Inadequate practices for hepatic encephalopathy management in the inpatient setting

Jawaid Shaw MD, MS, FACP FHM1 | Lisa Beyers MD2 | Jasmohan S. Bajaj MD, AGAF3

1Department of Internal Medicine, Division of Hospital Medicine, Virginia Commonwealth University, Richmond, Virginia, USA
2Department of Internal Medicine, Strong Memorial Hospital, University of Rochester, Rochester, New York, USA
3Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University and Central Virginia Veterans Healthcare System, Richmond, Virginia, USA

Abstract

Hepatic encephalopathy (HE) is an important complication of decompensated liver disease. Hospital admission for episodes of HE are very common, with these patients being managed by the hospitalists. These admissions are costly and burdensome to the health-care system. Diagnosis of HE at times is not straightforward, particularly in patients who are altered and unable to provide any history. Precipitants leading to episodes of HE, should be actively sought and effectively tackled along with the overall management. This mandates timely diagnostics, appropriate initiation of pharmacological treatment, and supportive care. Infections are the most important precipitants leading to HE and should be aggressively managed. Lactulose is the front-line medication for primary treatment of HE episodes and for prevention of subsequent recurrence. However, careful titration in the hospital setting along with the appropriate route of administration should be established and supervised by the hospitalist. Rifaximin has established its role as an add-on medication, in those cases where lactulose alone is not working. Overall effective management of HE calls for attention to guideline-directed nutritional requirements, functional assessment, medication reconciliation, patient education/counseling, and proper discharge planning. This will potentially help to reduce readmissions, which are all too common for HE patients. Early specialty consultation may be warranted in certain conditions. Numerous challenges exist to optimal care of hospitalized OHE patients. However, hospitalists if equipped with knowledge about a systematic approach to taking care of these frail patients are in an ideal position to ensure good inpatient and transition of care outcomes.

INTRODUCTION

Hepatic encephalopathy (HE) or portosystemic encephalopathy is defined as reversible neuropsychiatric symptoms resulting from acute or chronic hepatic insufficiency.1 It represents a wide spectrum of neurologic derangements, ranging from changes in personality to alterations in consciousness, cognition, and motor function.2 Hepatic encephalopathy imposes a multidimensional burden on patients who suffer from reported lowered health-related quality of life even when compared with patients with chronic liver disease (CLD), lower rates of employment, poor financial status, and worse sleep quality.3 CLD, and specifically cirrhosis, is estimated to affect 1.5 billion people worldwide and 0.3%–1% of adults in the United States.4–6 Hepatic encephalopathy is estimated to affect between 30% and 40% of...
patients with cirrhosis. In newly diagnosed cirrhosis cases, it was found that 34% had signs of decompensation at the time of diagnosis, with HE comprising 51.2% of these forms of decompensation. Patients with HE are commonly admitted to hospitals where hospitalists are usually directly charged with the management of such patients. This narrative review focuses on the challenges and inadequacies that hospitalists face in the management of HE patients while being hospitalized.

**Hospitalization in HE—Financial implications**

In 2012, it was estimated that liver disease accounted for 250,000 hospital admissions across the United States, with HE accounting for 0.33% of all inpatient admissions. An analysis of billing codes revealed a 24.4% increase in hospitalizations because of HE from 2010 to 2014. Even patients with covert HE (CHE) remain at increased risk of hospital admission. In addition to this, the burden of high hospital readmissions in patients with cirrhosis, for which HE remains the most common cause being as high as 26% at 30 days. However, some of these readmissions could be mitigated by adhering to appropriate pharmacological management and educational interventions directed at the patients. Estimated cost of these hospitalizations vary depending on the population and type of financial analysis. Data from a compilation of public databases yielded an estimated cost of $38,485 for single hospital admission for HE (median length of stay was 5.4 days). A study of the National Inpatient Sample estimated an annual medical cost of $11.9 billion in 2014 from hospitalizations with HE. As staggering as these numbers are, economic calculations fail to account for the impact of HE on quality of life.

**Diagnosis of HE—At times not so simple**

Although HE remains a common complication of CLD prompting thousands of hospitalizations per year, the consistent management of these patients can present a challenge for even the experienced hospitalist. When it comes to gathering history, any grade of HE can compromise the accuracy of the history of the present illness. Collateral information from families, friends, and other health-care contacts is often needed. Similarly, an accurate medication reconciliation, crucial to any admission, can present a significant challenge. Patients with even mild cases of HE may suffer from issues with short-term memory or have recently experienced changes in sleep–wake dysregulation, both factors that can contribute to missed doses of home medications, a common precipitant of HE. Again, collateral information from caretakers and pharmacy fill records may prove to be crucial tools when it comes to determining home medications.

