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Covert and Overt Hepatic Encephalopathy: Diagnosis and Management

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Abstract

Hepatic encephalopathy (HE) is part of a spectrum of neurocognitive changes in cirrhosis. HE is divided into two broad categories based on severity, covert (CHE) and overt (CHE). CHE has a significant impact on a patient's quality of life, driving performances, and has recently been associated with increased hospitalizations and death. Likewise, OHE is associated with increased rates of hospitalizations and mortality, and poor quality of life. Given its significant burden on patients, care takers, and the health care system, it's imperative for early diagnosis and management. In addition, a focus should also be directed on patient and family member education on the disease progression and adherence to medications. Treatment strategies include the use of non-absorbable disaccharides, antibiotics (i.e. rifaximin), and potentially probiotics. Other therapies currently under further investigation include: L-ornithine-L-aspartate, ornithine phenylacetate, glycerol phenylbutyrate, molecular adsorbent recirculating system, and albumin infusion.

Keywords

Cirrhosis; Covert Hepatic Encephalopathy; Overt Hepatic Encephalopathy; Hepatic Encephalopathy; Ammonia; lactulose; Rifaximin

INTRODUCTION

Hepatic encephalopathy (HE) is a prevalent complication of portal hypertension and cirrhosis that is seen in 50–70% of patients[1]. It manifests as a spectrum of neuropsychiatric abnormalities that is usually found in patients with portosystemic shunting and cirrhosis[2]. According to the new AASLD/EASL guidelines, HE is classified into 4 axes which consist of the type of the underlying problem, disease severity, time course, and onset (Table 1)[3]. These axes are critical to evaluate HE episodes in context of the underlying clinical

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condition. For example, describing the axes in a cirrhotic woman with her second episode of HE due to a urinary tract infection (UTI) who is disoriented to time with asterixis would be "Type C, Grade 2, Recurrent and Precipitated Overt HE". Defining each HE episode in these four axes would encourage clinicians to investigate potential root causes i.e. UTI in patients to prevent recurrence and potentially improve management.

According to severity, HE can be divided into two broad categories: covert HE (CHE) and overt HE (OHE)[4], which are both part of the spectrum of neurocognitive impairment in cirrhosis (SONIC)[5]. The prevalence of CHE has been reported in 30–85% of cirrhotics when tested[6,7], whereas OHE is estimated to occur in up to 30–50% in patients with cirrhosis, with an annual risk for development of 20%[8]. This incidence for development is also associated with high rates of hospitalizations, which continues to rise[9], along with increased healthcare cost[10]. In addition, there is substantial data to reflect its negative impact on patients' health related quality of life (HRQOL)[11], and on survival independent from the severity of cirrhosis[1,12,13].

CHE is regarded as the pre-clinical stages of OHE (which consists of minimal HE, MHE, and West Haven grade 1 HE[14]). The entity CHE was created by combining MHE and grade I HE because of the poor reliability of the grade I stage. Therefore under the new classification, OHE starts with grade 2 or with evidence of asterixis and disorientation. CHE has several prognostic implications[5]. It is associated with increased progression to OHE[15], poor HRQOL[16], and high risk for traffic violations and accidents[17]. CHE is also an independent predictor for death and hospitalizations[18].

The burden of CHE and OHE is vast given their effects on the patient, family and society. Considering that these syndromes affect HRQOL, driving, ability to work, and health care costs, it important for a clinician to recognize and treat CHE and OHE in an effort to improve these conditions. Thus, this review will cover the pathophysiology, diagnosis, and management of CHE and OHE.

PATHOPHYSIOLOGY

The pathophysiology of HE (overt and covert) is complex with multiple components, which act alone or in combination (Figure 1), with an end product of functional neuronal impairment. These components include ammonia, inflammatory cytokines, benzodiazepine-like compounds, and manganese deposition[19].

Ammonia

There is robust evidence that ammonia plays an important role in the pathogenesis of HE. Ammonia is generated from nitrogenous products in the diet, bacterial metabolism of urea and proteins in the gut, and from deamination of glutamine in the small intestine via glutaminase[20]. Normally, ammonia is converted to urea in the liver and then subsequently cleared by kidneys. A small amount is also cleared by skeletal muscle via glutamate. However, as a result of liver dysfunction, portosystemic collaterals and sarcopenia in cirrhosis, ammonia cannot be cleared adequately and subsequently ammonia concentration rises in the blood and crosses the blood-brain barrier (BBB)[21] leading to brain edema[22].

Continued exposure of ammonia in the brain also leads to other physiological disturbances. For example, ammonia may bind to the GABA receptor complex on astrocytes, which may trigger synthesis of neurosteroids, which are GABA agonists[23]. Other neurotransmitters, such as serotonin, acetylcholine, glutamate, and monamines, have also been suggested to contribute in the pathogenesis of HE.

Inflammation and Microbiota

Inflammation is an important patho-physiological component of HE. The pro-inflammatory milieu in cirrhosis is associated with liver inflammation and alterations of intestinal microbiota, which is worsened by infections, gastrointestinal bleeding and obesity. This pro-inflammatory milieu and gut dysbiosis[24] is associated with the release of pro-inflammatory cytokines, such as interleukin 1 (IL-1), IL-6, and tumor necrosis factor (TNF). These cytokines work in conjunction with ammonia to contribute to the development of cerebral edema in HE[25].

