Contemporary Understanding and Management of Overt and Covert Hepatic Encephalopathy

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Abstract: Hepatic encephalopathy (HE) is a major complication of liver disease that leads to significant morbidity and mortality. Caring for hospitalized patients with HE is becoming more complex, and the economic burden of HE continues to rise. Defining and diagnosing HE, particularly covert HE (CHE), remain challenging. In this article, we review new tools and those currently under development for the diagnosis of CHE and the latest advances in the acute and long-term management of overt HE (OHE) and CHE. In particular, we review the latest data on the use of lactulose and rifaximin for treatment of OHE and summarize the data on adjunctive agents such as sodium benzoate and probiotics.

Hepatic encephalopathy (HE) is a major complication of end-stage liver disease and acute liver failure. HE encompasses a spectrum of cognitive and motor abnormalities that range from minimal deficits, detected only with psychometric or neuropsychological tests, to overt coma, and is associated with diminished survival in patients with cirrhosis.[1] Overt HE (OHE) occurs in at least 30% to 45% of patients with cirrhosis as well as in 10% to 50% of patients who have undergone transjugular intrahepatic portosystemic shunt, and is one of the defining characteristics of acute liver failure. The median survival of patients with decompensated cirrhosis with OHE is approximately 2 years, compared with greater than 12 years in patients with compensated cirrhosis without OHE.[2] In patients hospitalized with decompensated cirrhosis, OHE was associated with a 3.9-fold increase in the risk of death ($P<.01$) and was a negative predictor of survival after adjusting for Model for End-Stage Liver Disease score (hazard ratio, 2.57).[3] In patients undergoing elective transjugular intrahepatic portosystemic shunt for recurrent variceal bleeding or refractory ascites, severe HE was associated with a 3.7-fold increase in the risk of death ($P<.01$).[3] The overall mortality of hospitalized patients with cirrhosis presenting with HE or altered mental status is significantly higher than in cirrhotic patients presenting with normal mental status (35% vs 16%; $P<.001$).[4]

The care of patients with HE is becoming increasingly more complex and challenging. A report from the Nationwide Inpatient

Sample revealed trends in inpatient care for HE in the United States.[5] From 2005 to 2009, the overall number of discharge diagnoses for patients with HE increased from 10.0 to 13.3 per individual patient discharge record (P<.001). In addition, hospitalized patients with HE had an increase in complexity and severity of illness; minor or moderate severity index designations decreased from 22.1% to 14.8%, whereas a severe index classification increased from 35.9% to 43.1% (P<.001). The economic burden of HE from 2005 to 2009 was high, with approximately 0.33% of all hospitalizations in the United States attributed to HE. Resource utilization, along with the average number of inpatient procedures during admission for HE, rose as the average length of an inpatient hospitalization increased from 8.1 to 8.5 days (P=.019). This led to a 55.1% increase in total charges for hospitalizations with HE (from $4.677 billion in 2005 to $7.245 billion in 2009). The proportion of HE patients transferred after an acute hospitalization to a skilled nursing facility, intermediate care facility, or another type of long-term care facility also increased significantly from 22.0% to 24.7% (P=.001), reflecting the persistent morbidity associated with HE following hospitalizations.[5]

The negative psychosocial and financial impacts of OHE and covert hepatic encephalopathy (CHE) on patients and their caregivers are becoming increasingly appreciated. A study of 104 patients with cirrhosis and their caregivers showed that patients with previous HE posed a higher caregiver burden as measured by the Perceived Caregiver Burden Scale (P=.019) and Zarit Burden Interview Short Form (P=.015). Patients with a prior episode of HE also reported worse financial status (P=.019).[6]

Classification and Clinical Presentation

HE can be classified according to 4 factors: the underlying cause, the severity of manifestations, the time course, and the presence of precipitating factors.[7] The traditional nomenclature developed by the Working Party at the 11th World Congress of Gastroenterology in Vienna, Austria in 1998 divided HE according to underlying disease: type A, encephalopathy associated with acute liver failure; type B, encephalopathy associated with portosystemic bypass without underlying intrinsic hepatocellular disease; and type C, encephalopathy associated with cirrhosis and portal hypertension or portosystemic shunts.[8]

