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Nursing Management of Hepatic Encephalopathy

ABSTRACT

This article provides a background of hepatic encephalopathy, its relation to liver disease as well as its prevalence in the United States. A literature review provides an overview of HE discussing the pathophysiology, evidence-based diagnosis, and grading of the disease severity as well as treatment options and interventions. A large emphasis of the article is placed on nursing's role of identifying and managing hepatic encephalopathy. The authors hope to provide clinical nurses with the tools and information needed to provide evidence-based care to this patient population. Pharmacologic therapies, as well as nutrition for these patients, are other topics reviewed. Education for nurses on the management of hepatic encephalopathy is important, as well as education needed for patients and families to support them through the treatment and follow-up care needed to manage hepatic encephalopathy. The authors also hope to provide nurses with education tips to provide the patients and families they care for during their hospitalization with HE, as well as on discharge from the hospital to prevent reoccurrence of symptoms.

Liver disease affects a large number of people all over the world. Hepatic encephalopathy (HE) is a complication of the disease that can progress quickly. The purpose of this article is to give an overview of the pathophysiology of HE, while reviewing treatment options providing insight to nurses caring for the patients. Then they may better teach the patient and family signs and symptoms along with management at home.

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Background

Hepatic encephalopathy is a common complication of liver disease that affects not only the quality of life of patients but also their families and caregivers. In the United States (U.S.), liver disease is most commonly caused by hepatitis C as well as fatty liver disease (Scaglione et al., 2015). Significant liver disease also results from excessive alcohol intake, nonalcoholic steatohepatitis, and autoimmune disorders. The quickest rising type of liver disease is nonalcoholic fatty liver disease due to the increased rate of obesity in Western countries (Burnham et al., 2014). However, cirrhosis is a final common pathway for many patients with severe liver disease, no matter what the cause.

Cirrhosis

Cirrhosis results from chronic liver disease due to a combination of inflammation, tissue fibrosis, nodule formation, and alteration or obstruction of hepatic vasculature (Tsochatzis, Bosch, & Burrough, 2014). Hepatic encephalopathy has been termed a “silent epidemic” by the U.S. Department of Health & Human Services. A study done by Scaglione and colleagues estimated the prevalence of cirrhosis in the U.S. to be 0.27%, which amounts to approximately 630,000 adults, of which 69% were unable to recall even being diagnosed with liver disease (Scaglione et al., 2015).

The same study showed that there was a prevalence of cirrhosis in patient autopsies, meaning that almost one third of patients with cirrhosis are undiagnosed. Cirrhosis and chronic liver disease combined are the 12th leading cause of death in the U.S. overall and fourth leading cause of death for patients aged 45–54 years (Heron, 2015). Analyses of economic factors revealed that hospitalization costs for patients admitted for cirrhosis were about 30% higher than those for other common illnesses such as heart failure and chronic obstructive pulmonary disease. The complexity of managing complications such as HE and ascites results in longer lengths of stay (DiPascoli et al., 2017).

Hepatic Encephalopathy

The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) defines *hepatic encephalopathy* as “a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological and psychiatric abnormalities ranging from subclinical alterations to coma” (Vilstrup et al., 2014, p. 717).

Patients with cirrhosis have up to a 50% chance of developing a milder form of HE (termed minimal or covert), during their course of care (Ferenci, 2017). Minimal or covert HE (mHE) produces very mild alterations in awareness and mood with symptoms such as anxiety or euphoria, sleep disturbances, tremors, and short attention span (Vilstrup et al., 2014). Patients with cirrhosis have a 47%–57% chance of developing serious HE (termed overt) within their first 5 years of diagnosis (Sharma & Maharshi, 2015). Of the patients with overt HE (OHE), 40% are likely to have a recurrence within 1 year (Sharma, Sharma, Agrawal, & Sarin, 2009). Overt HE is manifested by obvious personality changes, lethargy, disorientation, and neurological signs such as asterixis (flapping tremors), slow and slurred speech, progressing to somnolence and coma. Hepatic encephalopathy can be associated with and exacerbated by a variety of clinical factors such as constipation, infection, dehydration, and gastrointestinal (GI) bleeding (Table 1), though hyperammonemia is a central factor (Frederick, 2011).

In this article, we describe how to differentiate between severity levels of HE, monitor and correct precipitating factors, and promote patient safety. Nurses have central roles in determining the patient-specific therapeutic plan, evaluating the effectiveness of therapies to restore cognitive function and serving as key advocates. Moreover, nurses are central to enabling patients and families to learn to prevent, detect, and manage this serious complication.

In addition to societal costs, HE places a significant burden on patients and their families. During periods

TABLE 1. Potential Precipitating Factors of Hepatic Encephalopathy

Precipitating Factors of HE
Gastrointestinal bleeding
Sepsis/infection, including spontaneous bacterial peritonitis and urinary tract infection
Hypokalemia and/or metabolic alkalosis
Renal failure
Hypovolemia
Sedatives or tranquilizers
Constipation
Transjugular intrahepatic porto-systemic shunting (TIPS)

Note. Christina T. Vo, MSN, AGPCNP-BC. From Frederick (2011); Shawcross et al. (2016); and Vilstrup et al. (2014).

of HE, patients can exhibit atypical behavior, becoming belligerent, aggressive, and agitated, increasing the anxieties and fears of families and patients (Hansen, Sasaki, & Zucker, 2010). Hepatic encephalopathy also increases patient falls, motor vehicle accidents, and lost work days while significantly decreasing quality of life (Bajaj, 2010a; Sanyal et al., 2011). Therefore, HE exerts a significant impact on the physical, emotional, and financial well-being of both patients and families. The process of managing HE begins with accurate and timely diagnosis as well as determining the level of severity of the disease.

Pathophysiology of HE

Despite over 100 years of research, the exact pathogenesis of HE had been difficult to pinpoint (Ferenci, 2017). In-depth exploration of HE has been hindered by the inability to study the brains of patients with HE in vivo and from varying definitions and nomenclature of HE. The definition of HE, nomenclature to describe levels of severity, and standards of diagnosis and management have since been clarified by the 2014 AASLD and EASL practice guidelines (Vilstrup et al., 2014). An extensive discussion of the multifaceted pathogenesis of HE is beyond the scope of this article, but the key factors associated with HE and the nursing management of HE will be discussed. (Please see Cordoba, 2014; Ferenci, 2017; Wijdicks, 2016; and Vilstrup et al. for more detailed information.)

