GHAPP E-Newsletter Series

Clinical Hepatic Encephalopathy Update

Project ID: 5838

Target Audience

Nurse practitioners and physician assistants involved in the management of patients with chronic liver disease.

Educational Objectives:

At the conclusion of this activity, participants will be able to:

- Describe the symptoms, diagnosis and treatment of hepatic encephalopathy
- Identify the reasons for and factors associated with frequent hospital readmissions
- Implement changes in clinical practice based on the new data and recommendations presented

ANCC Accreditation

Annenberg Center for Health Sciences is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

A maximum of 1.0 contact hours may be earned for successful completion of this activity.

Physician Assistant Statement

This activity has been reviewed by the AAPA Review Panel and is compliant with AAPA CME Criteria. This activity is designated for 1 AAPA Category 1 CME credits. Approval is valid from 4/5/2021 to 4/5/2022 . PAs should only claim credit commensurate with the extent of their participation. AAPA reference number: CME-202397.

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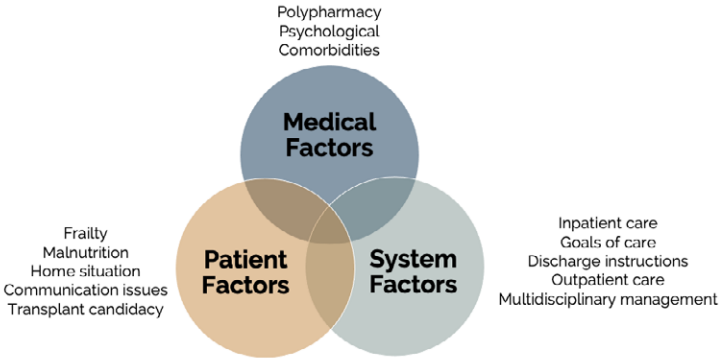
The end result of many forms of liver disease (e.g., hepatitis, fatty liver disease, alcoholic liver disease) is late-stage scarring, known as cirrhosis.[1] Advanced hepatic impairment in cirrhosis results in the inability to clear certain toxins, such as those derived from the gut (e.g., ammonia) and some inflammatory cytokines. As a result, these toxins enter the brain and cause neurological impairments, a common complication known as hepatic encephalopathy (HE).[2] In the US, the estimated prevalence of cirrhosis is approximately 5.5 million cases[3] and it is estimated that 30-50% of these patients have experienced HE. This is likely an underestimate, as most cirrhotic patients experience HE at some point during their disease.[4]

Clinically, HE patients present with a wide spectrum of neuropsychiatric abnormalities, ranging from mild cognitive dysfunction to coma and, in some cases, death. As a result, severity is categorized by minimal HE, with subtle manifestations that may be difficult to diagnose, or overt HE, with obvious symptoms that can result in hospitalization.[5] Minimal(M) HE may affect 30%-80% of patients with liver cirrhosis, but this number may be higher, since its covert nature makes it difficult to diagnose. Overt (O) HE is associated with poor survival, ranging between 15% and 42%.[2] In addition to debilitating symptoms and associated morbidity and mortality, HE is associated with poor quality of life and significant caregiver burden, routine activities like driving and working are impacted, hospital admissions and readmissions are frequent and healthcare costs are substantial.[6,7]

The rising prevalence of cirrhosis will likely result in more patients experiencing HE. There are standard measures that can be undertaken to forestall many of these complications and improve patient outcomes, but obstacles exist.[9] Diagnosis is not straightforward. Although increases in ammonia are often a common cause, plasma ammonia is not typically elevated and are therefore an unreliable marker. The first step in diagnosis is excluding other causes that alter levels of consciousness.[8] Once identified, the treatment of HE begins with the aim of improving mental status and requires active therapy. According to the 2014 Practice Guideline by the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver, treatment of an HE event involves correcting any precipitating factor(s) followed by management of the patients' mental status. Available therapies include lactulose, a non-absorbable disaccharide, and rifaximin, a non-absorbable locally acting antibiotic.[5,8] These medical treatments can potentially reverse the manifestations of HE and prevent recurrence, but the continuum of care for patients with cirrhosis is often referred to as a "revolving door" as most patients experience frequent episodes of HE which often result in hospital readmissions.[6,7] There are many factors that are responsible for hospital readmission in HE and they fall under three different categories: patient factors, medical factors and system factors (Figure).[1]

Reasons for HE Hospital Readmissions[1]



Data in cirrhosis patients have demonstrated that patient quality of care and outcomes are improved when advanced practice providers (APPs) work in conjunction with gastroenterologists and hepatologists. As such, APPs can benefit from training on specialty care, facilitating multidisciplinary team management and care coordination for cirrhotic patients.[1] This, the first Gastroenterology & Hepatology Advanced Practice Providers (GHAPP) e-newsletter, was written by an APP and geared toward APPs. It will serve as an update on the current state of HE, provide the most relevant and timely information on this topic and conclude on how these data and recommendations will clinically impact APPs practices.