DIAGNOSIS OF HEPATIC ENCEPHALOPATHY

CHE: DIAGNOSIS

CHE is a challenging diagnosis to make given that there is no disorientation or asterixis on examination. However, patients with grade 1 West Haven Criteria (WHC) HE, who are currently included in the realm of CHE, may have cognitive complaints brought by themselves or by their companions. Patients with CHE have abnormalities on psychometric testing, particular in areas of attention, executive functions, visuo-spatial coordination, and psychomotor speed/reactions times[26]. Thus, testing strategies focus on finding abnormalities using paper-pencil, computerized or neurophysiologic tests. The choice of which tests or battery to select should be driven by the availability of local normative data, cost, and expertise (Table 2). The strategies for diagnosis are screening with high-sensitivity tests that can then be used to determine whether patients are likely to have CHE or to test all relevant patient populations using recommended tests. Of the three categories of tests, 2 need to be abnormal in multi-center studies while 1 testing strategy may be enough for single-center studies in recent guidelines[3,4].

Paper-pencil Testing—A paper and pencil test battery called Psychometric Hepatic Encephalopathy Score (PHES) is often regarded as the gold standard[2]. PHES is highly sensitive and specific (96% and 100% respectively) for determining CHE (total cut-off score <-4), with a score < −6 conferring a poor prognosis[17]. In places where there are no PHES normative reference values, it is recommended that at least 2 of the following neuropsychological tests be used: NCT-A, NCT-B, block design, and digit symbol test.

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a 20–25 minutes paper-and-pencil battery to diagnose CHE[27]. It includes copyrighted sets of tests that assess cortical and subcortical domains. Lately however, it has not been used in this field due to two domains (language and delayed memory) being relatively preserved in CHE with relatively poor performance in HE[28].

Computerized tests—Inhibitory Control Test (ICT) is a computerized test that evaluates inhibition, attention span, vigilance, and working memory[29]. Here, a patient responds to target letters (such as X and Y) and not to lures (non X and Y targets). CHE is diagnosed when patients have longer reaction times, lower rate of target responses, and higher rate of lure responses with a sensitivity and specificity of 87% and 77% respectively[32]. The ICT is easy to administer, free, and validated, however it requires highly functional patients.

The Cognitive Drug Research (CDR) battery is another tool used to diagnose CHE[30]. Impairment in all domains characterizes a patient with CHE comparable to the PHES. CDR has good validity, easy to use, and inexpensive. However it has not been validated for the US population.

Lastly, the EncephalApp Stroop smartphone App[31] is a short and valid tool used to screen for CHE. The application tests psychomotor speed and cognitive alertness via measuring the time to correctly identify a series of symbols with different colors ("off-time") and printed words with different colors ("on-time"). A cut off of >190 seconds identified CHE with excellent accuracy[32]. The application is free, easy to use, accessible, and may be ideal for centers who do not have access to formal testing, or for clinicians who are interested in rapid screening to separate out patients who would otherwise test normal on formal testing.

Neurophysiological Testing—Electroencephalography (EEG) is an electrophysiological test that can be used to access neuropsychiatric impairments in cirrhosis[33]. The sensitivity for diagnosing HE ranges from 43% to 100%[34]. EEG is associated with both inter and intra observer variability. In addition, it is resource intensive by requiring a technician and a neurologist, costly, and thus may not be ideal to diagnose CHE.

The clicker flicker frequency (CFF) test measures cortical function, and correlates well with those of psychometric tests[35]. Here patients are shown light pulses at an initial frequency of 60Hz and gradually reduced by 0.1Hz per second. Patients are asked to identify the time of which of the light begins to flicker. A CFF below 39 Hz accurately diagnoses CHE by 73–83% and correlates well with PHES[36]. CFF can be affected by medications, age, and equipment used[5]. However even with its limitations, the CFF is a simple, valid, and effective tool that can be used to diagnose CHE.

Evoked potentials, visual, auditory, and somatosensory, have also been used to diagnose CHE[8]. These tests, however, are highly variable with inconsistent results.

Pragmatic approach to CHE screening and diagnosis: While most of the tests mentioned above are validated, they are often difficult to perform in clinical practice. So pragmatic cognitive solutions that can potentially be administered and interpreted by medical assistants, nurses or allied health practitioners are a potential "vital sign" could be relevant. It is also important to note that cognitive testing could also be performed outside the clinic on a separate appointment, such as prior to ultrasound etc. to reduce the burden on the clinic staff.

The simplest screening/diagnostic approaches are the use of HRQOL questionnaires such as 4 questions of the Sickness Impact Profile[37] and the use of EncephalApp Stroop[32]. If all 4

specific questions in the SIP ("I am eating much less than usual", "I am not doing any of my usual physican recreation or activities", "I do not maintain balance" and "I act irritable or impatient with myself") are positive, there is an 80% likelihood of CHE. Similarly as mentioned above, >190 seconds value on EncephalApp Stroop also has >80% sensitivity for CHE diagnosis.

These tests have good negative prediction value, therefore patients performing normally on them can potentially be re-tested in 6 months while only those who perform poorly could be referred for a treatment trial or more formal testing. In addition, collaboration with a psychologist for evaluation of these results or for further detailed testing may be needed for clinicians who require further interpretation and guidance

OHE: DIAGNOSIS

The diagnostic strategies for OHE are inconsistent given its subjectivity, and thus require careful attention in each case. Traditionally OHE severity is graded by the WHC[14], which now consists of stages 2–4 in the new classification. OHE is usually associated with a precipitating factor(s) such as: gastrointestinal bleeding, acute kidney injury, infection, constipation, electrolyte imbalances, and other forms of liver injury (alcoholic injury, portal vein thrombosis, hepatocellular carcinoma). OHE must be differentiated from other neurological diseases such as acute cerebro-vascular accidents (CVA), alcohol-related issues, and other forms of metabolic encephalopathy.