Role of Ammonia

Ammonia has been implicated as a key neurotoxin responsible for many of the symptoms of HE. The GI tract is the primary source of ammonia because it is produced by the digestion of protein by colonic bacteria and mucosal enzymes. From the GI tract, high

levels of ammonia proceed to portal blood. In a normal functioning liver, ammonia undergoes a high first-pass hepatic extraction of ~80%, with the rest converted to urea via the urea cycle, which is then rid from the body via urinary elimination (Cordoba 2014; Ferenci 2017).

In liver disease, hyperammonemia develops because of the liver's inability to produce urea as well as from bypassing of the liver's first-pass hepatic metabolism via portal-systemic shunts. In high levels, ammonia crosses the blood-brain barrier, which then triggers astrocyte (cell found in the brain) swelling and dysfunction. Ammonia and glutamate are converted to glutamine via the astrocytic glutamine synthetase process, which increases cerebral edema from the osmotic effect of glutamine (Cordoba, 2014; Wijidicks, 2016).

Elevated ammonia levels disrupt the balance of excitatory and inhibitory neurotransmitters, further exacerbating neurological and motor function decline (Felipo, 2013). Patients who have high ammonia levels can experience HE, but in chronic liver failure a higher ammonia level does not predict a more severe degree of HE. The correlation between high levels of ammonia and symptom severity is seen when a patient is in acute liver failure, so levels are trended to monitor the risk of HE and increase in intracranial pressure (Aldridge, Tranah, Shawcross, 2015). Because there is not a clear correlation

between the levels of ammonia during HE in chronic liver failure, ammonia may not be trended during treatment of an episode of HE (Aldridge et al., 2015).

Neurotransmitters

Various experimental models have found that other neurotransmitter systems are impaired in HE. Changes have been found in the GABA benzodiazepine-ergic, dopaminergic, serotonergic, and glutamate-ergic neurotransmitter systems (Ferenci, 2017). (Figure 1). Hypermanganesemia, which develops as a result of portal-systemic shunting and impaired biliary excretions in liver disease, has been linked to the Parkinsonian manifestations of HE (Cordoba, 2014). These extrapyramidal symptoms associated with hypermanganesemia are linked to altered dopaminergic function. Some initial studies have examined the role that neurosteroids, flumazenil, and bromocriptine or levodopa play in the treatment of HE with inconsistent results; further research is needed in this area (Ferenci 2017; Wijidicks, 2016).

Another proposed theory for the pathogenesis of HE is the role of neuroinflammation secondary to the release of proinflammatory cytokines and mediations in systemic inflammatory response (SIRs) and hyponatremia (Ferenci, 2017). Cirrhotic patients are functionally

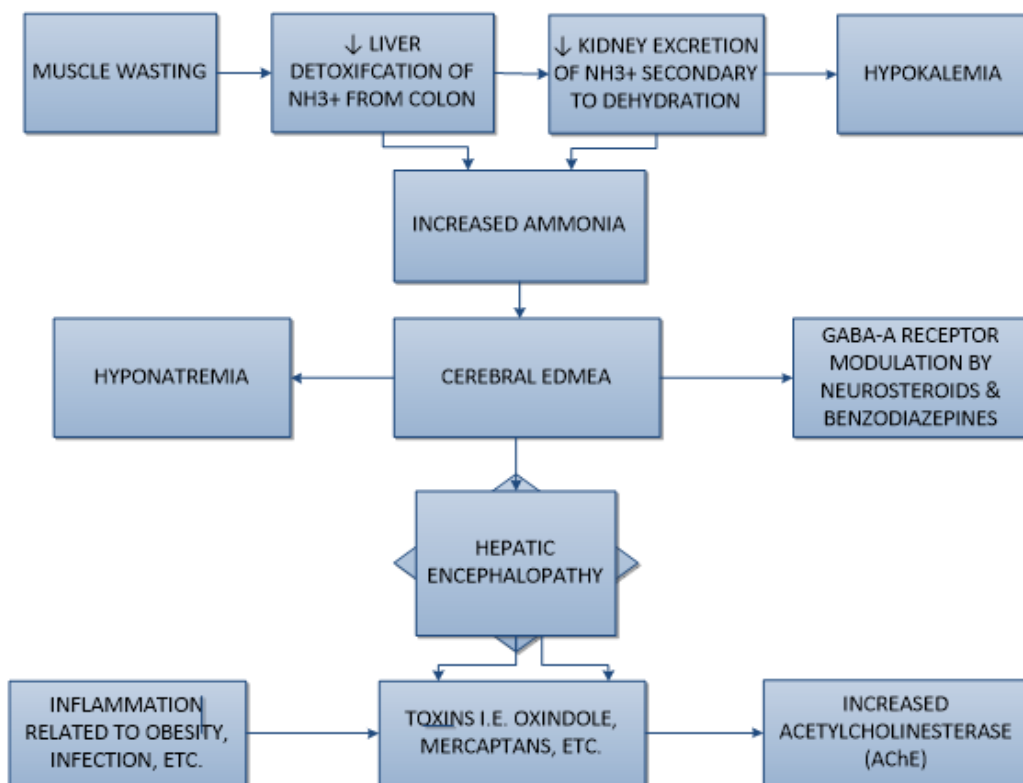


FIGURE 1. Hepatic encephalopathy. From “Current Concepts in the Pathophysiology and Management of Hepatic Encephalopathy,” by R. T. Frederick, 2011, *Gastroenterology & Hepatology*, 7(4), pp. 222–233. Used with permission.

immunocompromised, but it is unclear if the infections or the neuroinflammatory response worsen HE symptoms. Additionally, hyponatremia may enhance the effects of hyperammonemia on cerebral edema (Cordoba, 2014).

