Review Article

The role of the hospitalist in the continuum of care for patients with hepatic encephalopathy: treatment of inpatient episodes and preventing outpatient recurrence and readmissions

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Abstract: Hepatic encephalopathy (HE) is a common complication of advanced cirrhosis that is seen in the majority of patients at some point. Manifesting as a wide spectrum of neuropsychiatric abnormalities, HE has many consequences; increased morbidity and mortality, bothersome symptoms affecting quality of life and routine activities (e.g., working, driving), substantial caregiver burden, frequent hospital admissions and readmissions and associated economic strains. The manifestations of HE are potentially reversible with medical treatment, frequently in the inpatient setting, and preventable with outpatient maintenance of remission. However, breakdowns across the continuum of care for HE patients are responsible for frequent hospital readmissions; hospitalists, who play a pivotal role in improving the management of HE, can improve these outcomes. The authors are US hepatologists with expertise and experience in managing HE and members of the Chronic Liver Disease Foundation (CLDF), a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease. The goals of this article are to provide a thorough review of HE; to describe how HE is currently managed and identify ways to improve diagnosis and treatment; to review the role of the hospitalist in managing and preventing HE episodes; and to provide strategies to reduce hospital readmissions and improve outcomes.

Keywords: Hepatic encephalopathy (HE); treatment; recurrence; readmissions; prevention

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Introduction

Cirrhosis is characterized by inflammation leading to scarring (i.e., fibrosis) with the formation of regenerative nodules in the liver that cause architectural distortion. In early or compensated cirrhosis, patients are largely asymptomatic and have a favorable prognosis. As structural changes and increased intrahepatic vasoconstriction progress, patients develop overt complications of cirrhosis, referred to as decompensated cirrhosis. Hepatic dysfunction, portal hypertension, and the formation of collateral vessels (portosystemic shunts) ensue, and the disease becomes more complex. Hepatic encephalopathy (HE) is a common complication of advanced cirrhosis that manifests as a wide spectrum of potentially reversible neuropsychiatric abnormalities, which includes a subclinical covert (CHE) and clinically apparent overt HE (OHE) dimension (1). As

most cases of HE within the hospital are OHE, OHE will be discussed throughout the rest of this paper and referred to as HE.

In the US, the estimated prevalence of cirrhosis is approximately 5.5 million cases (2). It is estimated that 30–50% of cirrhotic patients experience HE, but given the difficulties in diagnosis, the true prevalence of HE is likely substantially higher. Studies suggest that the majority of cirrhotic patients will experience HE at some point during their illness (3,4). The CDC ranked cirrhosis as the 11th leading cause of death in the US in 2017 (5).

Data suggest that HE results in the utilization of more healthcare resources in adults than any other manifestation of liver disease (6). As a result of the severity of HE and the increased risk of mortality (7), emergency room visits and hospital admissions are common and, as such, hospitalists are integral to HE management. However, hospital readmissions are frequent and are often a direct result of disease mismanagement or interruption of continuity of care. With the ability to manage varying aspects of patient care, hospitalists can help resolve the disconnect that exists as an HE patient moves across the continuum of care (8) and play a pivotal role in providing appropriate management of HE in order to improve outcomes.

The authors of this article are US hepatologists with expertise and experience in managing HE and members of the Chronic Liver Disease Foundation (CLDF), a nonprofit 501(c)(3) educational organization dedicated to raising awareness of liver disease. The goals of this article are to provide a thorough review of HE; describe ways to improve diagnosis and treatment; review the role of hospitalists in managing and preventing HE episodes; and ultimately provide strategies for how hospitalists can contribute to achieving the ultimate goal, which is to reduce hospital readmissions and improve outcomes.

Defining HE

Pathophysiology

The pathophysiology of HE is complex (9). Multiple factors are believed to functionally impair neuronal cells, with ammonia (NH3) considered the primary factor. Urea from dietary proteins are metabolized to NH3 by gut bacteria; NH3 is then metabolized by the liver and cleared by the kidneys. In cirrhosis, hepatic dysfunction impairs the metabolism of NH3 and portal hypertension shunts blood through portosystemic collaterals, concentrated with NH3, to the brain (10). After crossing the blood-brain-barrier, NH3 initiates pathophysiologic processes responsible for neuronal impairment and ultimately leads to the neurologic manifestations associated with HE. However, multiple recent and prior investigations have determined that serum NH3 levels are not necessarily reflective of the sum total of these pathophysiological changes (11,12) and NH3 activity is not reflected by serum NH3 levels.