The grading of HE has traditionally been defined by the West Haven Criteria (WHC), also known as the Conn score.[8] Grade 0 represents no abnormalities, grade 1 represents mild OHE, and grades 2 through 4 represent more obvious symptomatic OHE. In CHE, there are no clinical signs or symptoms of OHE; however, patients have neuropsychological deficiencies that can be detected with psychometric or neuropsychological testing. CHE occurs in up to 80% of patients with cirrhosis.[9,10] Patients with CHE tend to have poor quality of life, diminished work productivity, and increased traffic violations and accidents. The presence of CHE can predict the subsequent development of OHE. In 63 patients with cirrhosis who were monitored over a mean of 4.8 years, 84% of patients who initially presented with CHE subsequently developed OHE.[9]

In OHE, there is a wide spectrum of symptomatic presentation. Using the WHC, patients with grade 1 HE have nonspecific symptoms such as increased fatigue, poor short-term memory and concentration, and insomnia. Patients with grade 2 exhibit more obvious symptoms such as confusion, changes in personality, bizarre behavior, and slurred speech. In grade 3, patients are stuporous. Grade 4 is characterized by coma, either responsive or unresponsive to noxious stimuli.

In 2009, the Hepatic Encephalopathy Scoring Algorithm (HESA) was created as an adaptation of the WHC that includes validated neuropsychological tests.[11] More recently, in 2011, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) suggested the Spectrum of Neurocognitive Impairment in Cirrhosis (SONIC) classification system. This system is based on a spectrum of disease that includes unimpaired, CHE (minimal HE and grade 1), and OHE (grades 2-4).[12] Table 1 summarizes the proposed classifications of HE.

HE can be further categorized as episodic; recurrent, with bouts of HE that occur within 6 months or less; or persistent, in which behavioral changes form a pattern, are always present, and are interspersed with relapses of OHE.[7] HE can also be categorized as precipitated or spontaneous (nonprecipitated).[7,8] Patients with chronic persistent HE do not achieve complete resolution of symptoms. This article refers to type C HE in the setting of chronic liver disease and portal hypertension.

Pathogenesis

The pathogenesis of HE is complex and multifactorial, and elevated ammonia levels have been implicated as a key component. Ammonia is generated by the metabolism of glutamine into glutamate and ammonia by enterocytes in the small bowel and by the catabolism of dietary protein and urea by colonic bacteria urease enzyme activity. Increased ammonia in advanced liver disease is a consequence of impaired metabolic capacity of the urea cycle in the liver and intra- and extrahepatic portosystemic shunting of blood related to portal hypertension. Muscle wasting, or sarcopenia, which is common in patients with

Table 1. Proposed Classifications of HE

	WHC[8]	HESA[11]	SONIC[12]
Unimpaired			• Mental status: not impaired • Specialized tests: not impaired • Asterixis: none
Grade 0	**No or minimal HE** • No abnormalities detected		**Covert HE** • Mental status: not impaired • Specialized tests: impaired • Asterixis: none
Grade 1	**Mild overt HE** • Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impaired performance of addition	**Clinical assessments** • Sleep disorder • Tremor **Neuropsychological assessments** • Complex computations • Construction ability • Shortened attention span • Depression At least 4 indicators present, either clinical or neuropsychological	Same as grade 0
Grade 2	**Overt HE** • Lethargy or apathy • Minimal disorientation for time or place • Subtle personality changes • Inappropriate behavior • Impaired performance of subtraction	**Clinical assessments** • Lethargy • Disoriented to time • Slurred speech • Hyperactive reflexes • Inappropriate behavior **Neuropsychological assessments** • Slow responses • Anxiety • Amnesia to recent events • Simple computations At least 2 clinical and 3 neuropsychological indicators present	**Overt HE** • Mental status: from disorientation through coma • Specialized tests: not specifically required but will be abnormal • Asterixis: present (except in coma)
Grade 3	**Overt HE** • Somnolence to semi-stupor, but responsive to verbal stimuli • Confusion • Gross disorientation	**Clinical assessments** • Somnolence • Confusion • Disoriented to place • Bizarre behavior/anger/rage • Clonus/rigidity • Nystagmus/Babinski sign **Neuropsychological assessments** • No mental control At least 3 indicators present, either clinical or neuropsychological	Same as grade 2
Grade 4	**Overt HE** • Coma (either responsive or unresponsive to noxious stimuli)	**Clinical assessments** • No eyes open • No verbal response • No reaction to simple commands **Neuropsychological assessments** • Not applicable All 3 indicators present	Same as grade 2

HE, hepatic encephalopathy; HESA, Hepatic Encephalopathy Scoring Algorithm; SONIC, Spectrum of Neurocognitive Impairment in Cirrhosis; WHC, West Haven Criteria.

cirrhosis, and renal dysfunction can also contribute to hyperammonemia and the development of HE.