Overall, the symptoms of HE have been attributed to cerebral edema and impaired neurotransmitter systems, which have been linked to infections, hyponatremia, and hypermanganesemia. However, hyperammonemia with its effects on cerebral edema and reduced neural metabolic function remains the central factor in our current understanding of HE (Cordoba, 2014; Ferenci, 2017; Vilstrup et al., 2014; Wijdsicks, 2016). As such, much of the research and treatment developed for HE has aimed at reducing the absorption of ammonia from the GI tract with non-absorbable disaccharides such as lactulose (Wijdsicks, 2016). In addition to the concern for infections that can increase ammonia in cirrhotic patients, GI bleeding can increase levels due to a large nitrogenous source for ammonia production; dehydration can lead to hyponatremia and worsening cerebral edema; and constipation results in decreased ammonia excretion, leading to hyperammonemia (Cordoba, 2014; Ferenci, 2017; Wijdsicks, 2016).



Other than liver transplantation, the only surgical procedure with any documented effectiveness in modifying the underlying cause of HE is a transjugular intrahepatic portosystemic shunt (TIPS), which may reduce portal hypertension and decrease the risk of GI

bleeding and recurrent ascites (Punamiya & Amarapurkar, 2011). However, HE development is highest within 30 days of a TIPS procedure and has been associated with larger diameter shunts due to decreased blood flow to the liver, which leads to hyperammonemia from bypassing the liver's first-pass metabolism (Punamiya & Amarapurkar, 2011). An understanding of the pathogenesis and precipitating factors of HE enables nurses to target assessments, anticipate impending complications, treat precipitating factors, and titrate therapies in collaboration with the healthcare team.

Grading of HE

Among clinicians, the most widely accepted diagnostic tool for HE is the West Haven Criteria, which rates the neurological status according to five grades (Table 2): mHE or Covert HE may produce some alterations in psychometric or neuropsychological testing with no obvious clinical alterations; Grade I produces very mild alterations in awareness, personality and mood changes such as anxiety and euphoria, altered sleep and shorter attention span, along with tremor. West Haven criteria of minimal and Grade I exhibit the same symptoms of covert HE. OHE begins with Grade II and higher ratings. Patients with Grade II HE display more obvious personality changes, including lethargy, disorientation to time, inappropriate behavior, and neurological signs such as asterixis (flapping tremors) and slow and slurred speech. Patients rated as Grade

TABLE 2. Hepatic Encephalopathy Grades

GRADE	Impairment		SONIC Criteria
0	Normal	Normal	Normal
MHE ^a	Normal examination findings. Subtle changes in work or driving	Minor abnormalities of visual perception or on psychometric or number tests	}  Covert
1	Personality changes, attention deficits, irritability, depressed state	Tremor and incoordination	
2	Changes in sleep-wake cycle, lethargy, mood and behavioral changes, cognitive dysfunction	Asterixis, ataxic gait, speech abnormalities (slow and slurred)	}  Overt
3	Altered level of consciousness (somnia), confusion, disorientation, and amnesia	Muscular rigidity, nystagmus, clonus Babinski sign, hyporeflexia	
4	Stupor and coma	Oculocephalic reflex, unresponsiveness to noxious stimuli	

Note. MHE = minimal hepatic encephalopathy. From "Management of Hepatic Encephalopathy in the Hospital," by M. D. Leise, J. J. Poterucha, P. S. Kamath, & W. R. Kim, 2014, *Mayo Clinic Proceedings*, 89 (2), pp. 241–253. Adapted with permission.

III tend to be somnolent, confused, severely disoriented, and display bizarre behavior. When coma is present, patients are rated at Grade IV on the West Haven scale (Bajaj, 2010b; Vilstrup et al., 2014). The West Haven criteria have been used in numerous trials for the classification of OHE, but is less precise in detecting mHE since mHE lacks the classical symptoms of OHE.

Even mHE in decompensated cirrhosis patients has a negative impact on their quality of life. The prevalence of mHE has not been extensively studied, and was originally thought to affect about 24%–30% of patients. Now with additional research and more descriptive inclusion criteria, mHE in decompensated cirrhosis is estimated to occur in 44% of patients (Mina, Moran, Ortiz-Olvera, Mera, & Uribe, 2013). Although numbers vary, it is important to know that mHE is difficult to diagnose and is not usually tested at outpatient appointments. mHE should be assessed for during hospitalization, even for an unrelated condition. Minimal or covert HE can lead to an increased risk for hospitalization. Prior diagnosis of mHE is associated with the development of a patient's first episode of OHE. Therefore, detection of covert HE informs the clinician of the increased risk for OHE, and the need to provide family and caregivers with education about signs, symptoms, and management of HE to identify it earlier, and even prevent future hospitalization (Patidar et al., 2014).

Tools Used for Grading

The Psychometric Hepatic Encephalopathy Score (PHES), a battery of five paper-and-pencil tests, is the current recommended tool to test for mHE (Vilstrup et al., 2014). Despite being validated for use in the mHE population, applicability of this tool in a typical clinical setting is low since these tests must be administered by a neuropsychologist. Although this test is recommended for the diagnosis of mHE, because it has not been validated, it is not currently used in the inpatient or outpatient setting for diagnosis. Multiple other tools may be helpful, such as the Hepatic Encephalopathy Scoring Algorithm, the Critical Flicker Frequency test, and a novel smartphone application called the Stroop App. These tools are a bit challenging, and only sometimes used by providers as they still require further validation for this population (Vilstrup et al., 2014).

Nursing Management of HE

Patients who are admitted to the hospital typically have at least Grade II classification of OHE. General supportive care of OHE includes providing adequate nutritional support, maintaining fluid and electrolyte balance, administering pharmacologic agents to manage high ammonia levels, preventing and treating

constipation, and ensuring patient safety. Identification of the factors that precipitate worsening of symptoms is critical and nurses play a key role in both this process and in educating patients and families to reduce future episodes (Vilstrup et al., 2014) (Figures 2 and 3).

Nursing Assessment

Hepatic encephalopathy may occur with other complications of liver disease such as ascites, hyponatremia, pulmonary vascular complications, and esophageal varices. A comprehensive nursing assessment is crucial to ensuring appropriate care and patient safety. It should include the patient's level of responsiveness; sensory and motor abnormalities; fluid, electrolyte, and acid–base imbalances and the expected plus problematic effects of treatment measures. Regular evaluation of these behaviors, lab values, and deviations from normal baseline status are assessment priorities in HE (Lewis, Heitkemper, & Dirksen, 2008).

