Hepatic Encephalopathy in LTC Residents: Missing a Potential Cause of Change in Mental Status in Patients With Cirrhosis

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Abstract: Hepatic encephalopathy (HE) is a frequently overlooked cause of change in mental status in older long-term care (LTC) residents with cirrhosis. HE is common in all patients with cirrhosis but especially in older residents of LTC facilities. Diagnosis is difficult due to the slow emergence of symptoms, including deficits in consciousness, intellect and neuromuscular function, and the ability of other diseases to mimic these symptoms. Delirium in older patients with HE is often misdiagnosed, thereby precluding disease-modifying treatment. Elevated blood ammonia levels may be associated with HE due to impaired hepatic detoxification that is not offset by metabolic activity of other organs. Early diagnosis and treatment optimization depend on the vigilance and expertise of an interdisciplinary team. The mainstay of treatment for overt HE is lactulose through its actions on intestinal microbiota. Its combination with rifaximin is best at preventing recurrence. Effectiveness of lactulose itself depends on accurate dose titration and patient adherence. Other less frequent treatment modalities include embolization of portosystemic shunts, nutritional and exercise modifications, and probiotics and liver transplantation. Identification and management of HE can improve quality of life for LTC residents impacted by this condition.

Key words: hepatic encephalopathy, cirrhosis, lactulose, rifaximin, long-term care
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Nursing home residents typically suffer from numerous comorbidities of which those associated with mental decline are prominent and progressive. There are many etiologies possible for a change in mental status. Lack of consideration of these multiple etiologies may lead to inappropriate medical therapies increasing morbidity and costs (**Table 1**).[1]

Potential causes of these etiologies and precipitating events can be quite extensive. This is particularly true for hepatic encephalopathy (HE), a frequently overlooked cause of delirium. HE is defined as a spectrum of neuropsychiatric abnormalities in patients with liver dysfunction after exclusion of brain disease. It can be characterized by personality changes, intellectual impairment, and a depressed level of consciousness. HE is most commonly a syndrome observed in patients with cirrhosis.[2] Subtle signs of HE are observed in nearly 70% of patients with cirrhosis. Cognitive impairment associated with cirrhosis results in more health care utilization than any other manifestation of liver disease.[2]

Given its extremely high prevalence, HE should be a condition that long-term care (LTC) providers are readily able to diagnose and treat.[3] However, due to its episodic nature, slow progression, and symptoms that overlap those of other

Table 1. Neuropsychiatric Symptoms/Abnormalities Which Might Indicate and Be a Part of Hepatic Encephalopathy

Behavior / Personality changes	Level of Consciousness and Awareness
Increased fidgeting	Bizarre behaviors, extremely different actions for this resident
Change in cooperation	Alteration in consciousness
Difficulty in attention	Glasgow coma definitions
Change in task segmentation ability	West Haven Criteria
Focus fluctuation	Significant cognitive changes
Orientation fluctuation	Withdrawal and inactivity and minimal engagement
Liver flap	Coma
Delirium symptoms	Shifting attention
Sleep cycle alteration-night-day confusion	
Calling out, making sounds, moaning	
Less interest in surroundings	
Change in verbalization	
Change in socialization	
Withdrawal from activities or meals	
Altered ability to dress, eat, or participate in activities of daily living	
May seem intentionally obstinate	
Unusual agitation	
Combativeness	

diseases, clinicians need to be both knowledgeable and vigilant regarding its prevalence, pathophysiology, diagnosis, and treatment. This article highlights these elements with particular emphasis on issues likely to be encountered by LTC staff and resident caregivers.

Diagnosis and Prevalence of HE in Patients With Chronic Liver Disease

HE is a disease in which the liver is unable to adequately remove systemic toxins—particularly ammonia—leading to changes in personality and impairment of consciousness, intellect, and neuromuscular functions. It is primarily associated with cirrhosis of the liver, but its pathophysiology is multifactorial. Other abnormalities such as portosystemic shunts (spontaneous, congenital, or iatrogenic), metabolic changes, adverse effects of drugs, and urinary tract infections can contribute to systemic accumulation of ammonia—which crosses the blood-brain barrier and leads to cerebral dysfunction.[4]