Diagnosis

When making the diagnosis of HE, the patient history should focus on changes in cognition, behavior, sleep patterns, work performance, and driving performance. A physical examination should be performed to evaluate patients for the presence of stigmata of cirrhosis and asterixis. Asterixis may be present in grade 1 HE, is often present in grades 2 and 3, and is absent in grade 4 (coma). In the SONIC classification system, asterixis is absent in CHE but may be present in OHE (except for coma).[12]

The initial evaluation should begin by excluding other causes of encephalopathy, such as electrolyte disturbances, hypoglycemia, and uremia. Ammonia levels, including total venous and arterial ammonia levels as well as venous and arterial partial pressures of ammonia, have been shown to correlate with the severity of HE, but there is substantial overlap in all of these ammonia levels by grade of HE.[13,14] In addition, a single ammonia value has limited utility in the diagnosis of HE.[13] Notably, numerous other conditions are also associated with elevated ammonia levels. Therefore, it is not recommended that ammonia levels be obtained as a general rule.

Overt Hepatic Encephalopathy

The diagnosis of OHE is made after excluding other causes of encephalopathy and mental status changes. In addition to making the diagnosis of OHE, it is imperative to identify and address precipitating factors of OHE, such as infection, upper gastrointestinal bleeding, medications, or electrolyte/volume disturbances. This recommendation is highlighted by a recent study of 1218 hospitalized patients with cirrhosis who were admitted from 2003 to 2006. Of the 1218 patients, 349 (29%) were admitted for acute mental status changes. The most common cause was HE, which was observed in 47% of patients. Other etiologies were sepsis or infectious causes (23%), metabolic causes (8%), exogenous drugs/toxins (7%), structural brain lesions (5%), psychiatric causes (1%), and miscellaneous causes (8%).[4]

Historically, the diagnosis of OHE was based on clinical findings, as seen in the WHC (Table 1). The HESA extended these criteria by adding simple neuropsychological tests that assess mental control and slow responses, amnesia of recent events, shortened attention span, simple and complex calculations, construction ability, anxiety, and depression. These additional tests are more useful in grades 1 and 2 than in grades 3 and 4, which are assessed primarily by the level of consciousness.[11]

Covert Hepatic Encephalopathy

Psychometric Tests

The diagnosis of OHE is made without psychometric or neuropsychological testing, but specialized testing is the basis for the diagnosis of CHE. However, there is no gold standard for the diagnosis of CHE, and various combinations of psychometric and neuropsychological tests have been proposed. The Working Party in 1998 recommended the use of the Psychometric Hepatic Encephalopathy Score (PHES). If the PHES was unavailable, the Working Party required that diagnosis of CHE include abnormal results from at least 2 of the following tests: Number Connection Test A (NCT-A), Number Connection Test B (NCT-B), block design test (BDT), or digit symbol test (DST).[8]

Pencil-and-paper psychometric tests used in the diagnosis of CHE include the PHES and the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). The PHES is comprised of a battery of 5 different tests: NCT-A, NCT-B, the DST, the line-tracing test, and the serial-dotting test. The PHES assesses attention, motor speed and accuracy, visual orientation, and visuospatial construction and has been validated for HE diagnosis in several European countries, but not in the United States.[15] The RBANS was originally designed for the diagnosis of dementia and screening of cognitive dysfunction in other conditions and measures anterograde and working memory, cognitive processing speed, language, and visuospatial function.[15] The use of both the PHES and RBANS in clinical practice is limited in applicability because they are time-consuming; require a psychologist to order, administer, and interpret the results; and can lead to results that are nonspecific and difficult to interpret. ISHEN guidelines from 2009 recommend using either the PHES or RBANS for the diagnosis and monitoring of CHE, but specify that the choice of test should be based on the availability of local translations and normative data.[16] At this point, the current clinical application of these tests in the United States is limited.