Identification of factors precipitating the current episode of OHE should be identified as well. Common problems contributing to acute worsening of HE include infections, GI bleeding, overuse of diuretics, electrolyte imbalances, and constipation (Vilstrup et al., 2014). Therefore, nurses should be alert for signs of HE when patients with underlying liver failure are admitted for other conditions, such heart failure, pneumonia, or surgical procedures that can disrupt normal fluid and electrolyte balance or pose a risk for infection. It is important to assess patient responses to treatment to collaborate with the medical team about needed modifications in the treatment plan. Also, the patient's response will inform the discharge planning process to prepare patients and families for preventing future episodes.

Level of Responsiveness

Level of responsiveness may range from mild confusion and slurred speech to coma. Regardless of the severity, family members and significant others are key informants to this specific assessment by providing data on baseline status and the timeframe of worsening symptoms. OHE can be identified on examination, but Minimal HE usually is not. Minimal HE is noticed by subtler changes to behavior, mood, or sleep disturbances in the patient and may require psychometric or neuropsychological testing to diagnose (Vilstrup et al., 2014).

Specific alterations in cognitive status of patients with OHE include impairments in attention, reaction time, confusion, and agitation (Shawcross et al., 2016). Baseline information on these parameters is important in planning care and monitoring patient's progress. Family members or significant others can provide invaluable input about the patient's baseline status, related to orientation and general behavior to aid in

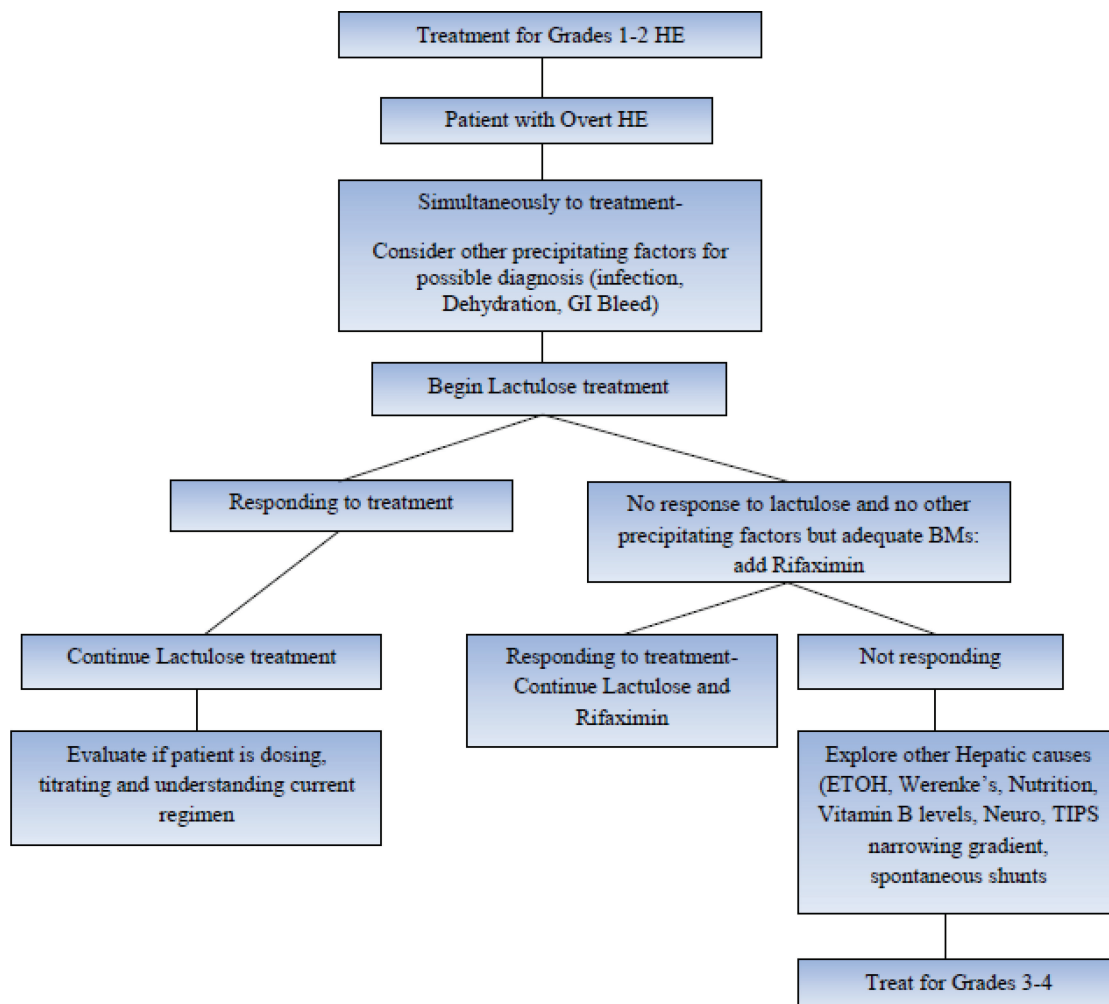


FIGURE 2. Treatment algorithm for hepatic encephalopathy. From “Management of Hepatic Encephalopathy in the Hospital,” by M. D. Leise, J. J. Poterucha, P. S. Kamath, and W. R. Kim, 2014, *Mayo Clinic Proceedings*, 89(2), pp. 241–253 Adapted with permission.

early detection of mHE. Examples of probe questions are as follows: “Has Mr. A recently been sleepier?”; “I noticed that Mr. A is very slow to respond to questions, how is he at home?” “Tell me about how Mr. A.’s mental status has changed over the past few days.” A comprehensive nursing assessment including family perceptions can aid in the detection of subtle changes like excessive sleepiness, sleep disturbances, and agitation.

Sensory and Motor Abnormalities

Asterixis (flapping tremor), muscle twitching, and hyperreflexia may be observed in patients with OHE. These can be accompanied by other neuromuscular impairments such as bradykinesia and hyperactive deep tendon reflexes. Bradykinesia means “slow movement” and can present as decreased facial expressions, increased stillness, or difficulty with performing repetitive tasks such as finger tapping.