Chronic liver disease (CLD) affects over 5.5 million people in the United States,[5] of whom more than 600,000 have cirrhosis.[6] Most of these patients develop HE at some point in their lives, with a substantial impact noted throughout the available literature.[7,8] Prevalence of CLD is increasing due to aging of the population, increased recognition and diagnosis of viral hepatitides, and increases in obesity and diabetes that leads to nonalcoholic steatohepatitis (NASH).[9] Specifically, Kabbany et al reported that between the periods 1999-2002 and 2009-2012, there was a 2.5-fold increase in prevalence of NASH cirrhosis.[10] Moreover, a recent study detected minimal hepatic encephalopathy (MHE) based on psychometric testing in more than half of patients with cirrhosis of the liver.[11]

In older adults, a number of geriatric conditions such as delirium, confusion, uncooperative behaviors, drowsiness, and drug toxicity can mimic the symptoms of HE, making diagnosis difficult.[12,13] At the earliest stage, symptoms of HE are subtle and often only noticeable on neuropsychological and psychometric

Table 2. Diagnostic and Therapeutic Roles of LTC Interdisciplinary Team

Discipline	Diagnostic	Therapeutic
Nursing team	Medication administration with comfort and polypharmacy monitoring Compliance of medication consumption critical Signs and symptoms of cognitive changes, liver flap, HE Minimum data set assessment for changes, interim assessment, clinically complex resident with exacerbation of symptoms care planning Education of resident and family Support services Community health transitions of care support and follow-up Certified nursing assistant monitoring of food acceptance during acute and chronic phases. Assist with activities of daily living during disease exacerbations and assist with eating critical.	Patient and family education on medications and compliance Disease trajectory Behavior interventions Palliative, progressive disease care, and education End-of-life hospice care
Pharmacist	Polypharmacy monitoring Drug-Drug interactions Evidedce-based pharmaceutical guides, disease specific evaluation Therapeutic response	
Primary care provider	Clinical history and physical Order psychometric tests	Prescribe lactulose and rifaximin Coordinate with other specialists on diagnostics and treatment
Neurologist	Evaluate electroencephalogram	Neurologic disease management, pain management
Psychologist	Stroop test / smartphone	Patient counseling
Psychiatrist	Assess psychiatric symptoms Alcoholic liver disease, withdrawal	Patient counseling, management of anxiety, depression, pain
Infectious disease specialist	Rule out or treat infectious diseases having symptoms similar to HE, or which might precipitate or exacerbate HE	Prescribe appropriate antibiotics
Endocrinologist	Severe hyperglycemia and poorly controlled diabetes	Ensure that patient's glycemic levels are well-controlled
Nephrologist	Rule out or treat advanced renal disease and uremia	Treat renal disease, advise multidisciplinary team of implications for clearance of ammonia and other toxic substances
Social worker	Get feedback from patient and family on adherence to therapy Support and counseling-person centered Monitor for cognitive changes	Coordinate with family and other caregivers to help ensure adherence to therapy, support system, adequate housing
Occupational therapist	Evaluate safety of home and work environments, skill evaluations, driving, other life skills and activities affected by HE	Advise patient, caregivers, and multidisciplinary team of these risks and interventions to minimize them
Physical therapy / rehabilitation nursing	Fall risk; balance and strength assessments	Staff, family, and patient education; multidisciplinary safety plan; exercise and activity plan
Dietitian	Evaluate adequacy of total caloric and protein intake	Adjust diet to mitigate frailty and sarcopenia

Abbreviation: HE, hepatic encephalopathy.

tests.[3] Although clinicians may question the value of investment in such tests, prior research has shown that these tests can portend eventual development of behavioral, personality, and functional aspects of HE, as well as hospitalization and death.[14]

Many medications commonly given to older adults can directly or indirectly (through interactions with other medications) result in adverse effects such as delirium and other symptoms associated with HE. A differential diagnosis with consideration of other causes of altered mental status should be completed prior to treatment initiation.