As there are no specific signs on physical examination findings, the diagnosis of HE should be made only after exclusion of other causes of neurologic dysfunction. However, a range of signs, including extrapyramidal findings, motor system abnormalities, and cerebellar signs can be seen. The most commonly cited motor symptom of HE is flapping tremor (asterixis), although the findings from other physical examinations, such as bradykinesia, rigidity, tremor, and dysarthria, may also be present. Structural factors affecting neurologic function should be considered, especially in the presence of focal neurologic findings on examination. Exogenous toxin-mediated encephalopathy should remain on the differential and a urine toxicology screen on admission is prudent. For the undifferentiated encephalopathic patient, nutritional deficiencies such as thiamine deficiency (and associated Wernicke’s encephalopathy) should be considered.

**Is there any role of ammonia measurements in HE diagnosis?**

It is a common practice to order ammonia levels when patients with a known history of HE get admitted. However, as per the current evidence, there seems to be no role for such practice and should best be avoided. The diagnosis of HE is entertained on the basis of clinical grounds and blood-ammonia levels offer limited useful information in terms of diagnosis or staging. Elevated ammonia levels have been found in as many as 69% of patients with no signs or symptoms of encephalopathy, making it a nonspecific diagnostic tool. Hence, trending the ammonia to “normal levels” is of limited utility in patients with overt HE (OHE) as the efficacy of treatment is primarily based on clinical improvement alone. This becomes pertinent as the normalization of ammonia levels may lag behind the clinical improvement in HE patients. However, in cases of normal ammonia levels in patients being treated for possible OHE, alternative diagnoses should be explored. Hospitalists should be aware of the fact that some medications can also cause elevations in ammonia levels, for example, sodium valproate, which is independent of HE and can be a source of confusion. In addition, blood sample collection (e.g., using a tourniquet) and processing techniques may as well cause inaccuracies with the ammonia measurements.

**Hunt for precipitants or triggers—A preferred approach**

There is considerable overlap between precipitants of HE and factors contributing to non-HEs. The American Association for the Study of Liver Diseases (AASLD) guideline recommends broad consideration of infection, electrolyte derangements, and gastrointestinal hemorrhage as potential sources for decompensation. In patients with ascites, diagnostic paracentesis remains a critical part of diagnostic workup and should be performed promptly after the presentation. Given the high rate of morbidity and mortality from spontaneous bacterial peritonitis, previous studies have demonstrated a reduced risk of death associated with early paracentesis in patients admitted with ascites. However, paracentesis can be especially...
HE AND INADEQUATE MANAGEMENT IN HOSPITALS

Classification—Grading and staging of HE

In its 2014 guideline, AASLD recommended classification for HE by four factors: underlying cause (Type A from acute liver failure, Type B from portosystemic bypass or shunting, and Type C from cirrhosis), time course (i.e., “episodic,” “recurrent,” or “persistent”), presence of precipitating factors (i.e., “nonprecipitated” or “precipitated”), and severity. The severity of HE manifestations is most pertinent to management in the inpatient setting and can be classified by several tools. The West-Haven Criteria (WHC) (see Table 2) are the most frequently used and overall considered the gold standard; however, one of the limitations of this scale is the subjective nature of patient assessment. These shortcomings have fostered an initiative to find new, more objective, and reproducible methods for grading HE, but these tests are not used in routine clinical practice by hospitalists. Some experts prefer to differentiate between grades of encephalopathy using the spectrum of neurocognitive impairment in cirrhosis classification, labeling them as “CHE” or “MHE” (WHC Grade I) and OHE (WHC Grades II–IV). Alternative severity grading systems for encephalopathy and easy to use in the clinical setting include the Glasgow Coma Score and the Richmond Agitation Sedation Scale.

Management of HE—Pharmacology is the key

At the heart of the treatment of HE, is the identification and treatment of a precipitating cause/s. In some cases, correction of this derangement alone may reverse HE. Beyond this, the nonabsorbable disaccharide, lactulose, remains the cornerstone of HE treatment. It is theorized that lactulose works to mitigate and reverse HE through its prebiotic effects, promoting beneficial gut flora, acidifying the gut lumen, and thus inhibiting ammoniagenic bacteria and promoting the growth of lactobacilli, which produces less ammonia. Acidification also prevents the absorption of ammonia within the stool. Lactulose is generally considered the first-line medication for the treatment of OHE as well as maintenance in those patients at risk for recurrence. As a part of its four-pronged approach in the treatment of OHE, the AASLD has recommended the

| Potential factors precipitating HE | Urinary tract infections, pneumonia, spontaneous bacterial peritonitis, and so on |
|----------------------------------|----------------------------------------------------------------------------------|
| GI bleeding                      | Benzodiazepines, GABAergics, opioids, PPIs                                        |
| Diuretic overdosing              | Hyponatremia, hypokalemia, hypo/ hypercalcemia                                   |
| Electrolyte derangement          | Noncompliance with lactulose                                                     |
| Dehydration                      |                                                                                  |
| Constipation                     |                                                                                  |
| Medication indiscretion          |                                                                                  |

Abbreviations: GABA, γ-aminobutyric acid; GI, gastrointestinal; PPI, proton pump inhibitors.