Fluid and Electrolyte Imbalances

Patients who are placed on disaccharides (lactulose) are expected to have more bowel movements since these agents remove ammonia through the GI tract. Although bowel movements are needed to clear the ammonia, monitoring the patient for diarrhea is essential since it can contribute to dehydration and electrolyte disturbances. The goal for medication management is for the patient to have 2–3 bowel movements a day (Vilstrup et al., 2014). The medication should be titrated to achieve this goal and diminish complications due to lactulose overuse (Vilstrup et al., 2014). Either hypokalemia or hyperkalemia may also occur in hypovolemic patients. Dehydration and hypovolemia are another potential cause of HE, so fluid lost through bowel movements or loose stools should be monitored closely. Consequently, daily weights and accurate monitoring of intake and output are required especially since the patient can be a poor historian.

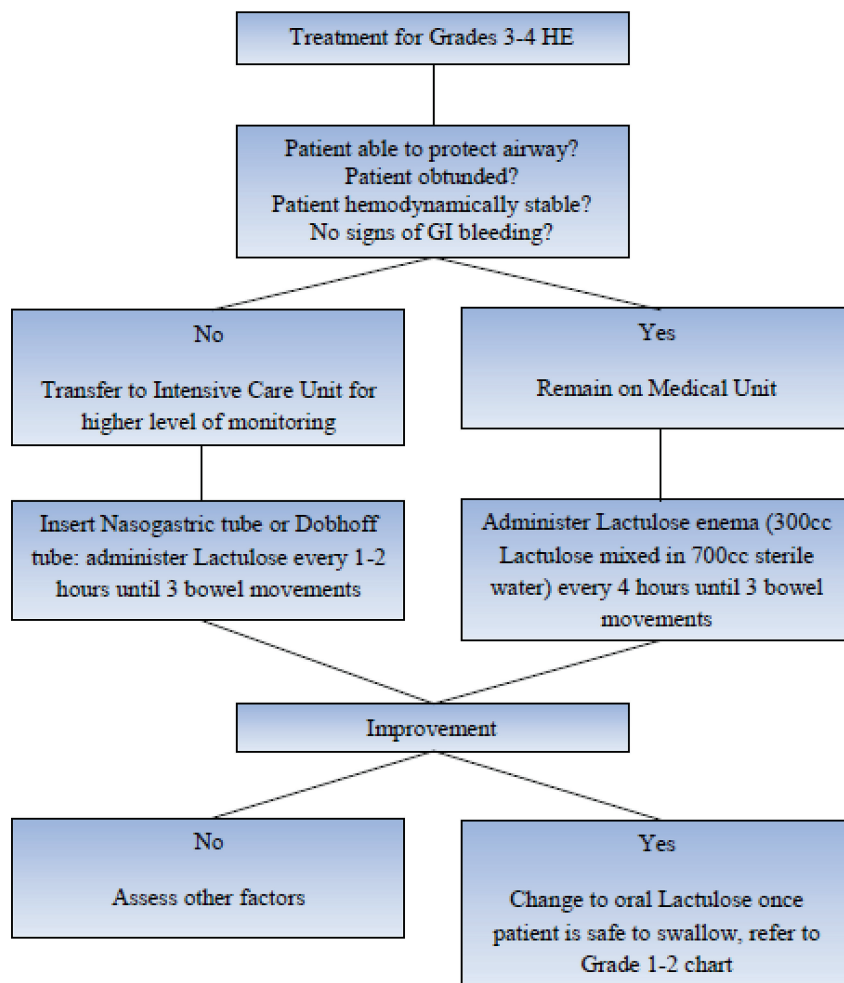


FIGURE 3. Treatment algorithm for hepatic encephalopathy. From “Management of Hepatic Encephalopathy in the Hospital,” by M. D. Leise, J. J. Poterucha, P. S. Kamath, and W. R. Kim, 2014, *Mayo Clinic Proceedings*, 89(2), pp. 241–253. Adapted with permission.

Monitor Neurologic Status

Neurologic status should be assessed and documented frequently. Significant changes such as sleeping for longer periods, difficulty arousing the patient, or agitation should be promptly reported to the physician. Sleep disturbances, like insomnia or hypersomnia, are common findings in patients with early HE because melatonin metabolism is affected. Difficulties in coordination and perception are also major problems in HE. Patients experience decreased attention span, poor coordination, and slower speed of processing information, which can put the patient at risk for falls both in the hospital and at home (Montagnese et al., 2014)

Nursing Management During Treatment

The treatment for HE is focused on reduction of ammonia levels through medications like nonabsorbable disaccharides (lactulose) and rifaximin. In addition,

any possible precipitating factors for HE need to be identified and treated. Risk factors for worsening HE include new onset or persistent GI bleeding, constipation, sepsis, hypovolemia of any cause but potentially related to the use of diuretics, persistent diarrhea or vomiting, electrolyte imbalance such as hyponatremia, surgical procedures of any kind but commonly TIPS. Use of anesthetic agents or narcotics requires care since the cirrhotic liver fails to metabolize these agents effectively thereby worsening mental status (Imani, Motavaf, Safari, & Alavian, 2014). With more severe levels of patient confusion, assessment of the patient’s overall acuity should determine the appropriate level of care. If the patient is too obtunded to protect his or her airway, is hemodynamically unstable or is experiencing excessive GI bleeding, the most appropriate site of care may be a critical care unit. Other than needed supportive care, treatment priorities focus on resolving the precipitating factors, if possible, and excreting the ammonia that is being produced.

Drug Therapy for HE

Lactulose

While the exact mechanism of action of lactulose is still being discussed, the currently accepted benefit results from the fermentation that this nonabsorbable disaccharide undergoes in the colon thereby increasing acid production leading to evacuation of ammonia (Leise, Poterucha, Kamath, & Kim, 2014, p. 544). Administration, while inpatient for an episode of HE, has shown improvement in patient mental status while simultaneously treating potential precipitating factors (Bajaj, 2010a).

Lactulose is usually taken orally until 2–3 bowel movements within 24 hours are achieved (Bajaj, Sanyal, Bell, Gilles & Heuman, 2010; Vilstrup et al., 2014). Once the goal bowel movements are achieved for the day, the patient may stop taking the lactulose and then resume doses the next day.