Interdisciplinary Team Approach to Care

A well-coordinated interdisciplinary team approach will be critical for assessment, treatment, evaluation, and ongoing monitoring for exacerbations of HE (**Table 2**). The management of HE involves consultation from many disciplines, including primary care physicians, nurse practitioners, physician assistants, nurses, dietitians, hepatologists, neurologists, psychiatrists, surgeons, pharmacists, and social workers.[15] Since the diagnosis is based primarily on a high index of suspicion followed by tests and consults to exclude alternative cause of symptoms, these

Table 3. West Haven System for Grading Symptoms of Hepatic Encephalopathy

	Grade	Symptoms
Covert	0	Minimal hepatic encephalopathy and previously known subclinical hepatic encephalopathy; lack of detectable changes in personality or behavior; minimal changes in memory, concentration, intellectual function, and coordination; asterixis is absent
	1	Trivial lack of awareness; shortened attention span; impaired addition or subtraction; hypersomnia, insomnia, or inversion of sleep pattern; euphoria, depression, or irritability; mild confusion; slowing of ability to perform mental tasks
Overt	2	Lethargy or apathy; disorientation; inappropriate behavior; slurred speech; obvious asterixis; drowsiness, lethargy, gross deficits in ability to perform mental tasks, obvious personality changes, inappropriate behavior, and intermittent disorientation, usually regarding time
	3	Somnolent but can be aroused; unable to perform mental tasks; disorientation about time and place; marked confusion; amnesia; occasional fits of rage; present but incomprehensible speech
	4	Coma with or without response to painful stimuli

specialists must work closely to conduct and share critical information that can contribute to a definitive diagnosis and timely management. All consultants and specialists on the interdisciplinary team should be aware of psychometric testing instruments, including the psychometric hepatic encephalopathy score (PHES) and inhibitory control tests (ICT), which have demonstrated high sensitivity and specificity in the diagnosis of covert HE or MHE disease.[16]

Interdisciplinary assessment is critical for care management and planning for residents with HE and fluctuating, complex symptoms. Planning for short-stay residents with unique needs should include ongoing careful assessment and monitoring with a goal of preventing readmissions to the hospital. Visiting nurses may be needed for in-home and follow-up care. Appropriate social and psychosocial services should be offered, with an emphasis on educating both residents and families about liver disease, HE, and disease trajectory. Referral to community- and hospital-based support groups should be sought to provide families and residents with psychosocial health maintenance. Appropriate literature and pamphlets for education must be provided with consideration of a level of health literacy appropriate for those utilizing the information.

The role of the LTC nurse in recognizing symptoms of HE is critical to resident care. Daily assessment by the nurse may prevent symptoms from progressing from minor non-life-threatening to life-threatening issues requiring urgent intervention. Behavioral symptoms may present to the team as disturbing or disruptive, and may cause difficulty in differentiation between conditions such as delirium, dementia, or psychosis. An interdisciplinary team assessment is critical to quickly and proactively diagnose symptoms, ensuring prevention of serious clinical change. However, when neuropsychiatric symptoms are less prominent, assessment of subtle changes in clinical status requires astute team assessment, collaboration, and communication.

Development of screening and management from a facility standpoint involves an interdisciplinary team that includes consultant pharmacists, medical directors, directors of nursing, and directors of education and quality. From a facility standpoint, the development of screening and management ideally involves assembling an interdisciplinary team of consultant pharmacists, medical directors, directors of nursing, and directors of education and quality. This team, by facilitating efforts focused on behavior management, as well as on the nuances of individualized care, can have a major impact on provision of evidence-based quality care for residents with HE.

Complexity of Diagnosis and Treatment of HE in LTC Patients

Diagnosis

Although the proximate cause of brain dysfunction in HE is thought to be related to elevated ammonia, its levels are not closely correlated with symptoms and the diagnosis of HE must be made primarily on the basis of clinical observations.[16] Brain imaging by computed tomography scan is not helpful, insofar as it has not been shown that any structural changes correlate with clinical parameters of HE.[17,18] Thus, diagnosis begins with the recognition that the patient has advanced liver disease and other factors that may raise a clinician's index of suspicion, followed by other clinical and laboratory evaluations that may lead to more definitive findings.

Clinical symptoms specific to behavior and level of consciousness of HE are graded according to the West Haven Criteria (**Table 3**). Grades 0 and 1 comprise the general category of "covert" HE, where there is a lack of or minimally detectable clinical manifestations. These cases may require psychometric or neuropsychological tests to detect and confirm diagnosis. Grade 1 is designated for patients who appear to have some cognitive or behavioral losses such as minor lack of awareness, short attention span, or inverted sleep-wake cycle.