Clinically, patients with OHE demonstrate global neurological deficits. In stages 2–3, motor system abnormalities are clinically apparent. These include hyper-reflexia, hypertonia, asterixis, bradykinesias, rigidity, tremors, and ataxia. Note that asterixis is not pathognomonic for OHE as it can observed in other disease processes such as hypercarbia and uremia[8]. Mentally (either behaviorally or cognitively), patients may be aggressive, agitated, disoriented to time and place, display bizarre behavior, have personality changes, have slurred speech, lethargic or apathetic. In stage 4, patients are comatose and examination will reveal diminished or absent deep tendon reflexes, with the presence of pyramidal tract signs without asterixis.

Currently there are no "gold standard" laboratory markers that can be used to diagnose OHE but rather are useful to define precipitating factors or alternative explanations for altered mental status. While elevated blood ammonia levels are often found in OHE in large population studies, in an individual patient however, it is often not useful as a diagnostic test[38]. On the other hand, a normal ammonia level in a cirrhotic with altered mental status should question the diagnosis of OHE[3]. In addition, venous ammonia levels are influenced by multiple factors, including how the sample was collected: the use of a tourniquet, fist clenching, and whether the sample is placed immediately on ice[38]. Lastly, though not routinely recommended as a diagnostic tool for HE, brain imaging (CT and MRI[39]) can help exclude other intracranial pathology.

MANAGEMENT OF CHE AND OHE

The treatment and management of HE depend on its severity and acuity. Patients with CHE are mostly managed as an outpatient using non-absorbable disaccharides, antibiotics (i.e. rifaximin) and other agents. Based on its severity, OHE can be managed both as outpatient or inpatient with similar agents. Goals of therapy for CHE include the prevention of OHE and OHE-related hospitalizations, improve HRQOL, prevent hospitalizations, and mortality. The goals of therapy for OHE episodes are to diagnose and treat the inciting factor, as up to 90% of patients will have a precipitant[40], and improve mental status. In addition, after an episode of OHE, therapy should also be directed in preventing recurrence, improve HRQOL, and consideration for liver transplant. A focus should also be directed on patient and family member education on the disease progression and adherence to medications. An algorithm for the management of CHE and OHE can be found on Figure 2.

The treatments are studied in the context of

A. CHE

B. Episode of OHE

C. Secondary prevention of OHE

Overview of medications for HE therapy

Non-absorbable Disaccharides—Lactulose and lactitol are common non-absorbable disaccharides used for HE treatment. When administered, they are degraded by microbiota in the colon to short chain organic acids creating both an acidic environment and an osmotic gradient in the intestinal lumen[20]. The acidic environment created is hypothesized to reduce ammoniagenic bacteria and convert ammonia to non-absorbable ammonium. In addition, the increased osmolality also causes intestinal cleansing via removal of excess fecal nitrogen through a laxative effect[20].

Lactulose is the most used disaccharide for the treatment of HE. It is usually administered as an oral syrup with dosages titrated for a goal of 2–4 soft bowel movements a day[20]. Lactulose can also be given rectally (300 ml in 700 ml of saline), which is preferred in those in whom oral administration is contraindicated (Grade 3 or higher WHC). Common side-effects of lactulose include flatulence, abdominal discomfort, and diarrhea. Lactitol (which is not available in the US) is a crystalline powder that is generally better tolerated and as efficacious as lactulose[20].

Antibiotics—The rationale of using antibiotics for HE is to prevent the production and absorption of gut-derived neurotoxins, such as ammonia, along with reduction in endotoxemia and inflammation[41]. Antibiotics that been studied include neomycin, metronidazole, vancomycin, paromomycin, and rifaximin, although only rifaximin remains in regular usage in the US.

For OHE, all the aforementioned antibiotics have been tested. However, inadequate sample size, adverse side-effects (such as ototoxicity and nephrotoxicity of neomycin), and the potential for resistance (vancomycin-resistant enterococcus) has limited their use. An

exception from these agents is rifaximin, which has the safest side-effect profile and largest evidence base.

Rifaximin is a gut specific, non-absorbable oral antibiotic that has a broad spectrum of activity against both gram positive and gram negative bacteria, and anaerobic enteric bacteria[41]. It binds to the bacterial DNA dependent RNA polymerase and disrupts RNA synthesis. It is approved by the U.S. Food and Drug Administration (FDA) for only secondary prevention of OHE. The most common side-effects reported include flatulence, abdominal pain, headaches, and constipation.

Probiotics—Probiotics are live microbiologic dietary supplements that alter the intestinal balance of microflora in the gut. The mechanism of action of probiotics in HE is thought to be the deprivation of substrates for potentially pathogenic bacteria and providing a healthy environment for beneficial bacteria[42]. At this time, however, neither the mechanism nor the optimum probiotic organism has been identified or have been studied against each other. Adding to the complexity is the lack of standardization of these agents in the US, and that they do not fall under the review of the FDA.

CHE Management

It is important to note that most studies in CHE did not measure outcomes data such as hospitalizations, OHE prevention, or death. But rather had endpoints such as improvement in HRQOL and cognitive testing.

Numerous controlled trials comparing lactulose or lactitol to placebo have shown improvement in the psychometric and neurophysiologic variables for CHE, but did not show any improvement in mortality[43,44,45,46,47] (Table 3). In a meta-analysis including 9 randomized controlled trials (RCT) comparing lactulose to placebo or with no intervention, lactulose significantly reduced the risk of no improvement in neuropsychological tests, prevented the progression to OHE, and improved HRQOL[48]. However larger, blinded studies are needed to better analyze this issue.