Classification and clinical presentation

Grading HE is an important part of the clinical assessment. Originally, the West Haven criteria categorized HE from grade I to grade IV based on various clinical parameters (13,14), but these criteria were considered too subjective. In recent years, the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) reached a consensus regarding classification and nomenclature of HE. The ISHEN criteria describe HE as covert (CHE), which is detected using specialized testing, and overt (OHE), which is detected by clinical symptoms. The American Association for the Study of Liver Diseases (AASLD) guidelines refer to both classification systems (1) *Table 1* describes these criteria and the HE symptoms characteristic of each stage. OHE is responsible for hospitalizations, and is the condition that hospitalists can intervene on and improve outcomes.

The burdens of HE

HE negatively impacts patients' lives

There are multiple negative impacts of HE on health-related quality of life. Patients may suffer from sleep disturbances, which manifest as sleep-wake inversion (restless nights and excessive daytime sleepiness) (15). They can lose the ability to work and/or manage the household and may refrain from recreational activities (16). HE can interfere with patients' social lives with feelings of disease stigmatization leading to social isolation (17). Defects in visuospatial assessment, attention, memory, response speed, information processing, and increased fatigue are all symptoms that affect driving ability (18). As HE progresses, high levels of supportive care needs result in increased dependency on others (6). Caregivers are also adversely affected as hospital readmissions increase and independence decreases (19-21).

The manifestations described above contribute to impaired

Table 1 Hepatic encephalopathy classifications, according to ISHEN and West Haven Criteria, and associated symptoms (1,9,13,14)

ISHEN	West Haven Criteria	Symptoms
Covert	Minimal	No clinical evidence of mental change, but with psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations
	Grade I	Trivial lack of awareness; euphoria or anxiety; shortened attention span; impairment of addition or subtraction; altered sleep rhythm
Overt	Grade II	Lethargy or apathy; disorientation of time; obvious personality change; inappropriate behavior; dyspraxia*; asterixis (i.e., flapping tremor)*
	Grade III	Somnolence to semi-stupor responsive to stimuli; confused*; gross disorientation; bizarre behavior
	Grade IV	Coma*

*Most common symptoms upon presentation of HE. Adapted from references (1,9,13,14). ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism.

quality of life (22). This has been well established in many studies; quality-of-life scoring systems show that most physical, mental, and social domains are severely compromised in HE patients (16).

Frequent hospitalizations, recurrence, and readmissions

HE is primarily managed in the hospital setting (23) and is the most common cause of patients' initial liver disease-related hospitalizations (24). HE is responsible for ~100,000–150,000 annual US hospital admissions (25). The development of HE during hospitalization is also common; up to 80% of HE episodes are precipitated by an event such as infection or gastrointestinal bleeding (26). Even in its mildest form, HE is a risk factor for future, more severe episodes (1); one study estimated that risk of recurrence increased by 23% with every unit increase in the number of prior overt HE episodes (27). Most patients require maintenance medications at discharge to protect against HE recurrence, but data indicate that this need is not being met, resulting in a revolving door of HE episodes and readmissions. *Table 2* shows that HE readmissions are frequent, and HE is often the most common reason for readmission in patients hospitalized with decompensated cirrhosis (16,19,28-32).

Rehospitalization for HE can lead to severe consequences in an already seriously ill patient. In one study, patients with more frequent readmissions had a significantly higher risk of subsequent mortality (hazard ratio 1.08 per unit increase in hospitalization rate, P<0.001).

Repeated episodes may cause irreversible neurologic damage. Bajaj and colleagues showed that defects associated with HE (e.g., deficits in memory, response inhibition, and learning) were persistent and cumulative after subsequent episodes (20). Additionally, patients' quality of life may be affected by the fear of recurrence (33).

Economic burdens

The economic burden of HE is substantial. Medication costs, morbidity and mortality, quality of life, and outpatient care contribute to this economic strain (34), but hospitalization costs are the largest contributor to overall HE-related costs (35). HE-related hospitalization costs have continued to rise, with one analysis estimating that these costs escalated from $4.68 billion in 2005 to $7.25 billion in 2009. Also, the proportion of patients with major and extreme severity of illness significantly increased (P<0.0001), as did the average length of inpatient stay (from 8.1 to 8.5 days; P=0.019) (25). As expected, frequent readmissions contribute to cost. In an analysis of hospital readmission costs in cirrhotic patients, per-patient costs were $73,252 for those readmitted within 30 days, $62,053 for those readmitted after 30 days, and $5,719 (outpatient costs) for those not readmitted (30).