Grades 2-4 are designated as "overt." Grade 2 refers to patients who are disoriented with regard to time and may also show lethargy, apathy, dyspraxia, asterixis, personality changes, and inappropriate behavior. Patients with Grade 3 symptoms manifest disorientation with regard to space, confusion, gross disorientation, and bizarre behavior. Grade 4 is the most severe and patients are in a coma, not responding to even painful stimuli.[19]

HE is further subdivided by putative cause: (A, acute liver failure; B, portosystemic bypass without liver disease; C, chronic liver disease), frequency: (episodic, recurrent, persistent); and whether episodes of HE occur spontaneously or are precipitated by other factors.[3] Precipitants are involved in approximately 80% of cases and include factors such as gastrointestinal bleeding, infection, centrally-acting medications, renal failure, portosystemic shunts, and constipation.[20-22] Comorbid conditions impacting the liver and potentially contributing to the symptom manifestation and confusion may include hepatitis C, alcohol abuse disorder, and fatty liver with geriatric implications.[23]

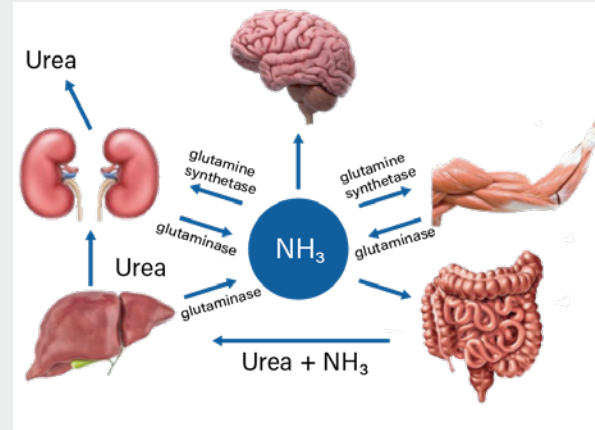
Pathophysiology

Whereas the primary mediator of encephalopathy in HE may be ammonia crossing the blood-brain barrier, the precise causes of that elevated ammonia are not well understood. Blood levels are influenced by the regulation of ammonia by means of hepatic detoxification but also by varying degrees of detoxification in skeletal muscle mass, intestinal absorption, gut microbiota, and renal production and excretion. Additionally, with the development of cirrhosis, portal hypertension causes shunting of ammonia-rich blood to the systemic circulation without detoxification, thereby causing a rise in the level of ammonia and exacerbation of the disease. The pathophysiologic process is illustrated in **Figure 1**.

Importance of Nutrition and Exercise

CLD with cirrhosis is associated with both undernutrition and sarcopenia, which together with cognitive decline comprise the construct of frailty–an independent predictor of mortality.[24] Sarcopenia is a consequence of inadequate intake of amino acids and other nutrients, and loss of muscle mass due to inactivity. Addressing both of these deficits offers a nonpharmacologic approach to lowering ammonia levels and improving morbidity and mortality in patients with HE.

Nutrition. Cirrhotic patients commonly experience malnutrition and sarcopenia, resulting in reduced survival. Consensus recommendations of the International Society for Hepatic Encephalopathy and Nitrogen Metabolism recommend optimal daily caloric intake of 35 to 40 kcal/kg and protein intake of 1.2 to 1.5 g/kg ideal body weight and provision of night time supplementation.[25] Zinc is occasionally helpful where there is deficiency or confirmed losses.



Pathophysiology of hepatic encephalopathy:
- Cirrhosis-related reduction of urea elimination and of glutamine synthetase activity increase blood ammonia levels.
- Decreased glutamine synthetase activity in other organs exacerbates increased blood ammonia levels.
- Elevated ammonia crosses the blood, brain barrier, leading to astrocyte swelling and hepatic encephalopathy.

Figure 1. Pathophysiology of hepatic encephalopathy
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Research has debunked the notion that reduced protein intake can decrease ammonia burden by virtue of lowering nitrogen load.[26] Recommendations now encourage small, frequent protein meals throughout the day with a nighttime snack of complex carbohydrates.[25] This is often optimized in conjunction with a nutritional support team.