Although lactulose use has had good outcomes for inpatient and outpatient use, there remain some challenges with medication adherence. In one cohort of patients observed, 69% were readmitted with HE because of failure to take the drug appropriately and consistently, attributed to lack of education on lactulose (Leise et al., 2014). The adverse effects of lactulose include GI discomfort such as nausea, diarrhea and abdominal cramping, dehydration, hypernatremia, and perianal skin irritation (Vilstrup et al., 2014). Loose stools and more frequent bowel movements are changes that some patients struggle with depending on their degree of mobility and cognitive function. Strategies for managing these expected results should be integrated into the education plan.

Enabling patients and caregivers to fully engage in the treatment plan requires that they understand the purpose and benefit of the medication and have helped in planning how to manage its expected effects and sustain their participation in treatment. Patients are likely to need assistance in titrating the appropriate dose. If there are zero bowel movements, the dose should be increased. If there are greater than four large bowel movements a day, then the drug should be stopped for that day to prevent dehydration. The patient would then restart lactulose the following day. Given the cognitive problems associated with HE, recruiting a committed family member or caregiver to support the patient can make an important contribution to success.

Rifaximin

Once patient-precipitating factors of HE are corrected and confusion has resolved, a plan for long-term prevention of HE must be established. This plan may include the use of rifaximin, an antibiotic that is minimally absorbed by the gut. Rifaximin's antibiotic properties

remain concentrated to the GI tract, decreasing the amount of bacteria in the gut that produce ammonia (Welliver, 2013). The drug binds to the enzyme that replicates ribonucleic acid (RNA) and blocks deoxyribonucleic acid (DNA) replication and ultimately protein synthesis causing bacterial cell death (Welliver, 2013). There are no data proving that this antibiotic is as effective as lactulose in improving HE when used alone, but when used in combination these drugs can lengthen the time between HE occurrences (Vilstrup et al., 2014).

The Food and Drug Administration (FDA) has not yet approved rifaximin as a first-line therapy for episodic OHE, but has approved it as a secondary prevention for OHE (Leise et al., 2014). The combination therapy of lactulose and rifaximin has been shown to reverse acute HE and decrease length of hospital stay and therefore is commonly used in the hospital and continues into outpatient treatment (Leise et al., 2014).

Supplements

Another potential supplemental treatment option is Zinc. While research on zinc as a treatment agent is sparse, cirrhotic patients commonly have a zinc deficiency (Leise et al., 2014). There are enzymes in the body that assist in ammonia detoxification; these are found in the muscle and liver and are zinc dependent. A decrease in liver function and muscle mass can lead to lower zinc levels, leading to an increase in ammonia (Amodio et al., 2013). Zinc supplementation with a dose of 200 mg t.i.d. (Mohammad, Zhou, Cave, Barve, & McClain, 2012) has shown benefits in liver function and in nutrition levels but more clinical trials are needed to determine the best zinc dosing (Table 3).

Pain Management

Analgesics in Cirrhosis

Pain management proves to be challenging in patients with liver disease for all clinicians. Many commonly used analgesics are metabolized via the liver, and when it is not functioning properly, it can result in adverse side effects. Analgesics can cause an increased risk for oversedation and some clinicians may feel unsafe to use, leading to undertreatment of pain in patients with cirrhosis. Other risk factors, in addition to oversedation, are worsening renal function, inducing HE, portal hypertension, and GI bleeding (Imani, Motavaf, Safari, & Alavian, 2014).

Hepatic clearance of analgesics usually depends on three things: hepatic blood flow, plasma binding proteins, and hepatic enzymes. Analgesic drugs are usually absorbed from the GI tract and then passed directly to the liver, being metabolized before it even enters the body's systemic blood flow. If the hepatic flow is altered in anyway, possibly reduced, or bypassed by

TABLE 3. Hepatic Encephalopathy and Associated Medications

Medications			
Name of Medication	Lactulose	Rifaximin	Zinc Sulfate
Mechanism in hepatic encephalopathy (HE)	<ul style="list-style-type: none"> Metabolized in the gut by bacteria; the metabolism of lactulose creates an acidic pH in the stomach/colon; this acidic pH prevents ammonia from diffusing into the blood^a Enhances elimination of ammonia by expediting expulsion of stool^a 	<ul style="list-style-type: none"> Broad spectrum: covers Gram negative and positive bacteria^a Eliminates gut bacteria that produce ammonia^a 	<ul style="list-style-type: none"> Liver is main organ responsible for zinc metabolism^b Low serum zinc concentrations compared to high blood ammonia concentrations^b Zinc deficiency contributes to liver disease^b
Adverse reactions	<ul style="list-style-type: none"> Endocrine: dehydration, hypernatremia, hypokalemia^c GI: abdominal cramps/distension/distress, diarrhea^c 	<ul style="list-style-type: none"> Cardio: peripheral edema (15%)^d CNS: dizziness (13%), fatigue (12%)^d GI: Nausea (14%); irritable bowel syndrome with diarrhea (2%–3%)^d 	<i>Frequency not defined</i> <ul style="list-style-type: none"> CNS: dizziness, headache^e GI: abdominal cramps, diarrhea, nausea, vomiting^e
Monitoring parameters	<ul style="list-style-type: none"> Changes in mental status^c Serum electrolytes^c Serum ammonia^c Bowel movements, fluid status^c 	<ul style="list-style-type: none"> Changes in mental status^d Hypersensitivity reactions (less than 2% incidence of angioedema, anaphylaxis, skin rash)^d 	<ul style="list-style-type: none"> Changes in mental status^e
Administration considerations	<ul style="list-style-type: none"> Recommended dose: 25 mL twice daily^a Available as oral solution 10 g/15 mL^c May be mixed with fruit juice, water, or milk^c Titrate for production of 2–3 bowel movements daily^c 	<ul style="list-style-type: none"> Recommended dose: 550 mg twice daily^a May be taken with or without food^d Tablets may be crushed^d 	<ul style="list-style-type: none"> Recommended dose: 220 mg (elemental zinc 50 mg)^e

Note. Ingrid Pan, Lauren Simonds, Pharm D., BCPS Pharmacy Department, Hospital of the University of Pennsylvania.