There is limited evidence for rifaximin in the management of CHE[49,50]. Rifaximin has been shown to improve the driving ability in patients with CHE and also improve cognition[49]. This was further validated in a study by Sidhu et al[50] where the authors concluded rifaximin significantly improved cognitive function and HRQOL. However at the current prices, rifaximin is cost-prohibitive for treatment for CHE[51].

Probiotics have shown potential for the management of CHE. In a meta-analysis of 9 studies, the use of probiotics significantly reduced the risk of no improvement of MHE[52]. Furthermore, in a recent open label trial by Lunia et al[53], 3 month use of probiotics was found to be effective in preventing the first occurrence of OHE and had improved scores in cognitive testing. VSL #3 probiotics has also shown efficacy for improvement of CHE[54] and awaits further validation. Furthermore, probiotics have been found to reduce endotoxemia in patients with CHE. In a phase 1 controlled trial of Lactobacillus GG vs placebo, CHE patients taking Lactobacillus had reduced levels of endotoxemia, TNF-alpha, and dysbiosis[55].

OHE Management

The use of lactulose or lactitol for OHE has been the mainstay of therapy despite its variable efficacy in trials[56,57,58,59] (Table 3). It should also be noted that these studies were small and underpowered. In a meta-analysis by Als-Nielsen et al[60], when compared to placebo or no intervention, non-absorbable disaccharides had no statistically significant effect on mortality, but did show to reduce the risk of no improvement of OHE. Thus far there is insufficient evidence that lactulose is efficacious for OHE, however, there is an overwhelming clinical anecdotal experience and comfort for the use of lactulose, which accounts for the lack of placebo RCT for HE.

A number of studies have been performed comparing rifaximin with other antibiotics or lactulose/lactitol in the treatment of OHE (table 4)[61,62,63,64,65,66,67,68,69,68]. Rifaximin has shown to be superior to lactulose and other antibiotics in patients with OHE[70]. In view of the data, rifaximin has a definite role in the management of OHE and there are trials on the way to further validate its role.

Unlike CHE, the data for probiotics in OHE are inadequate given the sample size, different probiotics used, and questionable duration of treatment. In a Cochrane meta-analysis of 7 CHE/OHE trials[71] there were no reported differences of probiotics compared to lactulose with respect to reduction in ammonia levels and improvement in mental status. The analysis did show an advantage of probiotics to no treatment in all-cause mortality, number of adverse events, and HRQOL.

Secondary Prevention of OHE

Data for nonabsorbable disaccharides for secondary prevention for OHE have been sparse. In an open labeled RCT, Sharma et al[72] showed that lactulose was able to prevent recurrent OHE. However, in the real-world this is often not tolerated in the US population, where 46% of recurrences were due to lactulose misuse[73].

Bass et[68] al showed that rifaximin (vs. placebo, >90% on lactulose) was more effective in preventing OHE over 6 months compared to placebo. In a follow up long term open label study, rifaximin continued to provide a reduction in the rate of HE-related and all-cause hospitalizations, without an increased rate of adverse events[74]. This was further validated by Bajaj et al[75] in a placebo cross-over sub-analysis. Furthermore, in a recent meta-analysis[76] that included 19 RCT with 1370 patients, rifaximin was found to have a beneficial effect on secondary prevention of OHE, increased the proportion of patients who recovered from OHE, and reduced mortality.

Probiotics have also been studied for secondary prevention. In an open-labeled trial[77], VSL#3 was found to be similar to lactulose for secondary prevention. This was confirmed in a double-blind, randomized VSL#3 trial[78] where the VSL#3 arm resulted in significant reduction in recurrent OHE episodes and hospitalizations, all-cause hospitalizations, and had improved cirrhosis severity. The use of probiotics still needs validation in terms of which specific organism(s) are to be used and ensuring pharmaceutical-grade products --which are often unavailable.

Other therapies

L-Ornithine-L-Aspartate, Ornithine Phenylacetate, and Glycerol Phenylbutyrate—L-ornithine-L-aspartate (LOLA, not available in the US) can reduce blood ammonia levels via stimulating both the urea cycle and glutamine synthesis[19]. It has been studied extensively with better results with its intravenous rather than oral formulation across the HE spectrum[79,80,81,82,83,84].

Ornithine phenylacetate (OP) [85] and glycerol phenylbutyrate (GP) [86] are drugs that have shown to reduce ammonia levels and promise for the treatment of both OHE and secondary prevention. Further trials are underway for both OP and GP in the management of HE.

Zinc—Low levels of zinc leads to impairment of the urea cycle enzymes and glutamine synthetase, thus leading to elevated ammonia levels[19]. Zinc supplementation for the treatment for HE has been limited given the small number of trials and subjects, however, results from these studies have shown decreased ammonia levels and an improvement in cognitive testing[87]. Thus, the current role of zinc supplementation is in patients who are zinc deficient and who are resistant to usual therapy for HE.

Albumin and Albumin Dialysis—Albumin infusion and using albumin dialysis (i.e. molecular adsorbent recirculating system, MARS) has been observed for the treatment of OHE. In a small trial of 56 patients[88], albumin infusion did not show faster resolution of OHE, but unexpectedly showed a mortality benefit in the albumin treated group. MARS dialysis has shown to improve OHE[89] and refractory HE[90], though there was no survival benefit seen.

Miscellaneous Agents—Other agents such as sodium benzoate, levocarnitine, acarbose, benzodiazepine receptor antagonists, have no significant role in the management of CHE and OHE given limited recent trial data[8].