Exercise. Exercise in patients with liver disease can improve functional capacity, increase lean body mass, and decrease risk of falls.[27,28] Exercise has the potential as an adjunct to improved nutrition to reduce the frailty of patients, which predisposes patients to higher ammonia levels and greater risk of falls. However, more studies are needed to clearly identify the parameters for which exercise can be safe and effective. LTC residents with multiple co-morbidities are likely to experience benefit from exercise, including improvements in depression and pain relief as a consequence of endorphin release.[29]

Treatment

According to the current American Association for the Study of Liver Diseases (AASLD) Practice Guideline, only overt hepatic encephalopathy (OHE) is routinely treated,[19] owing to the low degree of symptoms in "minimal" or "covert" HE. Primary prophylaxis for HE is generally not warranted, except in patients with cirrhosis who are at high risk for development of HE. An episode of OHE should be actively treated and followed up with secondary prophylaxis.[19] Long-term drug therapy following recovery from OHE as a means of preventing recurrence is

referred to as "secondary prophylaxis." The variety of symptoms as well as the relapsing-remitting nature of this disease require coordinated efforts of an interdisciplinary team over extended periods of time to monitor and manage it effectively.

Treatment consists of pharmacologic, psychosocial, and physical care interventions. Family and resident person-centered care is a best practice to ensure cooperative and coordinated care planning. Treatment can become very burdensome on both caregivers and on health care resources, and treatment decisions need to include consideration of these factors. Emphasis should be placed on individualized care by an interdisciplinary team for improvement of overall health care performance.

Lactulose and rifaximin. Optimal first-line treatment involves a nonabsorbable disaccharide—lactulose—which acts in three ways. First, it inhibits growth of ammonia-producing bacteria and promotes growth of beneficial microorganisms. Next, by acidifying the gut environment, it favors conversion of ammonia to ammonium. Last, it has a laxative effect, which helps to remove nitrogen-containing substances from the intestines. The 2014 Practice Guidelines of the European Association for the Study of the Liver (EASL) and the AASLD recommend that lactulose is used as a first-line agent in episodes of OHE and then continued to prevent further episodes.[19] The most recent Cochrane analysis found that nonabsorbable disaccharides showed benefit regarding mortality in randomized controlled trials evaluating acute, overt HE (risk ratio, -0.36) and regarding serious adverse effects in randomized controlled trials evaluating both acute and chronic HE subgroups (risk ratio, 0.42).[30]

The antibiotic rifaximin, a nonsystemic antibiotic confined to the gastrointestinal tract, has also proven efficacious in treating HE by altering the intestinal microbiota. It is also used as an additive to lactulose. The combination of lactulose plus rifaximin has been shown to be significantly more effective in reversing HE than lactulose alone (AASLD-EASL 2014 guidelines number 25 and 26).[19,31]

Current AASLD guidelines recommend combined lactulose plus rifaximin for prevention of HE after the second episode.[20] Rifaximin has excellent characteristics, including a slow rate of systemic absorption, a broad spectrum of antibiotic activity, and a low frequency of side effects.[32] This particular guideline on combination therapy is given the highest recommendation (Grade 1, A, 1) based on scientific merit and cost-effectiveness.[33] Bass et al demonstrated that rifaximin significantly reduces the risk of an episode of HE compared with placebo over a 6-month period (hazard ratio [HR] with rifaximin, 0.42; 95% [CI], 0.28-0.64; $P < .001$). A breakthrough episode of HE occurred in 22.1% of patients in the rifaximin group compared with 45.9% of patients in the placebo group. A total of 13.6% of the patients in the rifaximin group had a hospitalization involving HE compared with 22.6% of patients in the placebo group (HR, 0.50; 95% CI, 0.29-0.87; $P = .01$). More than 90% of patients received concomitant lactulose therapy. The incidence of adverse events reported during the study was similar in the two groups, as was the incidence of serious adverse events.[33]

Lactulose can be given orally or rectally and adjusted to a dose that achieves two to four bowel movements per day. Lactulose is the first choice for treatment of intermittent OHE while rifaximin is an effective add-on for prevention of recurrence of OHE. Rectal administration of lactulose has implications for end-of-life medication administration and support. Polyethylene glycol, which may have practical limitations in an LTC population due to its volume of ingestion, is an evacuant laxative facilitating catharsis of the gut. In a well-designed randomized controlled trial, it was shown to be as effective as, and perhaps superior to, lactulose, considering the speed of resolution of HE and reduction in length of hospital stay.[34]

In consideration of the proven effectiveness of lactulose, the dosage needs to be individually titrated for each resident to achieve bowel movements consistent with the interdisciplinary team goal. This poses challenges both in terms of adherence as well as unpleasant side effects of excessive bowel movements and diarrhea, which may even lead to volume depletion and electrolyte abnormalities. Approximately 50% of HE recurrence is related to either inappropriate dosing of lactulose or lack of adherence.[35] These challenges are accentuated by the mental deficits and polypharmacy experienced by many LTC residents and thus require ongoing assistance from the interdisciplinary team, community health care providers, and formal and informal caregivers.