^aFrom “Hepatic Encephalopathy,” by E. F. Wijdicks, 2016, *New England Journal of Medicine*, 375 (17), pp. 1660–1670.

^bFrom “The Role of Zinc in Liver Cirrhosis,” by K. Grüngreiff, D. Reinhold, and H. Wedemeyer, 2016, *Annals of Hepatology*, 15 (1), pp. 7–16.

^cFrom “Lactulose,” Lexi-Drugs. Lexicomp. Riverwoods, IL: Wolters Kluwer Health. Retrieved February 1, 2017, from <http://online.lexi.com>

^dFrom “Rifaximin,” Lexi-Drugs. Lexicomp. Riverwoods, IL: Wolters Kluwer Health. Retrieved February 1, 2017, from <http://online.lexi.com>

^eFrom “Zinc Sulfate,” Lexi-Drugs. Lexicomp. Riverwoods, IL: Wolters Kluwer Health. Retrieved February 1, 2017, from <http://online.lexi.com>

portal shunts, more of the drug enters the systemic system. Therefore, if a patient has impaired hepatic blood flow, the initial dose of an analgesic should be reduced. Some patients with liver disease may have more impairment with hepatic excretion, rather than shunting, so maintenance doses may need to be reduced to prevent accumulation. Some analgesics are protein bound, and if a patient has low albumin that may cause elevated drug levels, so doses in these patient may need to be reduced. The drug half-life has also been proven to increase because of the drug accumulating in the plasma (Soleimanpour, Safari, Nia, Sanaie, & Alavian, 2016). All these factors combined

make prescribing and managing pain difficult for clinicians caring for this patient population.

Acetaminophen

Acetaminophen is one of the most widely used analgesics for pain relief, but sometimes avoided in patients with liver disease because of the risk of liver damage with potential overdosing. Studies show that acetaminophen intake in conservative doses may be safe to use in patients with liver disease. FDA guidelines recommend that long-term use of acetaminophen in inpatients with liver disease, not currently drinking, should be at a reduced dose between 2 and 3g per day (Imani

et al., 2014, p. 3) and American Liver Foundation recommends less than 3g per day (Hayward, Powell, Irvine, & Martin, 2015, p. 213).

Nonsteroidal Anti-Inflammatory Drugs

Use of nonsteroidal anti-inflammatory drugs (NSAIDs) poses a high risk to patients already having liver disease because of how significant their side effects can be. The reduction of platelet synthesis that NSAIDs can have on the body can lead to thrombocytopenia and coagulopathy problems in cirrhotic patients. This side effect can be so significant in the liver patient that it has the potential to cause varices, both esophageal and cardiac (Imani et al., 2014). Because of this, NSAIDs in liver disease should be used with caution, or avoided if possible (Imani et al., 2014).

Opioids

Most of the commonly prescribed opioids are metabolized by the liver. Because of reduced or impaired hepatic blood flow, protein binding and hepatic enzymes, and the half-life of these drugs increased in this population, opioid therapy is extremely challenging. With an increased half-life, drugs like morphine, hydromorphone, and oxycodone cause increased levels of the drugs systemically, which may result in a greater risk for side effects and drug toxicity (Soleimanpour et al., 2016).

Interestingly, codeine is not metabolized in patients with hepatic failure and has no effect on these patients with liver disease because of its relation to enzyme reduction. The effects may not relieve any pain, but they can still result in the drug accumulating and respiratory depression side effects (Imani et al., 2014; Soleimanpour et al., 2016).

Methadone and fentanyl are protein-bound drugs, so dose reduction is needed in patients with hypoalbuminemia. They also are dependent on enzyme activity, so may not even have therapeutic effects on patients with liver disease. Tramadol is another opioid used for pain control but because the “metabolic enzymes of the liver are reduced in patients with liver failure, the drug may not be metabolized properly, reducing the effects of the enzymes” (Soleimanpour et al., 2016, p. 8)

It is suggested to proceed with caution when prescribing and administering any opioids for pain management because of their high-risk effects on patient with chronic liver disease like sedation, constipation, and confusion, which are precipitating factors to induce HE. Doses may need to be lower with longer intervals between these doses for patient safety. Patients using opioids for pain control should be closely monitored by a provider to assess for any side effects (Imani et al., 2014). Close attention should be paid to patients prescribed opioids with a history of alcohol abuse for possibility of cross-addiction.

Nutritional Support

Nutrition has a close correlation to health in cirrhotic patients. Moderate to severe malnutrition is seen in 75% of patients with HE (Romeiro & Augusti, 2015, p. 2943; Vilstrup et al., 2014) and is considered a risk factor for development of HE. Serious complications of malnutrition include refractory ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, and variceal hemorrhage (Chadalavada, Sappati Biyyani, Maxwell, & Mullen, 2010, p. 258).

Prior recommendation to reduce protein intake to prevent or manage HE is no longer considered valid because protein deficiency can cause muscle breakdown, thereby increasing the release of amino acids and ammonia production causing or worsening HE (Amodio et al., 2013). Nutritional support for patients with HE should include maintaining an energy intake of 35–40 kcal/kg/day, with a protein intake of 1.2–1.5 g/kg/day (Vilstrup et al., 2014). Protein restriction is reserved for patients who are severely protein-intolerant or for very short periods for patients with GI bleeding until symptoms resolve (Amodio et al., 2013). Dairy and vegetable proteins are preferred but are usually much less palatable. A fiber-rich diet is recommended to encourage fecal ammonia excretion, while avoiding diarrhea that could potentially induce HE in patients already taking lactulose.

Small meals throughout the day are encouraged with a late-night snack. Frequent meals eliminate the need for a patient to become overly hungry throughout the day, possibly using their glucose stores, and releasing more amino acids and elevating ammonia levels (Amodio et al., 2013). Having a late evening snack can be another source of caloric intake, shortening the time between eating overnight.