The Current State of HE

The AASLD treatment guidelines for HE endorses active treatment for episodes of OHE. Pharmacologic therapy involves reducing the nitrogen in the gut. Lactulose, administered orally, through a

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nasogastric tube or via retention enemas, is recommended by the AASLD as first-line treatment for HE and works by increasing fecal nitrogen excretion and, subsequently, stool volume. Unfortunately, this cathartic effect coincides with unwanted side effects like cramping, diarrhea and flatulence.[7,8] Rifaximin is a minimally absorbed non-systemic, oral antibiotic that decreases ammonia-producing gut bacteria, thereby lowering serum ammonia. The most common side effects (≥10%) associated with rifaximin use in HE are peripheral edema, nausea, dizziness, fatigue and ascites.[9] The AASLD recommends rifaximin as an effective add-on therapy to lactulose for prevention of OHE recurrence.[8]

Poor Survival Despite Treatment with Current Standards of Care

The World Journal of Gastroenterology published data on the clinical outcomes of patients after an episode of HE treated with current standards-of-care. Of the 188 patients included and followed for a mean period of 12 ± 13 months, 107 (57%) died and 32 (17%) received orthotopic liver transplantation. The most common causes of death were decompensated chronic liver disease (57%) and sepsis (19%). The probability of survival was 44% and 35% at 12- and 24-months, respectively. The authors concluded that poor survival continues to be an issue in patients who have experienced HE.[10]

Unacceptably High Hospital Readmissions

Even in its mildest form, HE is a risk factor for future, more severe episodes.[7] As such, the AASLD treatment guidelines recommend secondary prophylaxis after just one episode of OHE. Rifaximin added to lactulose is the best-documented agent to maintain remission in patients who have already experienced one or more bouts of OHE while on lactulose treatment after their initial episode of OHE.[11] Although these facts are not disputed, hospital readmissions for HE are common. The North American Consortium for the Study of End-Stage Liver Disease cohort followed 1,353 patients formerly hospitalized patients with cirrhosis for three months post-discharge. Of these patients, 53% were readmitted (n=535; 316 with one, 219 with two or more) and these rates were consistent across study sites. Patients with cirrhosis and with worse Model for End-Stage Liver Disease (MELD) score or diabetes, those taking prophylactic antibiotics, and those with prior HE were more likely to be readmitted.[12]

Alarmingly Low Use of Preventative Therapies

The high rate of hospital readmissions in HE may be attributed, in part, to the underuse of preventative therapies. Among patients discharged after HE exacerbations, it is estimated that only 64% patients received the medication(s).[8] Evaluation of real-world claims data found that more than one-third of patients, previously hospitalized for HE, do not refill their prescribed medications to prevent recurrence.[5] Literature has shown better adherence rates and tolerability of rifaximin as compared to lactulose. A study evaluating precipitating factors for HE found lactulose non-adherence as the most frequently reported factor by 51% to 53% of patients.[13] Two trials have reported mean adherence rates to rifaximin treatment between 84% and 92%.[14,15] In a retrospective study, patients received rifaximin and lactulose for a time period of 6 months. The study defined compliance as adherence with at least 75% of medication. The results showed that 92% of patients in the rifaximin group and 31% of patients in the lactulose group were compliant.[16] Patient dissatisfaction regarding the gastrointestinal side effects associated with lactulose could be the factor that limits its long-term use.

COVID-19 Has Impacted the Quality of Long-Term Cirrhosis Care

The response to the COVID-19 pandemic has limited access to quality care in patients with long-term diseases like cirrhosis. A recent article by Tapper and colleagues describes that this impact unfolds over 3 waves:[17]

The COVID-19 Impact on the Long-Term Care of Cirrhotic Patients[18]

1. An intense period with prioritized high-acuity care with delayed elective procedures and routine care during physical distancing,
2. a challenging 'return to normal' following the end of physical distancing, with increased emergent decompensations, morbidity, and systems of care overwhelmed by the backlog of deferred care,
3. and a protracted period of suboptimal outcomes characterized by missed diagnoses, progressive disease and loss to follow-up.