Inpatient assessments and treatment

A diagnosis of exclusion

The diagnosis of HE is primarily based on the exclusion of other causes of brain dysfunction (1,9). As shown in *Figure 1*, when a patient presents with symptoms and physical findings consistent with HE, recognizing and excluding other common disorders and identifying precipitating

Table 2 Data on HE recurrence, hospital admissions, and readmissions

Study	Patients and methods	Results
Volk *et al.* (19)	Retrospective chart review. 402 patients with decompensated cirrhosis; 276 patients with ≥1 non-elective readmission	34% of first admissions were for HE; 314 (78%) readmitted during follow-up; median time to first readmission was 67 days, with 14% of patients re-admitted within one week and 37% re-admitted within one month; of the 165 re-admissions within one month, 36 (22%) were judged to be possibly preventable; HE was one of the three most common causes for possibly preventable re-admissions
Bajaj *et al.* (20)	North American Consortium for the Study of End-Stage Liver Disease cohort. 1,353 inpatients with cirrhosis in 14 centers	53% readmissions occurred (n=535; 316 with one, 219 with two or more); consistent rates across sites; the leading causes were liver-related (n=333; HE, renal/metabolic, and infections)
Kim *et al.* (27)	Nationwide Inpatient Sample data analysis. 65,072 discharge records associated with hospitalization for complications of cirrhosis	41% of hospitalizations among patients with cirrhosis were attributed to HE; HE associated with a two-fold higher probability of in-patient mortality (P<0.01)
Tapper *et al.* (28)	Analysis of 119,722 unique index admissions with cirrhosis	The 30- and 90-day rates of readmission were 12.9% and 21.2%; among patients with more than three complications of cirrhosis, 24.2% were readmitted within 30 days and 35.9% were readmitted within 90 days; HE was most strongly associated with readmission within 30 and 90 days (odds ratio, 1.77 for each)
Neff *et al.* (29)	Premier Research Database (information from >500 US hospitals). 8,766 patients discharged from June 2010 to December 2011 with primary diagnoses of HE	Incidence rates for all-cause readmissions were 27.4% (30 days) and 56.4% (one year); rates for HE-related readmissions were 17.6% (30 days) and 39.5% (1 year)
Chirapongsathorn *et al.* (30)	2,075 patients with index cirrhosis-related hospital admissions	655 patients readmitted within 30 days of hospitalization (32% readmission rate); HE-related readmissions within 30 days of hospitalization accounted for 13.6% of all readmissions
Masadeh *et al.* (31)	One-year retrospective chart review. 139 patients admitted with a complication related to liver cirrhosis (36% with HE)	31% of patients overall were readmitted within 30 days; 47% of these cases were attributed to HE; HE was the most common cause of readmission within 30 days, followed by fluid overload
Di Pascoli *et al.* (32)	57,720 hospitalizations in Italy due to liver disease from 2006 to 2008	Encephalopathy and ascites were the complications with the highest rates of readmission

Adapted from references (19,20,27-32).

factors that alter the level of consciousness is the first step (1,9). It is also important to recognize that multiple precipitating events may frequently coexist (36). Finally, patients with noncirrhotic portal hypertension are also at risk for HE (37).

Clinical evaluation, laboratory tests, and cerebral imaging are recommended in a patient with suspected HE (*Figure 1*) (9). Clinical evaluation involves obtaining a detailed history about symptoms and medications (including those for pre-existing HE, over-the-counter and illicit substances), and performing a physical examination (neurologic, psychiatric, and assessment of exacerbating factors) (9). There is no specific biochemical diagnostic test for HE, but a complete laboratory evaluation can help to exclude other factors and/or causes. Serum NH3 levels are rarely useful, as the levels do not correlate with symptoms and do not change practice (1,38). While the positive predictive value is poor, a low serum NH3 in a confused patient likely indicates the absence of HE (1). The combined increased risk of falls in HE and increased risk of bleeding with chronic liver disease (as a result of coagulopathy and thrombocytopenia) put patients at risk for subarachnoid, intracranial hemorrhage or a cerebral vascular event and warrants cerebral imaging in patients with no prior history of HE (9).