NUTRITIONAL MANAGEMENT

The AASLD and ISHEN recommends that patients with cirrhosis should have 1.2g/kg to 1.5g/kg of protein daily to maintain muscle mass[3,91]. In addition, increasing intake of branched-chain amino acids (BCAAs) may be beneficial for HE, but did not show any mortality benefit and improvement in HRQOL. BCAA's are not readily available in the US.

MANAGEMENT OF REFRACTORY HE

There are rare instances where a patient will have continued recurrences of OHE despite optimal medical management and compliance. Here it is imperative to search for other possible reasons such as spontaneous portosystemic shunts (Figure 2). In those patients in whom HE does not improve despite aggressive medical therapies, liver transplant is the definitive treatment.

FUTURE DIRECTIONS

Future directions for the study of HE includes convenient, rapid, and validated methods to diagnose CHE, as well as better objective methods to diagnose the severity of OHE. This is paramount as early recognition could impact morbidity and mortality, and HRQOL. At this time therapy for CHE can be used in selected cases for psychosocial purposes as further trials are needed to substantiate the role of therapy in routine clinical practice. Clinicians should also be meticulous in the management of patient after an episode of OHE, by helping preventing further episodes, liver transplant evaluation, and education on how to administer their medication. There are numerous newer agents under study to add to our armamentarium.

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Listing of Abbreviations

HE	hepatic encephalopathy
CHE	covert hepatic encephalopathy
OHE	overt hepatic encephalopathy
SONIC	spectrum of neurocognitive impairment in cirrhosis
MELD, HRQOL	health related quality of life
MELD	model for end-stage liver disease
BBB	blood brain barrier
IL	interleukin
TNF	tumor necrosis factor
GABA	γ-aminobutyric acid benzodiazepine system
WHC	west haven criteria
PHES	psychometric hepatic encephalopathy score
NCT-A	number connection test
ISHEN	International Society for Hepatic Encephalopahty and Nitrogen Metabolism
RBANS	the Repeatable Battery for the Assessment of Neuropsychological Status
ICT	inhibitory control test
CDR	cognitive drug research
AUC	area underneath the curve

EEG	electroencephalography
CFF	critical flicker frequency
CVA	cerebro-vascular accidents
RCT	randomized controlled trials
FDA	Food and Drug Administration (FDA)
LOLA	L-ornithine-L-aspartate
OP	Ornithine phenylacetate
GP	glycerol phenylbutyrate
MARS	molecular adsorbent recirculating system
AASLD	American Association For the Study of Liver Disease
BCAA's	Branched-chain amino acids

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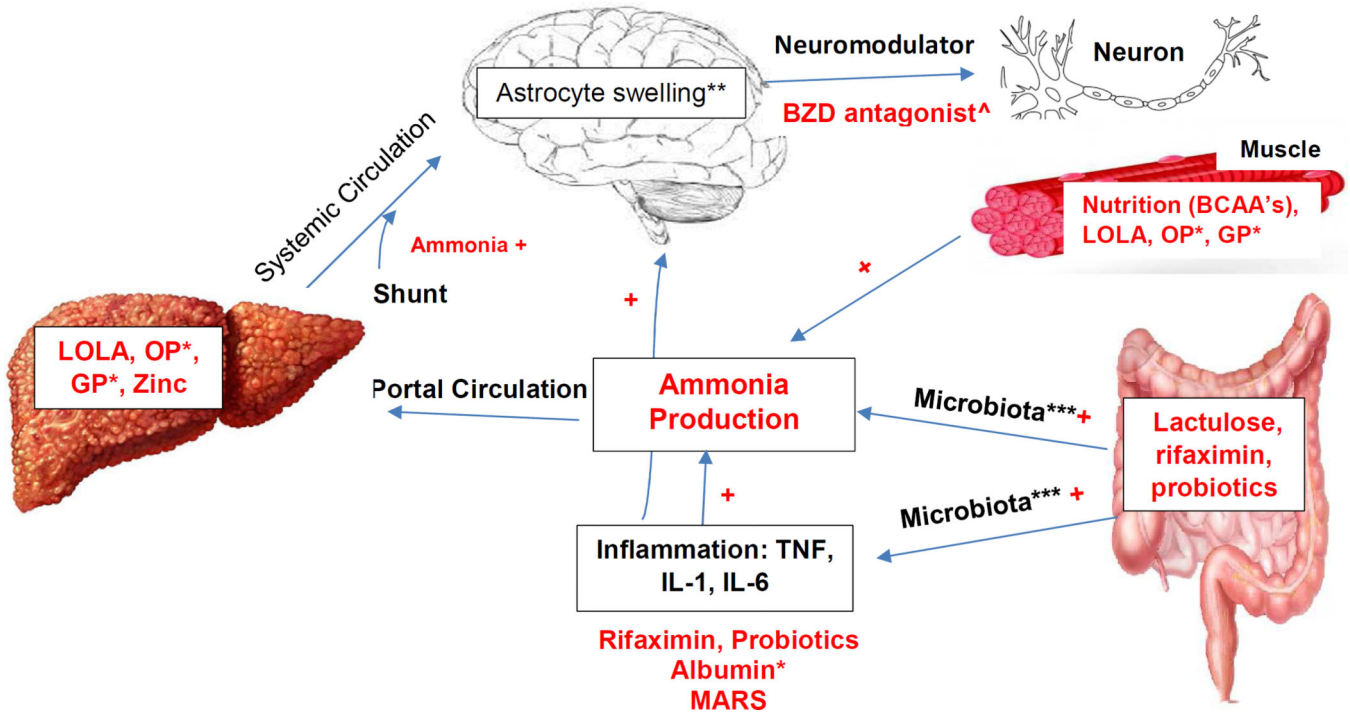

FIGURE 1. Pathophysiology and Potential Therapeutic Targets of Hepatic Encephalopathy

*Experimental therapy

** In the brain, astrocytes metabolize ammonia through glutamine synthetase, converting glutamate and ammonia to glutamine which is osmotically active. Increased levels of ammonia leads to an increased production of glutamine which changes the osmotic gradient and causes intracellular swelling and edema. In addition, neurons may be affected by increased "GABAergic tone" from synthesis of benzodiazepine like compounds from the intestinal flora.