This article offers suggestions to preserve the quality of cirrhosis care amidst a global pandemic. Their first suggestion is to implement proactive, rather than over reactive care. In terms of HE, this further reinforces the need for medications to prevent recurrence. In addition, they recommend coordinated care, which stresses the importance of APPs in HE management.[18]

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Improving Recurrence

A recent article by Flamm and colleagues entitled, "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" discusses the frequency of hospital readmissions for patients with HE and attributes them to breakdowns across the continuum care. The authors recognize that hospitalists play a pivotal role in improving the management of HE and suggest ways to improve outcomes. The article focuses on diagnosis and treatment during the inpatient period, as well as outpatient management. Rapid identification and correction of the precipitating factors for HE is considered first-line management, followed by confirmation of the suspected HE and formulation of a treatment plan.[7]

Precipitating Factors for HE[7]

Diabetic (hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis)
Alcohol (intoxication, withdrawal, Wernicke encephalopathy)
Drugs (benzodiazepines, neuroleptics, opioids)
Neuroinfections
Electrolyte disorders (hyponatremia and hypercalcemia)
Nonconvulsive epilepsy
Psychiatric disorders
Intracranial bleeding and stroke
Severe medical stress (organ failure and inflammation)
Dementia (primary and secondary)
Brain lesions (traumatic, neoplasms, normal pressure hydrocephalus)
Obstructive sleep apnea

The period after discharge for cirrhotic patients is often described as "a high risk one" because patients may be on new medications and their care is being transitioned from inpatient to outpatient.[2,7] Hospitalists play a critical role in ensuring that HE treatment goals are optimized. APPs can also be involved in these coordinated care efforts. The figure details the necessary steps to maintain a successful continuum of care for these patients. Because HE medications commonly require prior authorizations, it is recommended that the outpatient plan be formulated during inpatient treatment. When taken care of in advance, the prescription can be readily available upon discharge.

The Continuum of Care for HE Patients[7]

The choice of maintenance medication(s) is the same as those used for therapy of active disease. 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). As discussed, this is associated with poor patient satisfaction and noncompliance.[6] In addition, data indicate that HE recurrence and hospital readmissions are 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.[18]

The authors of this paper, in accordance with AASLD guidelines, stress that 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.[7,8] They also recognize that, in some cases, rifaximin monotherapy is the best option, especially in patients who poorly tolerate lactulose.[6,7] However, compliance with rifaximin may also play a role in recurrence. Patients often resist long-term use because they believe it will cause bacterial resistance. On the contrary, since rifaximin is only minimally absorbed, resistance has not been an issue and rates of Clostridium difficile infections are low.[7] The costs associated with rifaximin therapy may lead to non-adherence in some patients. Patients should be aware that savings plans and patient assistance programs are available through the manufacturer (for more information visit https://www.salix.com/therapeutic-areas/patient-focus). Educating patients and caregivers on these facts can improve outcomes.

A recent study by Tapper et al. sought to determine the effect

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on care-quality and outcomes for patients managed by APPs by performing a retrospective analysis of a nationally representative American commercial claims database (Optum), which included 389,257 unique adults with cirrhosis. Compared to patients never seen by an APP, management by an APP with or without gastroenterologists/hepatologists was associated with much higher rates of rifaximin use after discharge for HE (OR 1.31 [1.20, 1.44]) and lower 30-day readmissions (OR 0.68 [0.66, 0.70]).[1] In addition to improving adherence to medications, APPs can partner with specialists to make patients maintain follow-up appointments, monitor patients for symptoms of recurrence and alert the specialists if there are signs of deterioration.[7] In the article by Tapper and colleagues, the authors suggest that APPs may have a more important role in tasks that require additional efforts outside of traditional clinical workflow, such as assisting with prior authorizations for maintenance medications.[1] APPs can also be involved in counseling HE patients on driving. Specialists recommend that driving be discouraged in the setting of recent HE and that individual state requirements be consulted, since some may require that healthcare professionals refer potentially unsafe drivers to motor vehicle authorities.[6,7]

Evaluating the Role of Rifaximin Therapy Beyond Prevention of Recurrence

Currently, the only approved indication for rifaximin in cirrhosis is prevention of recurrent HE.[10] However, being an orally available, minimally-absorbed and safe medication, rifaximin has been studied in all aspects of HE. A recently published paper entitled, "The Use of Rifaximin in Patients with Cirrhosis" by Caraceni and colleagues summarizes some of the most recent and pivotal data on this drug (Table[19,20,21,22,23,24]). The manuscript concluded that, given its track record of acceptance by patients and efficacy in prevention of HE, further trials that evaluate the role of rifaximin in MHE and inpatient therapy of HE are needed.[19]