Inpatient treatment

Identification and correction of precipitating factors

The treatment of HE begins with the aim of improving

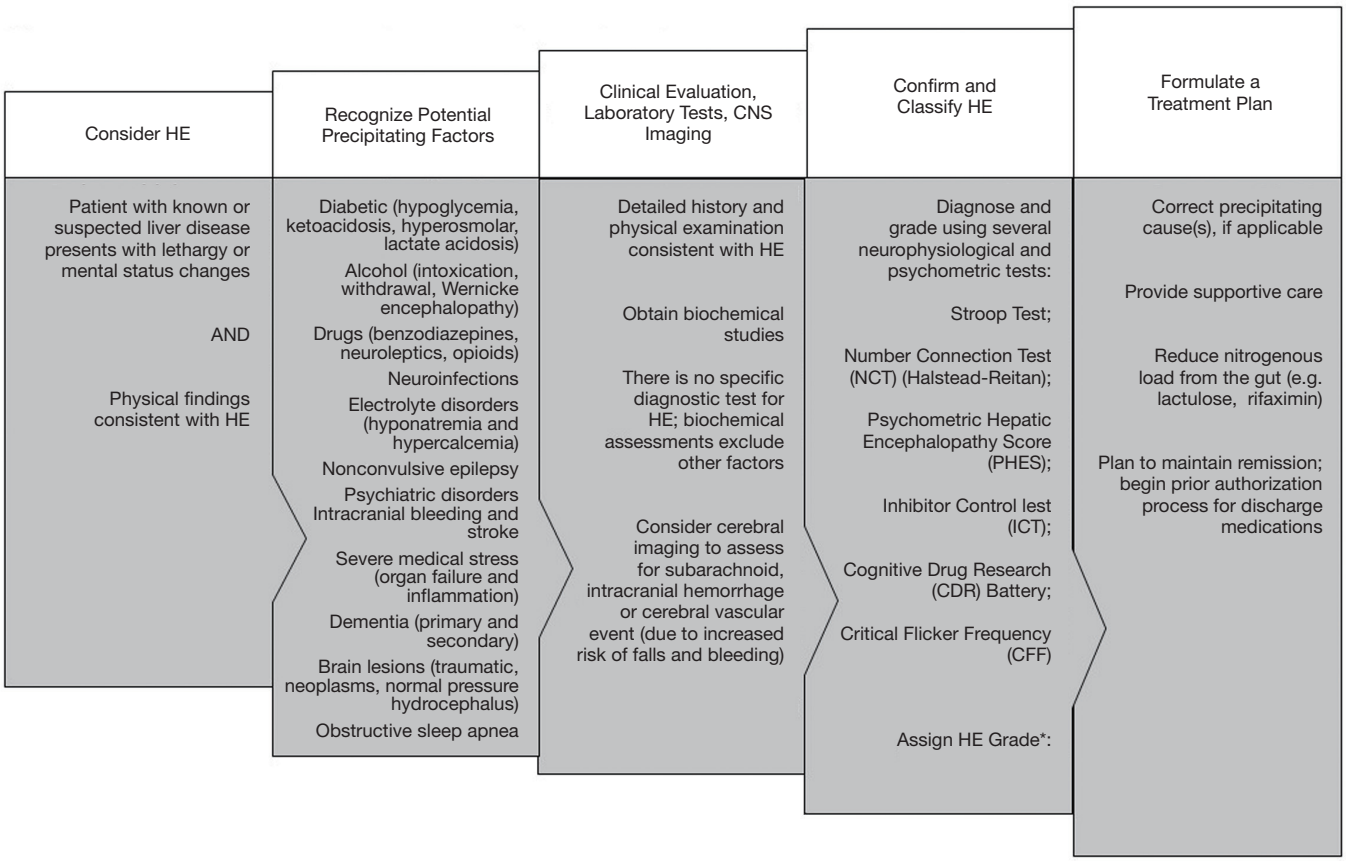

Figure 1 Diagnosis and treatment of hepatic encephalopathy in the hospitalized patient. *See *Table 1* for more details. Adapted from references (1,9). HE, hepatic encephalopathy; CNS, central nervous system.

mental status and requires active therapy (1). Treatment of episodic HE can be divided into inpatient induction/immediate treatment and outpatient maintenance of remission (21). *Figure 1* provides a suggested treatment plan for the hospitalized HE patient. Rapid identification and correction of the precipitant(s) is considered first-line management (39). Efforts should be made to treat infections, control gastrointestinal bleeding, and correct dehydration and electrolyte imbalances, for example (1,36).