### TABLE 2

| WHC grading | Clinical/neurological presentation |
|-------------|------------------------------------|
| Grade 0     | No abnormality detected            |
| Grade I     | Trivial lack of awareness          |
|             | Euphoria or anxiety                |
|             | Shortened attention span           |
|             | Impairment of addition or subtraction |
|             | Altered sleep rhythm               |
| Grade II    | Lethargy or apathy                 |
|             | Disorientation for time            |
|             | Obvious personality change         |
|             | Inappropriate behavior             |
|             | Dyspraxia                          |
|             | Asterix                            |
| Grade III   | Somnolence to semistupor           |
|             | Responsive to stimuli              |
|             | Confused                           |
|             | Gross disorientation               |
|             | Bizarre behavior                   |
| Grade IV    | Coma                               |

Abbreviations: HE, hepatic encephalopathy; WHC, West-Haven Criteria.
initiation of lactulose 25 ml every 1–2 h until two soft bowel movements occur, with titration thereafter to maintain two to three bowel movements per day. However, close titration of lactulose is crucial, as overuse can lead to complications, such as aspiration, dehydration, hypernatremia, perianal skin irritation, and hypokalemia, which can contribute to potential precipitation of HE. One of the benefits of lactulose in the encephalopathic patient is its ability to be administered both in oral and rectal formulations. This route of administration is usually determined by the clinician depending on the sensorium of the patients. Practically, the titration of lactulose, which is usually nursing-driven, can become challenging in hospitalized patients. To help improve this, order sets have been built into the electronic medical record by many hospitals. Continued lactulose use after an episode of OHE has resolved has been shown to prevent subsequent recurrence.

A more recently (2010) studied agent in the management of HE is rifaximin, which is a minimally absorbed nonaminoglycoside bactericidal antimicrobial with broad activity against enteric bacteria. Rifaximin might help to decrease the bacterial infection of the gut, altering the microbiota and hence, decreasing the gut translocation and inflammation. Currently, the addition of rifaximin to lactulose has been found to be superior to both treatment with lactulose or rifaximin alone, and it is typically used as an add on medication with lactulose in patients with recurrence of OHE despite adequate treatment with lactulose. At this time there are no strong data to support the use of rifaximin as a sole agent for the treatment of HE. But this may change as suggested by a recent trial, wherein it was shown that primary rifaximin use as compared to a placebo, in post-transvenous intrahepatic portosystemic shunt (TIPS) patients reduced the risk of OHE development.

Neomycin and metronidazole are other antimicrobials used as an alternative or additional agents for the treatment of OHE when first-line therapies are not working; however, these agents should be only used for short periods of time given their adverse side effect profiles. In a recent trial in hospitalized patients, the role of L-ornithine L-aspartate (LOLA) therapy has been shown to be promising when added to the standard of care therapies, in regards to improvement in HE grades, quicker recovery, and a short-term mortality benefit at 28 days. However, LOLA has not been approved yet for the mainstay of care in HE patients. In regards to hospital readmissions, a recent study estimated that 40% of hospital readmissions for HE are preventable with appropriate pharmacologic therapy, with a combination of lactulose and rifaxamin. This underscores the importance of ensuring that patients have access to these medications after discharge, in particular, if rifaximin was started in the hospital as a new medication. As in many instances, for rifaximin to be continued in the outpatient setting may require a preapproval process from the insurance, which needs to be completed prior to discharge. Another study of 402 patients discharged after admission for cirrhosis-related complications estimated that 22% of 30-day readmissions were preventable through patient education and lactulose adherence.

When to call consultations—A case-by-case approach?