Patient and Family Education

Since the patient may have cognitive deficits, the family or primary caregiver should be included in all teaching. Both patient and family benefit from an education on the general overview of HE and practical pointers about integrating treatments such as lactulose administration and prevention of precipitating problems such as dehydration and infection into daily activities. The management and educational plan should be individualized to the patient and be driven by a thorough nursing assessment. It is also beneficial to educate the patient and family on the precipitating factors of HE in order to prevent reoccurrences and spot HE early, in order to get sooner treatment and possibly prevent a hospital admission. A primary safety concern for patients with HE, and more pronounced in mHE, is their fitness to drive. Patients with HE or mHE can overestimate their driving abilities. This should be included when educating patients and families.

Patients should fill their prescriptions immediately upon discharge as to not miss any doses. An understanding of the reasoning for taking the medications, what to do if a dose is missed, and how to titrate lactulose are needed for effective home management (Donnelly, 2015). Education on polypharmacy should also be included. Polypharmacy is the simultaneous use of multiple drugs to treat one or more medical conditions and is associated with poor medication adherence and greater chance for patient–clinician miscommunication about medications. (Patel, 2017). Patients with liver disease can have multimorbidities and are prone to polypharmacy.

Weight tracking is also important, and should be recorded and reviewed at provider visits. If a large weight fluctuation, more than 10 pounds, is seen in a week, the patient should contact their provider (Donnelly, 2015). Patients should abstain from alcohol and avoid aspirin, ibuprofen and acetaminophen (Tylenol) as they may be harmful to the liver, and always consult with a provider before taking any of these (Donnelly, 2015). Good hand washing and avoiding sick contacts can help decrease the risk for infection.

Transplantation

After all treatment options for HE have been exhausted, a patient may be referred for liver transplantation. The evaluation not only includes a battery of tests similar to other solid organ transplants but also includes a Model for End stage Liver Disease (MELD) score in determining the patient's eligibility for a transplant and its urgency. The MELD is a calculation using a patient's blood chemistry laboratory values including serum creatinine, bilirubin levels, INR, and recently serum sodium. The score of the calculation can range from 6 to 40 and relates to prognosis of liver disease. A higher MELD score increases prioritization for an organ transplant (Martin, DiMartini, Feng, Brown, & Fallon, 2014). Serum sodium levels have been incorporated into the equation to prioritize those patients with increased mortality because of hyponatremia (Martin et al., 2014).

Conclusion

Hepatic encephalopathy is a chronic and often-progressive consequence of liver failure. However, patients can keep hyperammonemia under control with careful management of food and fluid intake, consistent use of agents such as lactulose and rifaximin, and early detection and reporting of problems likely to worsen the condition. Effective self-management is challenging. The patient's altered mental status coupled with the complexity of the treatment can make every day adherence challenging and problem solving very difficult. Optimal outcomes rely on active participation of a knowledgeable caregiver and strong partnership with

outpatient and, when needed, inpatient teams. Nurses are a critical link in helping patients and caregivers understand what is needed and in supporting their efforts to manage a complex set of problems.

Case Study

Alice is a nurse on a busy medical-surgical unit, her assignment today includes a new patient, Mr. Martin, who came to the emergency department, complaining of fever and increased fatigue. Mr. Martin has advanced Hepatitis C cirrhosis with a MELD score of 27 and is awaiting a donor for a liver transplant. Other significant problems include GI bleeding from esophageal varices within the past year and Type II diabetes.

The night shift nurse reported that he is sleepy but able to ambulate in his room without assistance. Alice introduces herself to Mr. Martin as he is trying to eat breakfast and notices that his hand tremors are pronounced. His wife is sleeping in a chair nearby. While doing her assessment, Alice notes that Mr. Martin is very slow to respond, and his speech is slow and slurred. He seems to be falling asleep as he is eating.

Although the patient is lethargic, he is easily arousable. He has a gag reflex, and his airway is not compromised. He is warm to the touch with easily palpable pulses throughout. Neurologically, the patient is slow to respond, disoriented to date and time but knows that he is in the hospital. Asterixis is noted; pupils are PERRLA. Muscle strength is even throughout. HEENT presents as dry mucous membranes and poor skin turgor. Sclera are jaundiced. Respiratory assessment was clear to auscultation bilaterally. Cardiovascular assessment reveals tachycardia but with a regular rhythm. His abdomen is distended, soft, and nontender. Mr. Martin has +2 bilateral lower extremity edema and his skin is jaundiced. His vital signs are as follows: temperature: 101°F, heart rate 110 beats/minute, blood pressure 104/78 mmHg, respiration rate 18 breaths/minute, and SpO₂ 94% on room air. This blood pressure is within normal range for the patient.

Mr. Martin does not remember why he came to the hospital. Thankfully, his wife awakens and notes that Mr. Martin has not been feeling well for a few days at home, but was reluctant to go to the hospital. He was having intermittent fevers, chills, and fatigue. She is anxious and provides important information that since he started feeling poorly, his food and liquid intake has been minimal, and he refused to take his medications including his lactulose and rifaximin. She denies any vomiting blood (hematemesis) or frank red blood in his stool (hematochezia) as well as use of any new pain or anxiety medications. With this helpful information from Mrs. Martin and her own nursing assessment, Alice is now ready to inform the physicians/advanced practitioners of the situation and to

collaboratively plan Mr. Martin's monitoring and treatment plan.

With the information from Alice, the team acknowledges that Mr. Martin's mental status has deteriorated since admission. According to West Haven Criteria, this patient most likely has Grade II HE. As the bedside nurse, Alice is asked if she feels comfortable caring for this patient on a general medical-surgical unit. Alice references the Treatment Algorithm for HE and because Mr. Martin's HE is a Grade II and he can protect his airway, she believes that he is appropriate for this unit. Plan of care at this point will be to restart the lactulose, monitor his oral intake and correct any dehydration, assess number and quality of bowel movements, identify and treat the source of the fever, and encourage the patient's participation in care. Alice is concerned about patient safety since he is more disoriented. He had been steady on his feet, but this needs to be continually reassessed and he will be assisted to and from the bathroom to prevent falls.

Mr. Martin was found to have spontaneous bacterial peritonitis a bacterial infection in his ascites fluid, confirmed by diagnostic paracentesis. He was treated with antibiotics and his fevers resolved. Lactulose medication treatment was continued until Mr. Martin had an adequate number of bowel movements each day, and his oral intake improved with return of his mental status to baseline. He responded well to the team's treatment plan and is now ready for discharge. 🌟

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