Treating HE

Pharmacologic treatment of HE relies on therapies that reduce the nitrogenous load from the gut. Lactulose is first-line therapy. It is a non-absorbable disaccharide that is fermented in the colon and metabolized by microbiota to produce lactic acid, thereby lowering colonic pH. The cathartic effect of lactulose can increase fecal nitrogen excretion with up to a four-fold increase in stool volume (40); this therapeutic effect also commonly causes abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence (1). Lactulose is administered orally, through a nasogastric tube or via retention enemas (1). For oral and nasogastric tube administration, 30 to 45 mL (20–30 g) is initially administered three to four times daily, with dose titration to produce two to three soft stools per day; for enemas, 300 mL is administered in 1 L of water (9).

The addition of rifaximin to lactulose is recommended, as this combination has demonstrated faster reversal of HE and shorter hospital stays (1,9). Rifaximin is a minimally absorbed, oral antibiotic that decreases NH3-producing gut bacteria, thereby lowering serum NH3 (9). Rifaximin is taken orally twice a day, with or without food, and does not require dose adjustments in hepatic or renal insufficiency. Older antibiotics that were previously used for HE include neomycin and metronidazole. Although these drugs still have their advocates (1), significant side effects (e.g., nephrotoxicity and ototoxicity with neomycin; neuropathy with metronidazole) limit their use (1,9).

Table 3 The efficacy of lactulose and/or rifaximin for HE remission

Maintenance medication(s)	Patients and methods	Results
Lactulose (41)	Open-label study; 140 patients randomized to daily placebo or lactulose after recovery from an episode of OHE; patient follow-up over a median of 14 months	19.7% of lactulose-treated patients (12 of 61) experienced recurrent OHE *vs.* 46.9% (30 of 64) in the placebo arm (P=0.001)
Lactulose (42)	Open-label study; lactulose (n=80), probiotics (n=77), or no therapy (n=78) in patients recovering from OHE	ITT results demonstrated a significantly lower rate of OHE for lactulose (37.5%) and probiotics (45.4%) *vs.* no treatment (64.1%)
Rifaximin and Lactulose (39)	Rifaximin (n=140) *vs.* placebo (n=159) for the secondary prevention of episodic OHE in adult patients with 2 or more previous episodes of unprecipitated HE (now in remission); the majority of patients (>90%) were taking lactulose	Breakthrough HE lower in the rifaximin group (31 of 140) *vs.* placebo group (73 of 159); hazard ratio of 0.42 (95% CI, 0.28–0.64; P<0.001); 50% reduction in hospitalizations for the rifaximin group (19 of 140) *vs.* the placebo group (36 of 159); similar AEs amongst the two groups
Rifaxmin (43)	Prospective study over 26 months in 127 patients receiving rifaximin for prevention of OHE recurrence	HE-related hospital admissions decreased (0.86 to 0.41 admissions/patient; P<0.001); mean length of stay decreased (8.85 to 3.79 bed days/admission; P<0.001); good tolerability (2.4% AE's)
Rifaximin *vs.* Lactulose (44)	Retrospective chart review of 145 patients who received lactulose (30 cc BID) for ≥6 months and then rifaximin (400 mg TID) for ≥6 months	Fewer hospitalizations (0.5 versus 1.6; P<0.001), fewer days hospitalized (2.5 versus 7.3; P<0.001), fewer total weeks hospitalized (0.4 versus 1.8; P<0.001), and lower hospitalization charges per patient ($14,222 versus $56,635) were reported during the rifaximin period; more patients had asterixis, diarrhea, flatulence, and abdominal pain during the lactulose period (P<0.001)

Adapted from references (39,41-44). ITT, intent to treat; BID, twice daily; TID, three times daily.

Assembling a maintenance plan: prevention of recurrence with chronic therapy

The latter half of the HE treatment plan involves outpatient maintenance of remission to prevent recurrence and future hospitalizations. This plan needs to be formulated during inpatient treatment in conjunction with the outpatient care team as some discharge medications for HE commonly require prior authorizations. Prior authorization for maintenance medications is recommended during inpatient treatment so that the prescription can be readily available upon discharge.