Computerized psychometric tests for the diagnosis of CHE include the Inhibitory Control Test (ICT) and Cognitive Drug Research assessment system. The ICT tests attention, response inhibition, and working memory. ICT may be advantageous because it can be administered by a medical assistant rather than a psychologist, but it is limited by its requirement for higher-functioning patients.[17]

Screening Tools

The Stroop effect evaluates the function of the anterior attention system and has been found to be sensitive for the detection of cognitive impairment in CHE, which has led to the development of a Stroop smartphone application to screen for CHE. This application was compared with

standard psychometric tests, the PHES, and ICT in cirrhotic patients with and without prior HE and age-matched controls.[18] The application was able to diagnose CHE patients with 78% sensitivity and 90% specificity with standard psychometric tests, the PHES, and ICT as the gold standards (all $P<.001$). The Stroop smartphone application takes less time to complete and appears to be a more accessible and practical tool compared to PHES and ICT. In the future, it may allow for wider screening for CHE.[18] However, further validation studies are needed.

Other screening tests for CHE have been developed, including a Sickness Impact Profile CHE score based on a formula that includes age, sex, and answers to 4 validated quality-of-life Sickness Impact Profile questions. When compared to a reference of 2 or more abnormal pencil-and-paper test results (ie, NCT-A, NCT-B, BDT, DST), this screening test identified patients with CHE (a score of 0 or higher) with 80% sensitivity and 79% specificity at baseline. At 6 months, sensitivity was 88% and specificity was 37%; at 12 months, sensitivity was 81% and specificity was 24%.[19] This screening test is relatively simple to administer in an outpatient setting, and can be used to identify patients with CHE.

Neuropsychological Tests

Neuropsychological tests used in the diagnosis of CHE include critical flicker frequency (CFF), electroencephalogram (EEG), and evoked potentials (the measurement of time between a stimulus and the brain's response). CFF measures the highest frequency at which the patient can distinguish a light that appears as a flicker rather than as a single light. This test is independent of language and easy to administer and interpret. A meta-analysis of 9 studies that included 622 patients found a pooled sensitivity of 61% (95% CI, 55%-67%) and specificity of 79% (95% CI, 75%-83%), and suggested that CFF could be used as an adjunct to psychometric testing.[20]

A 2011 study showed that an increase in the severity of cirrhosis was associated with slowing of EEG rhythms. The presence and degree of EEG alterations were shown to predict the occurrence of HE.[21] However, an EEG requires a neurologist and specialized equipment and, thus, is not routinely used in practice. Table 2 summarizes psychometric and neuropsychological tests and screening tools. [22]

A recent study of 559 patients with cirrhosis and 261 patients without cirrhosis compared CFF and the PHES while using the ICT for the diagnosis of CHE. The diagnostic agreement values between CFF and conventional and modified PHES for CHE were 54% and 47%, respectively.[23]

Despite significant developments, further work remains for developing an optimal and widely accepted diagnostic strategy to diagnose CHE.

Management of Overt Hepatic Encephalopathy

Nonabsorbable Disaccharides

The management of OHE focuses on the identification and management of any precipitating factors, such as infection, upper gastrointestinal bleeding, dehydration, constipation, electrolyte derangements, and medication-related adverse effects. The nonabsorbable disaccharides lactulose (β-galactosidofructose) and lactitol (β-galactosidosorbitol) have been used in the treatment of HE for decades. Lactulose was approved by the US Food and Drug Administration (FDA) in 1976 for the treatment of HE. Lactulose has cathartic effects and reduces ammonia levels by acidification of the colon, which facilitates conversion of ammonia to poorly absorbed ammonium and shifts colonic flora from urease to nonurease-producing bacteria. Side effects include dehydration, severe diarrhea, abdominal cramping, and flatulence. A systematic review of studies assessing the use of nonabsorbable disaccharides compared with placebo or no intervention showed that nonabsorbable disaccharides reduced the risk of no improvement in patients with HE (relative risk, 0.62) in 6 trials; however, in the subset of the 2 higher-quality trials, no significant effect was seen (relative risk, 0.92). Compared with placebo or no intervention, lactulose and lactitol had no significant effect on mortality. Interestingly, antibiotics were found to be superior to nonabsorbable disaccharides for HE. The overall conclusion was that nonabsorbable disaccharides seemed to improve HE, but this effect was only seen in low-quality trials.[24] Despite limited data on its efficacy, lactulose has become established as the first-line therapy for HE as recommended in clinical guidelines.[25]