Although most hospitalists are comfortable managing typical OHE patients, certain situations demand getting in touch with a specialist. Hepatology should be consulted in patients with HE who are post-TIPS, as consideration of a shunt diameter reduction may be an option for treatment. For patients presenting with OHE with relatively well-preserved liver function, the consideration of large, spontaneous portosystemic shunts may be an underlying precipitant for HE. In these cases, treatment includes potential embolization of the shunt, but the careful patient selection and liver function must be considered with the help of an expert consultation. Hepatic encephalopathy in acute liver failure warrants hepatology consultation as the management differs from that of HE in CLD. These patients are at high risk for morbidity and mortality with risk for progression to fulminating hepatic failure and the potential need for expedited transplant evaluation. And of course, GI and/or Hepatology teams need to be involved up front in cases of HE precipitated by GI bleeding for consideration of endoscopic procedures. In addition, in those cases of persistent OHE not responding to initial management by the hospitalist, the threshold for specialty consultation should be low, particularly if the patient is on the transplantation list or potentially a candidate for the same. The role of more frequent consultation with specialists has been explored as a potential quality improvement (QI) measure using various models. While mandatory gastroenterology involvement was found to be associated with improved guideline-adherent care, it did not improve readmission rates. However, the overall impact of QI initiatives in the care of OHE patients remains an area of future interest.

Nutritional management of HE patients—An under-recognized problem

Malnutrition is a common problem in hospitalized patients with cirrhosis. The most common indications for hospitalization in cirrhosis patients include HE, infections, volume overload, and gastrointestinal bleeding, which manifest with different signs and symptoms, including abdominal pain, distension, anorexia, and increased catabolic state. Many of the hospitalized patients have to be in nil per os state for various procedures or secondary to altered mentation in case of higher grades of OHE, and this sets the stage for further nutritional compromise in these already fragile patients. Further on, malnutrition is not given its due importance in the management of HE patients even when it is known that the presence of severe malnutrition leads to worsening symptoms of HE. As the severity of the liver disease increases, so does the severity of malnutrition, rising from 46% to 95% from Child–Turcotte Pugh Classes A–C. Sarcopenia, which is highly prevalent in cirrhosis patients (65%–90%), and myosteatosis are not only poor prognosticators for survival in cirrhosis patients but can contribute to HE. The reason being that skeletal muscle has a role in clearing ammonia via muscle-bound glutamine synthetase. Hence, sarcopenia may further...
exacerbate the manifestations of HE.\textsuperscript{49,50} Recently, it has been reported that myosteatosis and sarcopenia in malnourished cirrhosis patients are independently associated with MHE and further progression to OHE.\textsuperscript{51} Hence, it is imperative to address the nutritional status of patients with cirrhosis and HE with a view to improve their malnourished status in line with the nutritional guidelines. And to this end, hospitalization of cirrhosis patients in general and HE patients, in particular, presents a unique opportunity to address this problem.

Up front, nutritional assessment of hospitalized HE patients enlisting the help of registered dietitians (RDs) should be a norm rather than an exception. Various risk assessment tools are recommended to ascertain those who are at nutritional risk in cirrhosis patients, and one of the tools is the Royal Free Hospital Nutritional Prioritizing Tool (RFH-NPT).\textsuperscript{52,53} The advantages of RFH-NPT are that it is quick and simple and needs no formal training for application helping to stratify cirrhosis patients into low (0 point), moderate (1 point), and high-risk (2–7 points) nutritional categories.\textsuperscript{54} However, RFH-NPT is yet to be validated. Another such tool is the Liver Disease Undernutrition Screening Tool, which has been validated.\textsuperscript{55} These tools can be directly used by hospitalists and consideration is given for incorporation into the clinical practice. However, the most important role for RDs, once the nutritional status has been ascertained is to devise a guideline congruent dietary plan for the acutely ill, hospitalized HE patients and RDs can perform further thorough nutritional and anthropometric assessments. To this effect, organizations across the United States and Europe have laid out evidence-based guidelines for achieving the nutritional goals in patients with cirrhosis and HE.\textsuperscript{7,52,56} To summarize, energy recommendations range from 30 to 45 kcal/kg/day and protein recommendations are uniformly 1.2–1.5 g/kg/day. And there is a consensus across all the guidelines on avoidance of protein restricting diets.

As the patient population in the United States is getting more diverse, sensitiveness needs to be exhibited while formulating dietary plans for the individual patients keeping in view their dietary practices, and preferences, which may at times be relevant beyond guidelines.

Further on, educational intervention during the hospitalization of patients with cirrhosis can be used to tackle nutritional inadequacy by getting RDs involved early in the management of such patients, which has been associated with a reduction in length of stay (5.7 vs. 8.4 days; \( p = 0.004 \)) and 90-day readmissions (39.4% vs. 28.4%; \( p = 0.04 \)) as well.