***Microbiota may be responsible for the formation or release of products such as ammonia, endotoxins, indoles, oxindoles, and other gut derived toxins that may lead to cognitive impairment.

^Flumazenil (not currently used)

+Contributing factors

LOLA, L-ornithine L-aspartate; OP, Ornithine –phenylacetate; GP, Glycerol –phenylbutyrate; TNF, tumor necrosis factor; IL, interleukin; BZD, benzodiazepine receptor antagonist

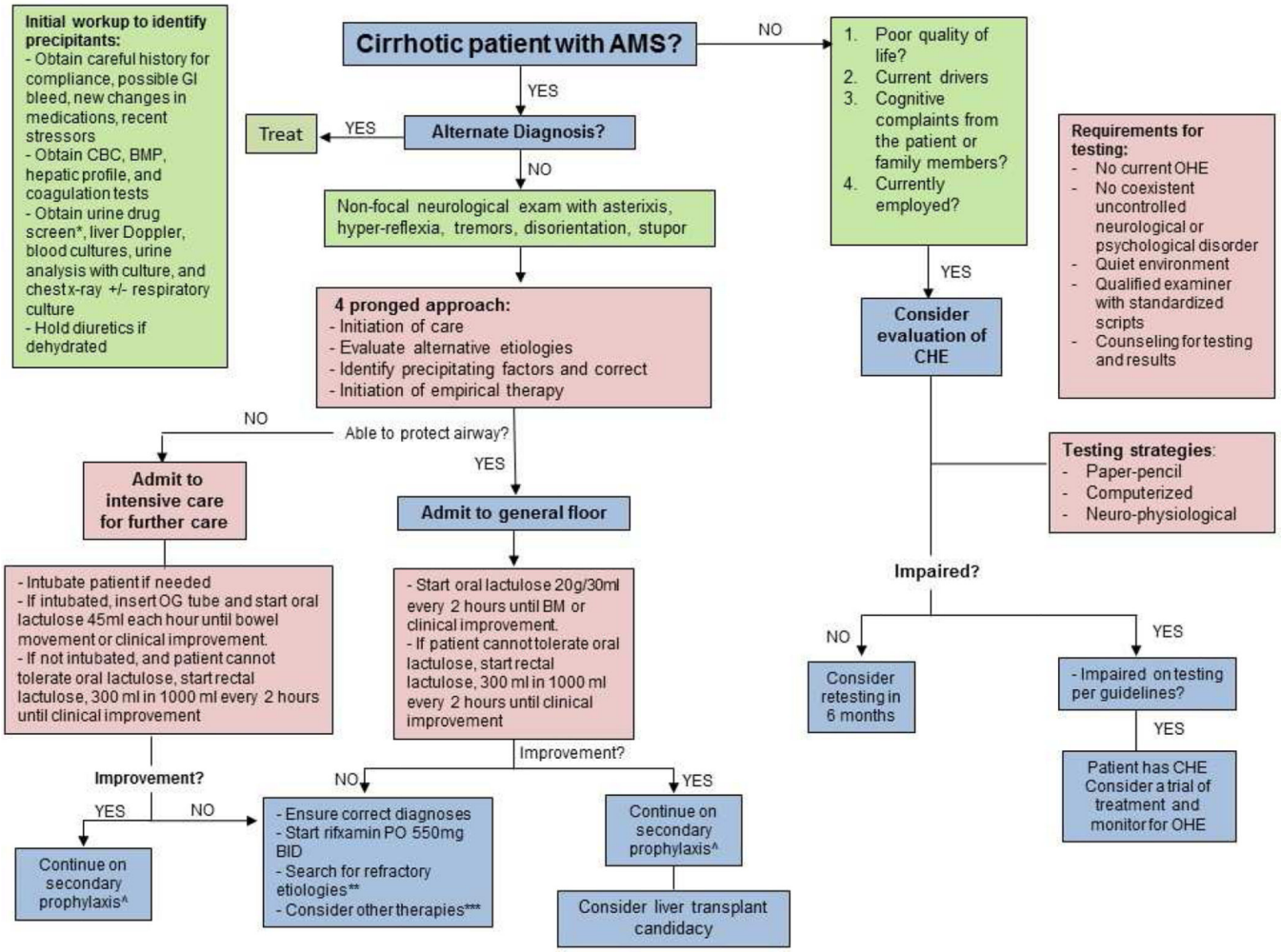

FIGURE 2. Management of Covert and Overt Hepatic Encephalopathy

* if suspicious based on history

** Potential reasons for refractory HE: worsening of liver disease only, failure to identify infection and dehydration, ileus, long acting sedative drug use, concomitant central nervous system diseases or metabolic diseases (i.e. hypothyroidism), transjugular intrahepatic portosystemic shunt dysfunction or supra-therapeutic shunt diameter (if present), profound zinc deficiency, and spontaneous portosystemic shunts.