Antimicrobial Agents

Many antimicrobial agents have been used in the management of OHE, including neomycin, metronidazole, and vancomycin. In general, these medications have been used as adjuncts to lactulose therapy for recurrent HE or as monotherapy for patients who did not tolerate lactulose. Antimicrobial agents are postulated to reduce colonic bacterial production of ammonia and other bacterial-derived toxins through suppression of intestinal flora. Neomycin is a poorly absorbed aminoglycoside antibiotic that was FDA-approved in 1970 for the treatment of OHE. However, evidence of its efficacy is limited, and the use of neomycin is tempered by concerns for potential ototoxcity and nephrotoxicity. Although occasionally utilized for the treatment of OHE, vancomycin and metronidazole have not been approved by the FDA for this indication. In addition, the use of metronidazole is limited by the risk of peripheral neuropathy with prolonged administration.

Table 2. Psychometric and Neuropsychological Tests and Screening Tools for Covert Hepatic Encephalopathy[14,17,18,21]

	Cognitive Domains Measured	Time of Administration	Comments
Psychometric Tests			
Psychometric Hepatic Encephalopathy Score	Attention, motor speed and accuracy, visual orientation, visuospatial construction	10-20 minutes	• Recommended by the Working Party for the diagnosis of CHE • Paper and pencil • No validated norms in the United States
Number Connection Test A	Concentration, psychomotor speed	30-120 seconds	
Number Connection Test B	Concentration, psychomotor speed, divided attention	1-3 minutes	• Requires psychologist • Greater complexity than Number Connection Test A
Digit Symbol Test	Psychomotor speed, attention	2 minutes	• Requires psychologist
Line-Tracing Test	Visuomotor and visuospatial skills	10 minutes	
Serial Dotting Test	Psychomotor speed	1-4 minutes	
Block Design Test	Visuospatial reasoning, psychomotor speed	10-20 minutes	• Paper and pencil • Requires psychologist
RBANS	Anterograde and working memory, visuospatial function, language, cognitive processing speed	25 minutes	• Paper and pencil • Requires psychologist • Recommended by ISHEN as an alternative to the Psychometric Hepatic Encephalopathy Score
Inhibitory Control Test	Attention, response inhibition, working memory	15 minutes	• Computerized • Requires highly functioning patients
Cognitive Drug Research	Attention, speed of memory, episodic and working memory	15-20 minutes	• Computerized • Requires a practice session in advance of testing
Screening Tools			
Stroop Smartphone Application	Attention	Minutes	• Reliable • Easy to use • Practical for an outpatient setting
Sickness Impact Profile CHE Score	Measurement of QOL	Minutes	• Formula using age, sex, and 4 Sickness Impact Profile questions • Easy to use in outpatient setting • Good accuracy in long-term follow-up
Neuropsychological Tests			
Critical Flicker Frequency	Visual discrimination	10 minutes	• Needs highly functional patients
Electroencephalogram	Generalized brain activity	Variable	• Requires a neurologist and specialized equipment
Evoked Potentials	Measurement of time between a stimulus and ability to detect it	Variable	• Auditory P300 has been used in the diagnosis of CHE

CHE, covert hepatic encephalopathy; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; QOL, quality of life; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Oral Antibiotics and Alternative Therapies

Rifaximin (Xifaxan, Salix) is an oral antibiotic that has a broad spectrum of activity against both aerobic and anaerobic gram-positive and -negative bacteria. It has minimal systemic absorption (<1%) and has a low risk for inducing resistance. Its preferential site of action is the small bowel. Although the use of rifaximin for the treatment of acute OHE has not been approved by the FDA, there has been increasing clinical use of rifaximin in this setting. A randomized, double-blind trial in 2003 comparing rifaximin to lactitol for acute OHE showed that rifaximin was as effective as lactitol in the treatment of grades 1 to 3 HE, and both rifaximin and lactitol were well tolerated.[26] A 2012 meta-analysis suggested that the clinical effectiveness of rifaximin was equivalent to that of disaccharides or other oral antibiotics (odds ratio, 0.96; 95% CI, 0.94-4.08) with a superior safety profile (odds ratio, 0.27; 95% CI, 0.12-0.59).[27] In 3 trials each, statistically significant improvements in EEG patterns and portosystemic encephalopathy sum (a sum of the degree of mental status abnormality scores, severity of asterixis, level of serum ammonia elevation, and the degree of EEG abnormality) were found in patients treated with rifaximin vs controls. The overall improvement in psychometric parameters between the rifaximin and control groups was statistically significant and favored the use of rifaximin. The authors concluded that rifaximin appears to be at least as effective as other conventional oral agents for the treatment of OHE and has a better safety profile.[27]