Use in HE	Supportive Data with Rifaximin
MHE Treatment	Double-blind RCTs have shown that rifaximin is better than placebo with respect to improvement in cognition, quality-of-life (QOL) and driving capability[20,21] Not currently cost-effective even to prevent major outcomes such as traffic crashes[22]
Inpatient therapy for HE	Small trials demonstrate that rifaximin may be useful in reducing blood ammonia and asterixis compared to selected therapies such as neomycin and non-absorbable disaccharides[19] A large, open-label study evaluated rifaximin compared to lactulose with clinical outcomes centered on survival and mental status recovery. Rifaximin therapy was better than lactulose in inpatient outcomes. Additional trials are warranted to replicate this finding.[23]
Prevention of recurrence	Bass and colleagues randomized 299 patients with multiple HE episodes into receiving daily rifaximin 550mg BID vs placebo over 6 months. The primary endpoint was breakthrough hospitalizations due to HE and patients in the rifaximin group had significant reduction in breakthrough events and hospitalizations over the 6 months.[12] This trial followed smaller-scale trials from Europe where long-term cyclical use was studied with good outcomes[19]
"Real-world" use of rifaximin	Open-label experiences and evaluation of placebo-assigned group that was subsequently given rifaximin showed continued reduction in HE-related episodes even outside the clinical trial setting.[24] Studies focused on changes in resource utilization before compared to after rifaximin showed that it can lead to reduction in HE episodes and admission and critical care admissions.[19]

Portal hypertension is the initial and main consequence of cirrhosis and is responsible for many of its complications. A transjugular intrahepatic portosystemic shunt (TIPS) is often inserted to treat the portal hypertension and associated complications. Unfortunately, HE often ensues 6 months post-TIPS placement in up to half of these patients.[25,26] Recently published data examined the effects of rifaximin in the prevention of OHE after TIPS placement. This large double-blind, multicenter trial studied 197 patients with cirrhosis undergoing TIPs. Patients were randomly assigned to receive rifaximin (600 mg twice daily) or placebo, beginning 14 days before TIPS and continuing for 168 days after the procedure. An episode of OHE occurred in 34% (95% CI, 25% to 44%) of patients in the rifaximin group (n = 93) and 53% (CI, 43% to 63%) in the placebo group (n = 93) during the post-procedure period (odds ratio, 0.48 [CI, 0.27 to 0.87]). No differences were noted in terms of transplant-free survival or adverse events. The authors concluded that rifaximin should therefore be considered for prophylaxis of post-TIPS HE.[27]

Despite the proven benefits of rifaximin, because the cost of treatment with rifaximin in combination with lactulose is higher than that of lactulose alone, there is uncertainty regarding the effect of treatment with rifaximin on overall healthcare costs. Volk and colleagues performed a claims-based analysis to assess healthcare costs and hospitalization rates associated with rifaximin therapy versus lactulose alone among patients at risk for HE. Investigators found that patients incurred significantly lower rates of HE-related and all-cause hospitalizations during rifaximin versus

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lactulose episodes, resulting in lower facility and professional costs. However, patients were not adherent in approximately 30% of rifaximin episodes. They concluded that cost savings may be possible if rifaximin adherence is improved in HE patients.[2]

Conclusions: The Impact of These Data/Recommendations on How APPs Practice

It is inevitable that an APP working the field of Gi and hepatology will encounter patients who suffer from HE. Whether this be on the inpatient or outpatient setting, it is important for the APP to be well versed in the signs and symptoms of how HE presents and to always be aware of its potential to manifest as mild symptoms. Often, it may not be the patient that makes the APP aware of potential HE, but rather the caregiver. Therefore, the APP should always interview the caregiver not just the patient.

The APP is uniquely positioned to assess and diagnosis HE in cirrhotic patients. APPs should be well trained in educating patients on proper titration of lactulose and safety of rifaximin. As noted in the newsletter, coordination between the inpatient and outpatient setting is critical to long-term management. If a patient is hospitalized for HE, outpatient planning should start during the inpatient admission to ensure a seamless transition. The inpatient team needs to communicate with the patient's outpatient provider about pending discharge and make efforts to get the patient scheduled for outpatient follow as soon as possible.

This article serves as an excellent overview with information APPs can use to make their practice better and raise the awareness of HE and improve the recognition and diagnosis of the condition. As noted, HE impacts 30-50% of patients with cirrhosis, therefore a significant number of patients.

Recognition and diagnosis are the first steps, followed by treatment initiation, and then management. It is a clinical diagnosis and the APPs expertise in symptom assessment and recognition makes APPs uniquely qualified to manage these patients.

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