Medication reconciliation and counseling—A golden opportunity not to waste

Medication reconciliation should ideally happen at each admission and change of services to the hospital and, of course, at discharge. As discussed, this presents a unique challenge if patients are altered, and the caregiver and pharmacy contacts are not available. However, hospitalists should employ concerted efforts to complete the medication reconciliation at the earliest opportunity. In some hospitals dedicated pharmacy support is available, which can be requested to help in completing such reconciliation. This becomes more important as evidenced in a recent study using pharmacy databases highlighting the fact that patients with decompensated cirrhosis may not be filling their medications appropriately or may be filling potentially harmful medications (e.g., opiates in 53%, PPIs in 46%, benzodiazepines in 14%, and nonsteroidal anti-inflammatory drugs in 10%).\textsuperscript{57} In the above study, specifically for HE, only around 63% and 32% had filled their lactulose and rifaximin prescriptions.\textsuperscript{57} In a NACSELD cohort, which studies hospitalized patients, the need for optimization of medication precipitated HE, aspiration pneumonia, and HE medications per se, as a QI measure has been put forth and hospitalists can seek guidance from these results.\textsuperscript{58} In this cohort (total of 2810 patients, with 659 on lactulose, 154 on rifaximin only with 859 on both medications, and 1102 on none of these agents), it was seen that those patients who are on lactulose only or both medications versus being on no therapy at all or rifaximin alone had significantly higher rates of HE at admission and during the hospital stay.\textsuperscript{58} However, reassuringly those patients with medication-related precipitants (total of 32% patients, with 21% lactulose related, 5% benzodiazepines, 4% opiates, and so on) had better outcomes as compared to other precipitants. Hence, hospitalization presents an opportunity to look at these discrepancies and try to rectify these by educating patients and by partnering with their caregivers and outside providers.

HE in post-TIPS and acute on chronic liver failure (ACLF) patients—Special situations

TIPS are indicated in patients with decompensated liver for the management of refractory ascites and bleeding varices, but this opens these patients to increased risk of HE, which can be recurrent at times.\textsuperscript{59} This is secondary to direct access of various neurotoxins into the systemic circulation. The presence of recurrent HE prior to TIPS, age, and liver dysfunction are risk factors for post-TIPS HE development.\textsuperscript{60,61} In addition to careful selection of patients prior to the TIPS procedure, these patients with HE should be treated medically with standard agents, such as lactulose and rifaximin, with careful titration of medications.\textsuperscript{62} In rare cases of refractory, HE not responding to medical management, shunt size revision, or occlusion may be warranted, in consultation with the specialists.\textsuperscript{60} Although not fully consolidated, one small study suggests that there may be some role for rifaximin in the primary prevention of HE, post-TIPS.\textsuperscript{39} ACLF is a clinical entity wherein there are at least two severe extrahepatic organ failures (shock, Grade III/IV HE, need for renal replacement therapy, or mechanical ventilation).\textsuperscript{63} When patients with ACLF develop Grade III or IV HE, their prognosis worsens as compared to those with no ACLF but with the same severity of HE.\textsuperscript{64,65} This points to the fact that brain failure in hospitalized
patients with cirrhosis is an independent prognostic marker. Hence, keeping a close watch on the development of OHE and aggressively treating both ACLF and OHE is the need of the hour in the hospitalized patients. Infections are very common (up to 40%) in patients with ACLF at admission in developed countries, which should be actively sought after and managed proactively, as these are known to precipitate OHE.

Advance care planning and goals of care discussions—An opportunity to pursue

Owing to time constraints and possibly secondary to focusing on the acute medical issues at hand, goals of care discussions can at times take a back seat. However, hospitalists already have the expertise of leading these discussions for patients with other chronic illnesses and are, hence, in a natural position to coordinate and lead such discussions in patients with end-stage liver diseases. This holds truer for those with a poor overall prognosis, and in particular, if there is no prospect of a liver transplant. These efforts are usually multidisciplinary and set the tone for the future management of such patients. Furthermore, this effort ensures that current and future management plans are aligned with the patient’s/family wishes. If possible, such discussions should be held prior to patients being in florid HE and hence, not being able to participate in such discussions. In such cases, the burden of decision-making falls on the surrogate health-care proxy if one has been nominated. Hospitalists can seek help in this area from recent guidelines on this topic.