In a study of 120 hospitalized patients with OHE (grades 2-4) who were randomized to receive lactulose plus rifaximin 1200 mg/day or lactulose plus placebo, 76.0% of patients in the lactulose/rifaximin group had complete reversal of OHE compared with 50.8% of patients in the lactulose/placebo group (P=.007).[28] Patients in the lactulose/rifaximin group had a shorter hospital stay (P=.001) and a significant decrease in mortality compared with lactulose alone (23.8% vs 49.1%, respectively; P<.05). The study also found significantly more deaths in the lactulose monotherapy group, which were attributed to a higher risk of sepsis compared with the lactulose/rifaximin group (P=.01). The authors concluded that combination therapy is more effective than lactulose alone for the improvement of OHE. They suggested that rifaximin decreased hospital mortality by reducing sepsis-related death and that combination therapy should be the standard of care for the treatment of OHE.[28]

L-ornithine–L-aspartate (LOLA), which provides a substrate for the urea cycle and lowers the serum ammonia concentration, has been used in the treatment of HE outside of the United States. A 2013 meta-analysis of 8 trials in patients with cirrhosis found that LOLA, when compared with placebo or no intervention, improved OHE according to a subgroup analysis of studies that were identified as having a low risk of bias.[29] The American Association for the Study of Liver Diseases (AASLD) recommends that LOLA be considered in patients who are nonresponsive to conventional therapy.[7]

Zinc, a cofactor in the urea cycle, is commonly deficient in patients with cirrhosis and HE. Supplementation may be beneficial for patients with HE because it may facilitate metabolism of ammonia.[30]

Patients with end-stage liver disease have a decreased plasma ratio of branched chain amino acids (BCAAs) to aromatic amino acids. It has been postulated that supplementation of BCAAs might improve OHE; however, a 2003 Cochrane review did not find convincing evidence that BCAA supplementation has a significant beneficial effect in patients with HE, and did not support its use.[31] Similarly, a meta-analysis in 2014 of BCAA therapy found poor-quality evidence that BCAA is associated with improvement in HE.[32] The AASLD recommends that BCAA be used as an alternative therapy in patients who are not responding to conventional therapy, but higher-quality data are needed.[7]

The gamma-aminobutyric acid-benzodiazepine receptor complex appears to be involved in neuronal inhibition in patients with HE. Flumazenil, a benzodiazepine receptor antagonist, has been used in the treatment of HE. A 2004 Cochrane review found that flumazenil had a significant beneficial effect on the short-term improvement of HE in patients with cirrhosis, but no significant effect on recovery or survival. Flumazenil was not recommended for routine clinical use, but further studies were suggested.[33] At present, there is no role for flumazenil in the treatment of HE.

Impairment of dopamine neurotransmission may play a role in HE, and treatment with dopaminergic agonists has also been considered. However, a Cochrane review in 2004 found no evidence that dopaminergic agonists are beneficial in patients with HE. Use of dopaminergic agonists was not recommended, but further clinical trials were suggested.[34] Dopaminergic agents are not recommended at this time for the treatment of HE.

Sodium benzoate is a food and beverage preservative that removes ammonia by increasing renal excretion; it reacts with glycine to form hippurate, which is excreted by the kidney. A recent review suggested that sodium benzoate may be a relatively safe and effective adjunctive agent for patients with HE and good kidney function.[35]

