcomes associated with UDCA therapy in PBC include reduced fibrosis progression, diminished need for liver transplant (LT), and improved LT-free survival. Nevertheless, up to 40% of PBC patients who are treated with UDCA for at least a year have an inadequate biochemical response and experience lesser benefits on long-term outcomes.[7] Response to pharmacologic therapy is assessed predominantly by reductions in serum alkaline phosphatase and bilirubin levels, 2 biochemical markers that accurately predict long-term outcomes in PBC.[8] The PBC GLOBE score (available at www.globalpbc.com/globe/) is a newly validated noninvasive assessment tool that uses readily available and objective variables (age, bilirubin, albumin, alkaline phosphatase, and platelet count) to accurately identify patients at risk for clinically important outcomes, such as the need for LT and mortality within the next 3, 5, and 10 years.[9]

Obeticholic acid (OCA) was recently licensed on May 27, 2016 by the US Food and Drug Administration. OCA is currently indicated for treating PBC, in combination with UDCA, in adults with an inadequate biochemical response to UDCA for at least 12 months, or as monotherapy in adults who cannot tolerate UDCA. OCA is a selective farnesoid X receptor (FXR) agonist derived from the naturally occurring chenodeoxycholic acid, an endogenous FXR ligand. FXR is a member of the nuclear bile acid receptor superfamily expressed in high levels in hepatocytes and enterocytes in the terminal ileum, and its activation results in suppression of cholesterol 7 alpha-hydroxylase (CYP7A1) and transcription of fibroblast growth factor (FGF) 19. CYP7A1 is the rate-limiting enzyme in bile acid synthesis from cholesterol. Accordingly, FXR activation markedly reduces the bile acid pool. Similarly, increased levels of FGF19 inhibit de novo synthesis of bile acids; nevertheless, this hormone also regulates several metabolic pathways, including insulin sensitivity and lipid metabolism. Furthermore, in animal models, FXR activation has proven to result in fibrosis regression.[10] The recommended OCA dosing is summarized in Table 1. Importantly, dose reduction is required in patients with severe hepatic dysfunction, as OCA is predominantly excreted by the liver (87%). Results from a recently published randomized, placebo-controlled trial demonstrate that OCA, administered with UDCA or as monotherapy for 12 months, results in marked improvement in biochemical markers in 47% of individuals treated with this agent compared with 10% of those who received the placebo.[11]

Several other drugs are currently under evaluation for treating patients with PBC and inadequate response to UDCA. However, none can be recommended at this time. Incomplete responders are at higher risk for progression toward biliary cirrhosis

and end-stage liver disease and are more likely to develop hepatocellular carcinoma compared with those who respond to UDCA.[12] Other recommendations in the management of patients with PBC are listed in Table 2.

PBC is the sixth leading indication for LT in the United States; pharmacologic therapy has resulted in a steady decline in the number of individuals requiring LT since UDCA approval.[13] Outcomes following LT for PBC are excellent and have been considered the benchmark for patient and allograft survival to which other indications for LT are compared. Although recurrence post-LT is relatively common, it has no significant impact on survival. Recent data from a retrospective study suggest that preventive administration of UDCA may markedly diminish recurrence of PBC 10 years post-LT.[14] These data need to be corroborated by prospective studies, and there are currently no data on the role of OCA and prevention of recurrent PBC post-LT.

Summary

PBC is a heterogeneous disease, and not all patients respond to first-line therapy with UDCA. Second-line therapy with OCA is available for nonresponders and for those who are intolerant to UDCA. Care for PBC patients must be individualized based on staging and appropriate risk stratification.

Disclosures

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