Accurate documentation leads to accurate coding—Needs improvement

Hospitalists, at times erroneously, document an episode of HE as altered mental status, which is not accurate. As per the current 10th revision of the International Classification of Disease-10, HE should be documented as metabolic encephalopathy (G93.41). Some of the other representative codes depending on the acuity, presence or absence of coma, and etiology, include chronic hepatic failure without coma (K72.10), chronic hepatic failure with coma (K72.11), alcoholic hepatic failure (acute, chronic, or subacute) without coma (K70.40), and alcoholic hepatic failure with coma (K70.41). Etiology of liver disease should be specified. Accurate and proper documentation leads to accurate coding, which will ultimately translate into accurate billing for the encounter. This is an area in need of much improvement and needs ongoing attention.
Hospital readmissions are a huge problem for cirrhosis patients, and HE predicates most of these readmissions. In an early study, this 30-day readmission rate can be as high as 37% in cirrhosis patients. However, in a recent multicenter study, from the North American Consortium for the Study of Liver Diseases (NACSELD), the readmission rate at 90 days was reported at 53%, with HE as one of the leading reasons for these readmissions. This calls for robust discharge and transition of care planning. Of late, technology, among other measures, is being leveraged to prevent such unwanted and costly HE readmissions using various methodologies with some success. One such health information (IT)-based technology intervention is the Patient Buddy App, which is an ongoing multicenter study, to find if IT can be used to decrease readmissions in cirrhosis patients. However, such use and acceptance of technology are not limited to cirrhosis only but to other GI diseases also. Clearly, this is a new frontier and will have a much more robust role in the future.

As is clear from the discussion there are challenges as well as opportunities for the optimal management of hospitalized patients with cirrhosis. Table 3 summarizes some of these challenges and possible solutions we may apply. A simple-to-use guideline-directed systematic approach is proposed for the hospitalists to follow for optimizing the care of such patients. Figure 1 summarize this proposed approach in easy-to-follow steps.

CONCLUSIONS

In summary, hospitalists are commonly charged with taking care of patients with HE in the community or academic settings. Hence, they should be well-equipped with the knowledge and develop a systematic approach to the overall management of these patients in the hospital setting. This is important as patients with decompensated liver disease and HE is very ill at initial presentation to the hospital and merit an expedited workup and management with or without the help of a subspecialist. Otherwise, these patients have the potential to deteriorate quickly leading to adverse outcomes. Systematic and guideline congruent management will largely optimize the clinical outcomes in these patients.

CONFLICTS OF INTEREST

Dr. Jasmohan S. Bajaj has the following conflicts of interest to declare: Grants to Institution: Bausch, Grifols and Cosmo. Advisory Board: Norgine. The remaining authors declare no conflict of interest.

ORCID

Jawaid Shaw http://orcid.org/0000-0001-6490-0639

TWITTER

Jasmohan S. Bajaj @jasmohanbajaj

REFERENCES

1. Rahimi RS, Brown KA, Flamm SL, Brown RS Jr. Overt hepatic encephalopathy: current pharmacologic treatments and improving clinical outcomes. Am J Med. 2021;134:1330-1338. doi:10.1016/j.amjmed.2021.06.007
2. Weissenborn K. Hepatic encephalopathy: definition, clinical grading and diagnostic principles. Drugs. 2019;79:5-9. doi:10.1007/s40265-018-1018-z
3. Elsaid MI, John T, Li Y, Pentakota SR, Rustgi VK. The health care burden of hepatic encephalopathy. Clin Liver Dis. 2020;24:263-275. doi:10.1016/j.cld.2020.01.006
4. Ge PS, Runyon BA. Treatment of patients with cirrhosis. N Engl J Med. 2016;375:767-777. doi:10.1056/NEJMra1504367

5. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: a systematic review of 118 studies. J Hepatol. 2006;44:217-231. doi:10.1016/j.jhep.2005.10.013

6. Scaglione S, Kliethermes S, Cao G, et al. The epidemiology of cirrhosis in the United States: a population-based study. J Clin Gastroenterol. 2015;49:690-696. doi:10.1097/MCG.0000000000000208

7. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60:715-735. doi:10.1002/hep.27210

8. Orman ES, Ghabril M, Emmett TW, Chalasani N. Hospital readmission for patients with cirrhosis and hepatic encephalopathy. J Hosp Med. 2019;14:157-160. doi:10.12788/jhm.3152

9. Pantham G, Post A, Venkat D, Einstadter D, Mullen KD. A new look at precipitants of overt hepatic encephalopathy in cirrhosis. Am J Gastroenterol. 2012;107:247-252. doi:10.1038/ajg.2011.314

10. Hirode G, Vittinghoff E, Wong RJ. Increasing burden of hepatic encephalopathy among hospitalized adults: an analysis of the 2010-2014 national inpatient sample. Dig Dis Sci. 2019;64:1448-1457. doi:10.1007/s10620-019-05576-9

11. Pantham G, Post A, Venkat D, Einstadter D, Mullen KD. A new look at precipitants of overt hepatic encephalopathy in cirrhosis. Dig Dis Sci. 2017;62:2166-2173. doi:10.1007/s10620-017-4630-y

12. Ferenci P, Lockwood A, Mullen K, Tarter R, Weissenborn K, Blei AT. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. Hepatology. 2002;35:716-721. doi:10.1053/jhep.2002.31250