Glycerol phenylbutyrate (GPB; Ravicti, Horizon Pharma) also reduces ammonia via a nonurea cycle pathway. GPB is a prodrug of sodium phenylbutyrate and sodium phenylacetate (Ammonul, Medicis), which reacts to glutamine to form phenylacetylglutamine and is excreted in the urine. GPB is approved for the treatment of urea cycle disorders. In a randomized, double-blind,

placebo-controlled, phase 2 trial of 178 patients with cirrhosis, the use of GPB reduced the proportion of patients who experienced a HE event when compared with placebo (21% vs 36%, respectively; *P*=.02).[36] GPB also significantly reduced the time to an initial HE event (hazard ratio, 0.56; *P*<.05) and total HE events when compared with placebo (35 vs 57, respectively; *P*=.04). The investigators suggested that GPB has treatment potential in patients with cirrhosis and HE.[36]

Probiotics

The role of probiotics in the management of HE is unclear. A 2011 Cochrane review of probiotics for patients with HE included 7 trials with a total of 550 patients.[37] When comparing probiotics to no treatment, there was a reduction in plasma ammonia levels but no significant difference in all-cause mortality, recovery from HE, adverse events, quality of life, or change of/withdrawal from treatment. Probiotics were not recommended, as they did not appear to alter clinically relevant outcomes.[37] A 2012 meta-analysis of 7 trials evaluating probiotics and synbiotics (probiotics and prebiotics) that included 393 patients suggested that probiotics/synbiotics, when compared to placebo or lactulose, improved HE (risk ratio, 1.40; 95% CI, 1.05-1.86; *P*=.02; intertrial heterogeneity, 5%), but did not find an effect on the outcomes of progression from CHE to OHE or prevention of worsening HE.[38] A 2012 study comparing lactulose, probiotics, and no treatment for secondary prophylaxis of HE suggested that probiotics were as equally effective as lactulose and were well tolerated.[39] However, additional trials are needed to determine the role of probiotics in the treatment of HE.

Other Therapies

The Molecular Adsorbent Recirculating System (Gambro) is approved by the FDA for the treatment of HE as a result of decompensated cirrhosis, but its widespread use has been limited by practical challenges in implementation and cost. Embolization of large spontaneous portosystemic shunts has been used for treatment of refractory HE attributed to portosystemic shunting. In a recently published retrospective study of 37 patients with refractory HE and single large spontaneous portosystemic shunts who underwent shunt embolization, 22 patients (59.4%) were free of HE within 100 days of embolization, and 18 (48.6%) remained HE-free over a mean follow-up period of 697 ± 157 days. A significant increase in de novo development or aggravation of preexisting varices, ascites, or portal hypertensive gastropathy was not shown. The authors concluded that the effectiveness and safety of embolization of these shunts were substantiated, provided that the preprocedural Model for End-Stage Liver Disease score was 11 or less.[40]

It is clear that HE is an indication of the severity of liver disease and portends a poor prognosis, and patients with advanced liver disease with HE should be assessed for liver transplant candidacy.

Primary Prophylaxis

The use of lactulose as primary prophylaxis for the prevention of an initial bout of OHE has been studied. In a 2012 randomized trial of cirrhotic patients without prior history of OHE, the number needed to treat (NNT) with lactulose was 4.6 to prevent an episode of HE. In patients with CHE at baseline, the NNT was 4.3 to prevent an episode of OHE.[41] Although this study concluded that lactulose was effective for the primary prevention of HE in cirrhotic patients, lactulose for primary prevention of OHE in cirrhotic patients has not yet been widely recommended. There may be a role for its use as a prophylactic agent in higher-risk patients, but further studies are needed to clarify this patient subset.

Secondary Prophylaxis

Lactulose is often used as secondary prophylaxis for the prevention of recurrent OHE. A randomized, nonblinded study of lactulose vs placebo for secondary prophylaxis of HE showed that 12 of 61 patients (19.6%) in the lactulose group developed an episode of HE, while 30 of 64 patients (46.8%) in the placebo group developed an episode of HE over a median follow-up of 14 months (*P*=.001). The authors concluded that lactulose is effective for the prevention of recurrence of HE in patients with cirrhosis.[42]