***Zinc supplementation, LOLA (if available), IV albumin and albumin dialysis, Ornithine phenylacetate, Glycerol phenylbutyrate, spontaneous porto-systemic shunts

^Maintenance therapy: 1) lactulose titrated to 2–3 soft BM a day; if intolerant of lactulose start rifaximin 550mg PO BID 2) If > 2 overt episodes start both lactulose and rifaximin; ensure compliance with lactulose along with education (an re-education).

AMS, altered mental status; GI, gastrointestinal; BM, bowel movement; CBC, complete blood count; BMP, basic metabolic panel; OG, oral gastric; CHE, covert hepatic encephalopathy; OHE, overt hepatic encephalopathy

TABLE 1

Modified Axes of Hepatic Encephalopathy

Type	Grade		Time course	Spont./Precip.
A (acute liver failure)	MHE	Covert	Episodic (one episode in 6 months)	Spontaneous (no precipitating factor found)
	1			
B (porto-systemic bypass)	2	Overt	Recurrent (>1 episode in 6 months)	
	3			Precipitated
C (cirrhosis)	4		Persistent (never returned to baseline)	

Adapted from Vilstrup el al 2014[3] with permission. MHE, minimal Hepatic encephalopathy; Spont, spontaneous; Precip, precipitated

TABLE 2

Testing for Covert Hepatic Encephalopathy

Test (Domains Examined)	Advantages	Disadvantages	Diagnoses	Outcome Prediction
Paper-Pencil				
PHES: NCT-A and B, digit symbol test, line-tracing test, and serial-dotting test (attention, processing speed, response inhibition, and visuo-spatial awareness)	Validated, gold standard	Lack of reference normative data in the US.	Score of <-4	Score <-6 predicted poor survival
RBANS (visuo-spatial, attention, language, immediate and delayed memory)	Has US reference data	Copyrighted, needs psychologist interpretation	Dependent on psychologist interpretation	not studied in HE; 2 domains not impaired in CHE
Computerized				
ICT (working memory, response inhibition, psychomotor speed)	Validated and does not require psychologist interpretation	Requires high functioning patients with working knowledge of a computer	high lures or weighted lures	Significant impairment leads to increased MV crashes and violations, and predicting OHE
CDR (attention, continuity of attention, speed of memory, and quality of episodic and working memory)	Not validated in US	Requires high functioning patients with working knowledge of a computer	Score of −5 to 15	Able to predict resolution of cognitive dysfunction post-transplant and TIPS
Continuous Reaction Time (sustained cerebral processing time, reaction time and response inhibition, and nerve inhibition)	Not validated in US	Requires adequate hearing no reference data for US.	CFTindex of <1.9	--
EncephalApp Stroop Application (psychomotor speed, cognitive flexibility)	Free, and can be used on a mobile platform. Has US reference data	Cannot be done in red-green color blind subjects	>190 seconds (on and off time)	Longer times can predict OHE episodes
Neurophysiological				
EEG (brain activity mean dominant frequency)	Can be used on all stages of HE without learning	Highly variable, requires neurologist interpretation	Dependent on neurologist interpretation	EEG plus MELD increases accuracy in predicting prognosis
CFF (visual processing and discrimination, general arousal)	Test can be administered at bedside	Requires high functioning patients and expensive equipment, needs binocular vision	CFF< 39 Hz	Can predict OHE
Evoked potentials (visual, auditory, and somatosensory)	Sensitive without learning effects	High variable results, requires neurologist interpretation	Variable, dependent on neurologist interpretation	Can predict the development of OHE

PHES, psychometric hepatic encephalopathy score; NCT, number connection test; RBANS, repeatable battery for the assessment of neuropsychological status; MELD, Model of Endstage Liver disease; ICT, inhibitory control test; CDR, cognitive drug research; EEG, electroencephalography; HE, hepatic encephalopathy; CFF, clicker flicker frequency, OHE, overt hepatic encephalopathy; CTP, Child-Turcotte-Pug; MELD, Model for Endstage Liver Disease; TIPS, transjugular intrahepatic portosystemic shunt

TABLE 3

Trials for the Treatment of Covert and Overt Hepatic Encephalopathy

Trial	Treatment	Total Pts	S tudy Design	Assessment	Efficacy
Covert Hepatic Encephalopathy					
Horsmans et al	Lactulose vs. placebo	14	RCT	Psychometric tests, ammonia levels	Lactulose > placebo for psychometric tests
Watanabe et al	Lactulose vs no treatment	36	RCT	Psychometric tests, ammonia levels	Lactulose > no treatment for psychometric tests
Dhiman et al	Lactulose vs no treatment	26	RCT	Psychometric tests	Lactulose > placebo
Prasad et al	Lactulose vs no treatment	61	NB-RCT	Psychometric tests, HRQOL	Lactulose > placebo for psychometric tests and HRQOL
Sharma et al	Lactulose vs lactulose + probiotics vs probiotics alone	105	NB-RCT	3 psychometric tests, ammonia levels	Lactulose + probiotics > lactulose > probiotics for all parameters
Bajaj et al	Rifaximin vs placebo	42	DB-RCT	Total driving errors, cognitive performance, SIP, ammonia levels, inflammatory cytokines	Rifaximin > placebo for total driving errors, cognitive performance, SIP, and anti-inflammatory markers
Sidhu et al	Rifaxmin vs placebo	94	DB-RCT	2 psychometric tests, SIP	Rifaximin > placebo for all parameters
Lunia et al	Probiotics vs placebo	160	OL-RCT	Psychometric tests, CFF, glucose and lactulose hydrogen breath test, ammonia levels	Probiotics > placebo for all parameters
Bajaj et al	Probiotic (Lactobacillus GG) vs placebo	30	RCT	Endotoxemia, TNF-α levels, dysbiosis	Lactobacillus > placebo for all parameters
Pratap Mouli et al	Probiotic (VSL#3) vs lactulose	120	OL-RCT	Psychometric tests, ammonia levels	VSL #3 = lactulose (non-inferior) for all parameters
Stauch et al	LOLA vs placebo	66	RCT	CHE (psychometric tests), ammonia levels, PEI, WHC grade	LOLA > placebo for all parameters
Kircheis et al	LOLA vs placebo	114	DB-RCT	CHE (psychometric tests), ammonia levels, PEI, WHC grade	LOLA > placebo for all parameters
Mittal et al	LOLA vs lactulose vs no treatment vs probiotics	160	OL-RCT	Psychometric tests, ammonia levels, HRQOL	LOLA = lactulose = probiotics for all parameters
Poo et al	LOLA vs lactulose	20	OL-RCT	Psychometric tests, WHC grade, asterixis, EEG	LOLA = lactulose for ammonia levels LOLA > lactulose for WHC grade, asterixis,