13. Nilan J, Feldman L. Ammonia levels and hepatic encephalopathy in patients with known chronic liver disease. J Hosp Med. 2017;12:659-661. doi:10.12788/jhm.2794

14. Lockwood AH. Blood ammonia levels and hepatic encephalopathy. Metab Brain Dis. 2004;19:345-349. doi:10.1023/B:MBED.00000043980.74574eb

15. Ong JP, Aggarwal A, Krieger D, et al. Correlation between ammonia levels and the severity of hepatic encephalopathy. Am J Med. 2003;114:188-193. doi:10.1016/s0002-9343(02)01477-8

16. Nicolao F, Efrati C, Masini A, Merli M, Attili AF, Riggio O. Role of determination of partial pressure of ammonia in cirrhotic patients with and without hepatic encephalopathy. J Hepatol. 2003;38:441-446. doi:10.1016/s0168-8278(02)00436-1

17. Stahl J. Studies of the blood ammonia in liver disease. Its diagnostic, prognostic, and therapeutic significance. Ann Intern Med. 1963;58:1-24. doi:10.7326/0003-4819-58-1-1

18. Howanitz JH, Howanitz PJ, Skrodzki CA, Iwanski JA. Influences of specimen processing and storage conditions on results for plasma ammonia. Clin Chem. 1984;30:906-908.

19. Kim JJ, Tsukamoto MM, Mathur AK, et al. Delayed paracentesis is associated with increased in-hospital mortality in patients with spontaneous bacterial peritonitis. Am J Gastroenterol. 2014;109:1436-1442. doi:10.1038/ajg.2014.212

20. Le S, Spelman T, Chong CP, et al. Could adherence to quality of care indicators for hospitalized patients with cirrhosis-related ascites improve clinical outcomes? Am J Gastroenterol. 2016;111:87-92. doi:10.1038/ajg.2015.402

21. Orman ES, Hayashi PH, Bataller R, Sidney Barratt A IV. Paracentesis is associated with reduced mortality in patients hospitalized with cirrhosis and ascites. Clin Gastroenterol. 2014;12:496-503.e491. doi:10.1016/j.cgd.2013.08.025

22. Kumral D, Qayyum R, Roseff S, Sterling RK, Siddiqui MS. Adherence to recommended inpatient hepatic encephalopathy workup. J Hosp Med. 2019;14:157-160. doi:10.12788/jhm.3152

23. Khungar V, Poorodd F. Hepatic encephalopathy. Clin Liver Dis. 2012;16:301-320. doi:10.1016/j.cld.2012.03.009

24. Mumtaz K, Ahmed US, Abid S, Baig N, Hamid S, Jafri W. Precipitating factors and the outcome of hepatic encephalopathy in liver cirrhosis. J Coll Physicians Surg Pak. 2010;20:514-518.

25. Devrajani BR, Shah SZ, Devrajani T, Kumar D. Precipitating factors of hepatic encephalopathy at a tertiary care hospital Jamshoro, Hyderabad. J Pak Med Assoc. 2009;59:683-686.

26. Tapper EB, Finkelstein D, Mittelman MA, Piatkowski G, Chang M, Lai M. A quality improvement initiative reduces 30-day rate of readmission for patients with cirrhosis. Clin Gastroenterol Hepatol. 2016;14:753-759. doi:10.1016/j.cgh.2015.08.041

27. Poh Z, Chang PE. A current review of the diagnostic and treatment strategies of hepatic encephalopathy. Int J Hepatol. 2012;2012:480309. doi:10.1155/2012/480309

28. Bajaj JS, Sanyal AJ, Bell D, Gilles H, Heuman DM. Predictors of the recurrence of hepatic encephalopathy in lactulose-treated patients. Aliment Pharmacol Ther. 2010;31:1012-1017. doi:10.1111/j.1365-2036.2010.04257.x

29. Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. Gastroenterology. 2009;137:885-891.e881. doi:10.1053/j.gastro.2009.05.056

30. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med. 2010;362:1071-1081. doi:10.1056/NEJMoa0907893

31. Gerard L, Carew KJ, DuPont HL. Rifaximin: a nonabsorbable rifamycin antibiotic for use in nonsystemic gastrointestinal infections. Expert Rev Anti Infect Ther. 2005;3:201-211. doi:10.1586/14787210.3.2.201

32. Patel VC, Lee S, McPhail MJW, et al. Rifaximin-alpha reduces gut-derived inflammation and mucin degradation in cirrhosis and encephalopathy: RIFSYS randomised controlled trial. J Hepatol. 2022;76:332-342. doi:10.1016/j.jhep.2021.09.010

33. Gluud LL, Dam G, Borre M, et al. Lactulose, rifaximin or branched chain amino acids for hepatic encephalopathy: what is the evidence? Metab Brain Dis. 2013;28:221-225. doi:10.1007/s11011-012-9372-0