Probiotics. Probiotics have been found to be effective for HE compared to placebo but not more so than lactulose.[36] Treatment of HE with probiotics is based on the concept that normalizing the gut microbiota, and thereby decreasing counts of pathogenic bacteria, will mitigate endotoxemia, blood ammonia levels, and liver disease.[37] With the caveat that most studies thus far on this topic have been of low quality, there is evidence that probiotics can be effective in reversing MHE, reducing hospitalization rate, and risk of progression to OHE compared with placebo or no treatment.[36,38,39] However, lactulose is consistently shown to be more effective by these measures and the usefulness of probiotics currently seems to be in combination with lactulose as well as for patients resistant or nonadherent to lactulose.

Embolization of portosystemic shunts. Resistance to rifaximin and lactulose could lead to consideration of embolization of portosystemic shunt as a treatment alternative. Evidence from retrospective studies suggests that this procedure decreases hospital admissions and improves survival, but adverse effects include gastroesophageal varices, worsening ascites, and renal dysfunction due to contrast-induced nephropathy.[40,41]

Table 4. Ongoing Care for Patients With HE[a]

Symptom / need	Assessment	Intervention
Systolic hypertension	Blood pressure, signs of headaches	Monitor vital signs QD for patients with liver failure, potential for HE
Increased muscle tonicity (partial or generalized)	Assess increased muscle tone	Monitor for changes in muscle tonicity, difficulty in moving, turning or repositioning.
Myoclonus (decerebrate posturing)	Assess muscle tightness, extremity positioning changes; fall risk; balance scores	Physical Therapy Restorative nursing plan (See **Figure 3**)
Dysconjugate eye movements	Monitor eye movements tonicity	Eye tracking charting: convergence, divergence
Fluid and electrolyte imbalance; clotting disorder	Changes in symptoms	Laboratory draws for electrolytes, bilirubin, prothrombin and pre-albumin; family and patient education; dietary consultation; maintain schedule
Mental status changes	Track behaviors, consciousness, aggression, uncooperative behavior, ability to attend to directions and details, and West Haven Criteria	Plan interventions which reduce distress and allow person-centered EBP care; utilize facility behavior tracking sheets; plan activity interventions; incorporate family into 1:1 intervention as needed.
Mood changes	Mood scores, depression evaluation, brief interview for mental status, anxiety score, mini-mental state exam, delirium	Person-centered daily care which accommodates needs of patients and family visits; testing and interventions supportive of EBP; meds per physician / NP orders
Activities of daily living changes	Monitor activities of daily living scores; task segmentation; SOB during care; mobility deficits	Care needs to be individualized
Eating assistance with caloric management	Weights; Assistance with eating	Small, frequent protein meals; monitor changes in food and fluid intake, as needed; labs as above; weights
Family-patient updates by interdisciplinary care conference team	Monitor for education deficits; Care questions	Team meetings; Rounds with situation, background, assessment, recommendation communication technique, or IPASS; Regular charting of involvement and updates during condition changes

Abbreviations: HE, hepatic encephalopathy; EBP, evidence-based practice.
[a]This is a list of potential symptoms and care needs often seen in patients with HE, along with corresponding recommended nursing assessments and interventions.