Trial	Treatment	Total Pts	S tudy Design	Assessment	Efficacy
					psychometric tests, EEG
Sharma et al	LOLA vs rifaximin vs probiotics vs placebo	124	RCT	Psychometric tests, CFF	LOLA = rifaximin = probiotics > placebo for all parameters
Alvares-da-Silva et al	LOLA vs placebo	64	DB-RCT	Psychometric tests, CFF, EEG, ammonia levels, Beck's anxiety-depression, HRQOL, prevention of OHE	LOLA > placebo for prevention of OHE
Acute Episode of Overt Hepatic Encephalopathy					
Simmons et al	Lactulose vs glucose	26	RCT	WHC grade, ammonia levels, stool production	Lactulose = glucose for all parameters
Rodgers et al	Lactulose vs sorbitol	6	Crossover RCT	WHC grade, EEG, ammonia levels	Lactulose = sorbitol for all parameters
Uribe et al	Lactulose or lactitol (enema) vs placebo	15	DB-RCT	Mortality, WHC grade	Lactulose > placebo for all parameters
Elkington et al	Lactulose vs sorbitol	7	DB crossover RCT	Stool pH, ammonia levels, EEG	Lactulose vs sorbitol for all parameters
Festi et al	Rifaximin vs lactulose	21	DB, DD-RCT	Neurological signs of HE, asterixis score, EEG, HNRB, ammonia levels	Rifaximin = lactulose for all parameters
Buci et al	Rifaximin vs lactulose	58	DB, DD-RCT	Neurological status, asterixis score, cancellation tasks, HRNB EEG, ammonia levels	Rifaximin > lactulose
Massa et al	Rifaximin vs lactulose	40	DB, DD-RCT	HE index severity, mental status, cancellation tasks, HRNB, EEG	Rifaximin > lactulose for all parameters
Fera et al	Rifamixin vs lactulose	40	DB, DD-RCT	Mental status, asterixis score, cancellation tasks, HRNB, EEG, ammonia level, PSI	Rifaximin > lactulose for all parameters
Mas et al	Rifaxmin vs lactitol	103	DB,DD-RCT	Mental status, asterixis score, EEG, PSI, psychometric tests	Rifaximin = lactitol for mental status and asterixis score; Rifxamin > lactitol for PSI, psychometric tests, and EEG
Leevy et al	Rifaxmin vs lactulose	145	Cross-over	WHC grade, asterixis score, hospitalizations	Rifaximin > lactulose for all parameters
Paik et al	Rifaxmin vs lactulose	54	OL-RCT	Ammonia levels, flapping tremor, mental status, HE index, psychometric tests	Rifaximin = lactulose for all parameters
Sharma et al	Rifaximin + lactulose vs lactulose	120	DB-RCT	Reversal of HE, mortality, hospital stay	Rifaximin + lactulose >lactulose for all parameters
Secondary Prevention of OHE					

Trial	Treatment	Total Pts	S tudy Design	Assessment	Efficacy
Sharma et al	Latulose vs placebo	140	OL-RCT	Psychometric tests,CFF, ammonia levels, re-admission for HE, mortality,	Lactulose > placebo for readmission for HE
Bass et al	Rifaximin vs placebo (>90% pts on lactulose)	299	DB-RCT	Time to first breakthrough HE, time to first HE-related hospitalization	Rifaximin > placebo for all parameters
Agrawal et al	Lactulose vs probiotics vs no therapy	235	RCT	Psychometric tests, CFF, ammonia levels, secondary prevention of OHE, mortality	Lactulose = probiotics > no therapy for secondary prevention of OHE
Dhiman et al	Probiotic (VSL #3) vs placebo	130	DB-RCT	Secondary prevention of OHE, all-cause hospitalizations, CTP and MELD score	Probiotics > placebo for all parameters

Pts, patients; RCT, randomized controlled trial; NB, non-blinded; DB, double blind; OL, open labeled; DD, double dummy; NCT, number connection test; MHE, minimal hepatic encephalopathy, SIP, sickness impact profile; CFF, clicker flicker frequency; NCT, number connection test; OHE, overt hepatic encephalopathy; TNF-α, tumor necrosis factor alpha; LOLA, L-ornithine-L-aspartate; PEI, portosystemic encephalopathy index; WHC, West Haven Criteria; CHE, covert hepatic encephalopathy; EEG, electroencephalography; HRNB, Halstead-Reitan Neuropsychological Battery; HE, hepatic encephalopathy; CPT, Child-Turcotte-Pugh; MELD, Model for Endstage Liver Disease