34. Bureau C, Thabut D, Jezequel C, et al. The use of rifaximin in the prevention of overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: a randomized controlled trial. Ann Intern Med. 2021;174:633-640. doi:10.7326/M20-0202

35. Jain A, Sharma BC, Mahajan B, et al. L-Ornithine L-aspartate in acute treatment of severe hepatic encephalopathy: a double-blind randomized controlled trial. Hepatology. 2021;75:1194-1203. doi:10.1002/hep.32255

36. Fanelli F, Salvatori FM, Rabuffi P, et al. Management of refractory hepatic encephalopathy after insertion of TIPS: long-term results of
shunt reduction with hourglass-shaped balloon-expandable stent-graft. Am J Roentgenol. 2009;193:1696-1702. doi:10.2214/AJR.09.2968

42. Laleman W, Simon-Talero M, Maleux G, et al. Embolization of large spontaneous portosystemic shunts for refractory hepatic encephalopathy: a multicenter survey on safety and efficacy. Hepatology. 2013;57:2448-2457. doi:10.1002/hep.26314

43. Ghouri R, Friderici J, Desilets DJ, et al. Outcomes associated with a mandatory gastroenterology consultation to improve the quality of care of patients hospitalized with decompensated cirrhosis. J Hosp Med. 2015;10:236-241. doi:10.1111/jhm.2314

44. Campillo B, Richardet JP, Scherman E, Bories PN. Evaluation of transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene covered stent graft. Dig Dis Sci. 2008;53:1706-1717. doi:10.1007/s10620-014-3391-0

45. McFarlane M, Hammond C, Roper T, et al. Comparing assessment tools for detecting undernutrition in patients with liver cirrhosis. J Nutr Health Aging. 2018;22:1181-1188.e1182. doi:10.1016/j.jnh.2016.04.009

46. Amadio P, Bemecur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. Hepatology. 2013;53:325-336. doi:10.1002/hep.26370

47. Tandon P, Raman M, Moutzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. Hepatology. 2017;65:1044-1057. doi:10.1002/hep.29003

48. Borhoeven SM, Gerner C, Lehmann J, et al. The Royal Free Hospital Nutritional Prioritizing Tool Is an independent predictor of deterioration of liver function and survival in cirrhosis. Dig Dis Sci. 2016;61:1735-1743. doi:10.1007/s10620-015-4015-z

49. McFarlane M, Hammond C, Roper T, et al. Comparing assessment tools for detecting undernutrition in patients with liver cirrhosis. Clin Nutr ESPEN. 2018;23:156-161. doi:10.1016/j.clnesp.2017.10.009

50. Ploth M, Bernal W, Dasarathy S, et al. ESPEN guideline on clinical nutrition in liver disease. Clin Nutr. 2019;38:485-521. doi:10.1016/j.clnu.2018.12.022

51. Thomson MJ, Lok ASF, Tapper EB. Appropriate and potentially inappropriate medication use in decompensated cirrhosis. Hepatology. 2021;73:2429-2440. doi:10.1002/hep.31548

52. Bajaj JS, O’Leary JG, Tandon P, et al. Targets to improve quality of care for patients with hepatic encephalopathy: data from a multi-centre cohort. Aliment Pharmacol Ther. 2019;49:1518-1527. doi:10.1111/apt.15265

53. Bhogal HK, Sanyal AJ. Transjugular intrahepatic portosystemic shunt: an overview. Clin Liver Dis. 2012;16:173-184. doi:10.1016/j.clld.96

54. Riggo O, Angeloni S, Salvatori FM, et al. Incidence, natural history, and risk factors of hepatic encephalopathy after transjugular intrahepatic portosystemic shunt with polytetrafluoroethylene-covered stent grafts. Am J Gastroenterol. 2008;103:2738-2746. doi:10.1111/j.1572-0241.2008.02102.x

55. Casadaban LC, Parvianin A, Minnoh J, et al. Clearing the confusion over hepatic encephalopathy after TIPS creation: incidence, prognostic factors, and clinical outcomes. Dig Dis Sci. 2015;60:1059-1066. doi:10.1007/s10620-014-3391-0

56. Desai M, Nutalapati V, Bansal A, et al. Use of smartphone applications to improve quality of bowel preparation for colonoscopy: a systematic review and meta-analysis. Endosc Int Open. 2019;7:E216-E224. doi:10.1055/a-0796-6423

How to cite this article: Shaw J, Beyers L, Bajaj JS. Inadequate practices for hepatic encephalopathy management in the inpatient setting. J Hosp Med. 2022;17:S8-S16. doi:10.1002/jhm.12897