Branched chain amino acids (BCAA). A preparation of amino acids (valine, leucine, and isoleucine), normally given orally or by nasogastric tube, has been postulated to alter the balance of amino acids in the brain as well as to provide energy supplementation. A recent Cochrane review of 16 randomized clinical trials found high-quality evidence of clinical benefit, but no effect on mortality, quality of life, or nutrition parameters.[42] Thus, for some patients who are intolerant to the recommended protein intake, BCAA supplements may be considered as a means of meeting this nutritional need without risking detrimental effects on the mental state (AASLD-EASL recommendation number 33).[19,43]

L-ornithine-L-aspartate: **(LOLA)**. A combination containing the amino acids ornithine and aspartic acid may be given by intravenous infusion, although it can be difficult to obtain and administer. A meta-analysis of 20 randomized controlled trials showed LOLA to be as effective as nonabsorbable disaccharides, with a trend toward superiority and few adverse effects.[44]

Liver Transplantation. OHE improves significantly and may reverse after liver transplantation, though signs of cognitive impairment persist in some patients.[45,46] Moreover, the prospect of patients with HE receiving a liver transplant in a timely manner may be hindered by the Model for End-Stage Liver Disease (MELD) score. Prior research has shown that the MELD score does not correlate well with this disease entity.[47]

Future therapeutic considerations. The following interventions have shown some promise, but are not yet approved for treatment of HE.

1. Polyethylene glycol administered through an NG tube for more rapid resolution[48,49]

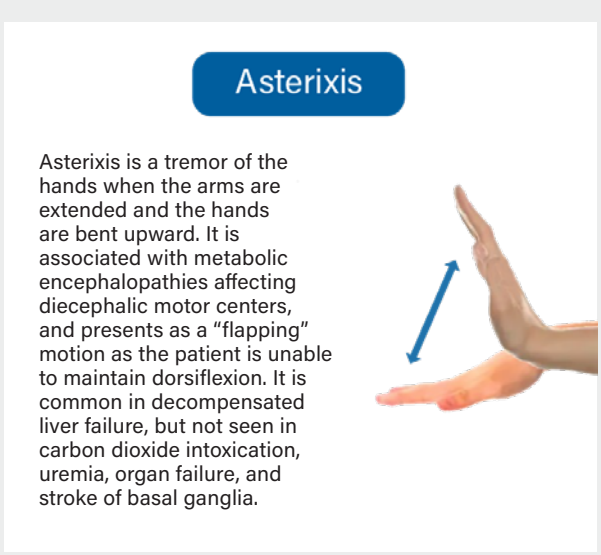

Figure 2. Asterixis: a motor abnormality seen in the early to middle stages of hepatic encephalopathy
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2. Glycerol phenylbutyrate[50]
3. Ornithine phenylactetate[51,52]
4. Extracorporeal devices such as Molecular Adsorbent Recirculating System for removal of ammonia in severe cases[53]
5. Fecal microbiota transplantation[54,55]

Palliative Care. When transplantation is not a feasible option, palliation and end-of-life care options are considered by the interdisciplinary team. The team must establish a person-centered approach for care. Recognition of patient and family goals that support quality of life is paramount.

The effectiveness of treatments for HE and other aspects of CLD has enabled older patients to survive longer with increasingly intensive care, often with substantial discomfort and suffering as well as considerable burden on families, caregivers, and the health care system.[56] Data from the United Kingdom show that referral to palliative care is low and over 66% of patients with liver disease die in the hospital after multiple inpatient hospital stays. The benefits of palliative care are numerous, including improved quality of life and prolonged survival.[57,58] Increasingly, patients and caregivers will need to weigh quality of life against efforts to sustain life, or at least consider these concurrently.

When palliative care services are chosen by a patient, the interdisciplinary care staff begins care with emphasis on education, comfort, and chronic condition management. Most events can be treated in the home or nursing home without the need for hospitalization. It is important that specific care goals are clearly understood, thereby preventing unnecessary rehospitalization. Conditions such as constipation and distress must be assessed, monitored, and proactively managed by staff. Education of the interdisciplinary staff is critically important because the signs of distress may not be immediately recognized and linked to manifestations of HE. As care becomes supportive, culminating in hospice service needs, the team secures hospice care services and approach care management with quality and comfort in mind to ensure timely clinical management and follow-up (See **Table 4** for symptoms, assessment, and nursing team interventions).