The choice of maintenance medication(s) is the same as those used for therapy of active disease. Although there are no randomized, placebo-controlled trials supporting the use of lactulose for maintenance of remission from HE, open-label data and clinical experience support its use (1). Lactulose continues to require titration to achieve two to three soft stools per day while avoiding diarrhea and its consequences (e.g., dehydration, electrolyte abnormalities); patient dissatisfaction regarding these side effects often limit long-term use (9). In fact, readmission persists despite lactulose use, which is possibly related to how unpalatable it is. According to AASLD guidelines, rifaximin added to lactulose is the best-documented regimen to maintain remission in patients who have already experienced one or more bouts of HE while on lactulose treatment after their initial episode of HE (1,39) In some cases, rifaximin monotherapy is the best option, especially in patients who poorly tolerate lactulose (9). *Table 3* summarizes data on the use of lactulose and/or rifaximin for maintenance of remission in HE (39,41-44).

Transitioning to the outpatient setting and outpatient management

The period after discharge for cirrhotic patients is often described as "a high risk one"; patients may be on new medications, and their care is being transitioned from inpatient to outpatient (19). Hospitalists play a critical role in ensuring that HE treatment goals are optimized. This includes stressing the need for compliance with maintenance HE medications, setting close interval follow-up appointments with outpatient providers, and involving family and/or caregivers in understanding the importance

of chronic medications and outpatient care. Careful counseling of family members and caregivers is critical to ensure adherence to medications, follow-up visits, and to alert the discharging facility in the case of deterioration. Unfortunately, hospitalists are often challenged with several obstacles when attempting to meet these goals.

Data suggest that most patients hospitalized for HE do not receive maintenance medications upon discharge. One study found, after reviewing insurance claim data for prescriptions filled in 2009 (n=13,623), 2010 (n=15,529), and 2011 (n=16,328) that 89.2%, 87.8%, and 86.4% of patients with HE had inpatient claims for HE, respectively, and 60.3%, 62.3%, and 63.9% did not receive ongoing treatment (29). Hospitalists oversee the maintenance plan, including prescribing the correct medications and helping the patient to have access to them following discharge. Patients should be made aware that if they cannot obtain the medications for insurance-related reasons, the outpatient provider should be contacted as they can often help obtain coverage. Patients and caregivers should be taught how to recognize the symptoms of HE and to appreciate the importance of long-term therapy.

Discharging a patient with HE also involves addressing the ability to drive, as this is an important issue. Although fitness to drive is known to be compromised in patients with HE, there are no definitive guidelines or laws for practitioners to refer to when advising patients about driving. Yet, driving in the setting of recent HE is not advised. It is also important to be mindful of individual state requirements, as certain states require that healthcare professionals refer potentially unsafe drivers to motor vehicle authorities (9).

Patient adherence remains a factor in the recurrence of HE; lactulose non adherence is the leading cause for hospital readmission or recurrence of HE (9). A retrospective chart review (*Table 2*) found that HE recurrence and hospital readmission were often associated with failure to appropriately titrate lactulose—specifically, inadequate number of bowel movements and lack of awareness of dose titrations. Also, there was a failure to communicate worsening symptoms to providers (29). There are also compliance issues with rifaximin. A common misconception is that long-term use of an antibiotic is unnecessary and that its use is associated with bacterial resistance. As rifaximin is only minimally absorbed, resistance has not been an issue and rates of *Clostridium difficile* infections are low. Hospitalists need to counsel patients on these facts, specifically that although rifaximin is an antibiotic, it needs to be taken long-term and noncompliance will greatly increase chances of readmission.

Conclusions

HE is a burdensome complication of cirrhosis that is characterized by episodic occurrences that frequently require hospitalization. The consequences of HE affect patients physically (symptoms that range from confusion and tremors to coma) and emotionally (decreased quality of life). Optimizing the continuum of care is critical to prevent HE recurrence and re-hospitalization, which involves monitoring precipitating factors, and ensuring that patients are compliant with appropriate maintenance medications. Lack of appropriate post-discharge care results in frequent HE-related hospital readmissions. Hospitalists play a central role in minimizing recurrence and hospital readmission by initiating a care plan with lactulose and rifaximin and counseling patients on the importance of chronic treatment.

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Footnote

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