Rifaximin was approved in 2010 by the FDA as a secondary prophylactic agent for use in the reduction of the risk of recurrence of OHE in patients with advanced liver disease. Its effectiveness in this setting was demonstrated in a randomized, double-blind, placebo-controlled trial of 299 patients in remission from recurrent OHE who were assigned to receive rifaximin vs placebo for 24 weeks.[43] Lactulose was neither mandated nor prohibited, and 91% of patients in each group used lactulose (with the same amount taken in each group). Breakthrough episodes of OHE occurred in 22.1% of the rifaximin group and 45.9% of the placebo group; the hazard ratio for the risk of a breakthrough episode in the rifaximin group compared with the placebo group was 0.42 (*P*<.001), reflecting a significant reduction in the risk of breakthrough OHE. The NNT was 4 to prevent 1 episode of OHE. Hospitalization involving OHE occurred in 13.6% of the rifaximin group and 22.6% of the placebo group, with a hazard ratio of 0.5 (*P*=.01). The NNT was 9 to prevent 1 hospitalization involving OHE. The incidence of adverse events in the rifaximin group was similar to placebo.[43]

A phase 3, open-label, long-term, maintenance study, and an extension of the previous trial, included

392 patients in an all-rifaximin group with a total of 510.5 person-years of exposure.[44] There were no new safety signals with long-term rifaximin use, and, incidentally, a reduction in all infection rates was noted. Rates of HE-related hospitalizations and all-cause hospitalizations in the rifaximin groups were lower than the rates in the historical placebo group. This study showed that rifaximin provided a continued decrease in HE-related and all-cause hospitalizations, without an increased risk of adverse events or change in survival rates. The authors concluded that rifaximin may be appropriate for long-term maintenance therapy for HE.[44]

Management of Covert Hepatic Encephalopathy

Rifaximin has also been studied in patients with CHE. In a study of 42 patients with CHE who were randomly assigned to receive rifaximin vs placebo for 8 weeks and were evaluated with a driving simulator, patients in the rifaximin group had reduced total driving errors (76% vs 33%; *P*=.013), a reduced number of speeding tickets (81% vs 33%; *P*=.005), and reduced illegal turns (62% vs 19%; *P*=.012) compared with the placebo group. Patients who were administered rifaximin had a significantly higher improvement in mean scores for the total battery of tests (*P*=.02). Patients with CHE also had a significant improvement in cognitive performance after treatment with rifaximin when compared with placebo.[45]

LOLA was also favored in improving CHE when compared with placebo or no intervention.[29] A randomized, placebo-controlled study of 63 cirrhotic patients with CHE who were administered LOLA or placebo for 60 days reported that LOLA did not significantly improve outcomes of psychometric testing, CFF, or the quality-of-life assessment. However, the LOLA group did have significantly fewer episodes of CHE at 6 months when compared with the placebo group (5.0% vs 37.9%; *P*=.016).[46]

Dietary Protein Recommendations

In the past, low-protein diets were recommended for patients with a history of OHE based on the presumption that the diets would lead to reduced ammonia production. However, more recent data have shown that maintenance of optimal nutrition, including protein, is paramount to prevent sarcopenia and further deterioration of functional status.[47] In general, cirrhotic patients with a history of HE should consume a high-energy diet with appropriate amounts of protein, and strict dietary protein restriction should be avoided. ISHEN guidelines published in 2013 suggest tailoring the amounts of daily energy and protein intake in patients with HE based on their nutritional status; for example, in adequately nourished patients who are normal or overweight, 35 to 40 kcal/kg of ideal body weight daily and 1.2 to 1.5 g protein/kg of ideal body weight daily are recommended.[47] Additional recommendations include the consumption of small frequent meals throughout the day, a late evening snack of complex carbohydrates, and 25 to 45 g of fiber daily as tolerated.[47]

Summary

HE, a major complication of end-stage liver disease and acute liver failure, results in significant morbidity and mortality. Guidelines for HE have recently been published by the AASLD and the European Association for the Study of the Liver. The classification system for HE continues to be refined, with recent suggestions to change to a continuous classification system that includes unimpaired, CHE (minimal), and OHE. The diagnosis of CHE is cumbersome, and although there is no definitive gold standard diagnostic strategy, tools are emerging that may be of more practical use in the clinical setting. Recent advances continue in the management of HE. Rifaximin in conjunction with lactulose is promising for the acute treatment of OHE, effective for secondary prophylaxis of OHE, and appears safe for long-term maintenance as prophylaxis. Other therapies such as LOLA and sodium benzoate may also be useful as adjunctive agents to lactulose in the treatment of OHE, although additional data are awaited. The role of probiotics in the treatment and prevention of OHE and CHE also awaits clarification. Regarding CHE, rifaximin is promising, although a uniform diagnostic strategy and definitive clinical endpoints for studies are needed.

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