Screening Considerations

Abnormalities on electroencephalogram tests have predictive value and may be considered in conjunction with PHES scores.[59] Despite the validation of these methods, the time and expense of conducting them limits their utility for routine screening. Recently, smartphone applications have been developed for visual psychological tests (Stroop, Encephal App) which correlate with psychometric tests.[60]

Critical diagnostic information can come from psychiatric consults, sleep evaluations, physical therapists, endocrinologists, neurologists, and nephrologists that is either consistent or discordant with a diagnosis of HE and can then be shared with a primary care provider. It is imperative to educate not only the patient but also family members who will provide resident support on early symptoms. Awareness of early signs and symptoms, such as reversal of the sleep-wake cycle, may provide clues to impending clinical changes. A symptom education guide sheet (**Table 1**) may be helpful for future reference. Asterixis, or "liver flap," (**Figure 2**), along with behavioral disturbances and constipation, could be prominent.[23]

It is also important to remain aware that although acute episodes of HE can be effectively reversed, the frequency and severity of these episodes typically worsen over time. Health care providers need to be alert for signs of disease progression. For most patients, adherence to treatment with lactulose and rifaximin can significantly decrease the incidence of breakthrough episodes and hospitalization.[33] Conversely, nearly half of all recurrent episodes are due to nonadherence to the lactulose regimen.[35] One study found that one of the most common causes of preventable hospital readmissions was the failure to effectively titrate lactulose, with resulting insufficient number of bowel movements and worsening symptoms of HE.[61] The LTC nurse and consultant pharmacist, in consort with the interdisciplinary team, will be instrumental in management of the medication regimen to ensure compliance and outcomes consistent with the plan of care.

Other Important Considerations

The frailty of many patients in LTC means that they have less ability to detoxify ammonia in muscle mass, greater risk of falls due to weakness, and dizziness due to central effects

of elevated ammonia levels. Moreover, in successfully managed cases, management of HE depends on coordination during transitions of care and follow-up across multiple care delivery environments. This can be especially difficult for patients who are transitioned between acute care, LTC, and community care settings. Despite availability of an array of medical, dietary, and surgical interventions that can reverse episodes of HE, palliative treatment must be seriously considered in some cases.

At all stages, HE is reversible through a number of dietary, pharmacologic, and surgical methods. However, risk of recurring episodes, hospitalization, reduced quality of life, and mortality generally increases with the severity and duration of untreated HE.[14,62] Furthermore, HE is associated with substantial economic costs to the health care system[62] as well as economic and social burden for family members and informal caretakers. In more severe cases, the burden for caregivers is comparable for that of caregivers of patients with Alzheimer disease, Parkinson disease, and stroke.[63,64]

Considering the Quadruple Aim

In 2014, an article in *Annals of Family Medicine* introduced the concept that improving health care performance should address not only the previous Triple Aims of enhancing patient experience, improving population health, and reducing costs, but also add a fourth aim: improving the clinician experience.[65] HE is a disease with multiple causes and precipitating factors, the treatment of which depends on vigilance and coordination among all health care providers and caregivers. As such, the interdependence of these Quadruple Aims is particularly evident. Successful diagnosis and treatment of HE depends on shared, updated knowledge among health care professionals at all levels of the subtle nature of initial symptoms, the importance of proactive responses to clinical indices of suspicion for HE, the array of safe and effective interventions, and the critical management necessary to ensure long-term patient adherence to therapy and sustained reversal of symptoms. With good communication among providers, caregivers, and patients, successful management of HE symptoms is achievable in most cases. Successful management of symptoms can lead to a reduction of health care burden through reduced hospitalizations, as well as improved clinician experience through increased confidence that their patients will receive comprehensive ongoing treatment with sustainable outcomes.

Conclusion

HE is a major complication of CLD which, when left untreated, may progress through stages of mild neurologic symptoms to more serious psychological and psychiatric disabilities, and even ultimately to coma and death. The symptoms are episodic, and in most cases can be reversed with nonabsorbable disaccharides such as lactulose in combination with the antibiotic rifaximin. A number of other dietary, medical, and surgical interventions have also demonstrated safety and efficacy in these patients, addressing either a root cause or a precipitant of HE. The Patient Driven Payment Model of LTC reimbursement provides opportunities to improve reimbursement in clinically complex residents. An interdisciplinary team assessment using both physical and psychosocial instruments to assess mood, confusion, physical, motor changes, anxiety, delirium, depression, level of consciousness, and PHES and ICT scores will be instrumental in capturing subtle changes. Synthesis of the unique diagnostic assessments of team members enables coordinated, evidenced-based interventions to deliver high-quality care for LTC patients with HE and liver disease. ■

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