

The Health Care Burden of Hepatic Encephalopathy



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KEYWORDS

• Hepatic • Encephalopathy • Cirrhosis • Liver transplantation • Liver disease • Cost

KEY POINTS

- Hepatic encephalopathy (HE) is a potentially reversible neurocognitive complication affecting approximately 30% of patients with cirrhosis.
- HE is responsible for tens of thousands of emergency department visits in the United States each year with an average cost of \$2858 per visit. Total inpatient charges associated with HE exceed 10 billion US dollars per year.
- In addition to health care costs, HE creates a large economic burden due to missed work and inability to drive and operate heavy machinery.
- There are significant psychological and financial costs associated with being a primary caregiver for a patient with HE.

INTRODUCTION

Hepatic encephalopathy (HE) is a potentially reversible neurocognitive complication of liver cirrhosis. There are more than 600,000 adults in the United States living with cirrhosis,¹ with HE occurring among roughly 30% of cirrhotic patients.² HE can manifest with a spectrum of neurologic abnormalities, from subclinical changes to significant confusion and coma. It also increases morbidity and mortality associated with cirrhosis³; the survival probability after a first episode of HE is 42% at 1 year and 23% at 3 years.⁴ In this article, the authors review the significant economic burden that HE imposes on caregivers and the US health care system.

PATHOPHYSIOLOGY OF HEPATIC ENCEPHALOPATHY

The pathophysiology of HE is complex and is an ongoing area of investigation. Liver dysfunction leads to a buildup of blood-derived products, which believes to alter

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the permeability of the blood-brain barrier.³ Ammonia, bile acids, metals, and electrolyte imbalances all play integral roles in the development of HE.³ Increased ammonia levels may lead to cellular swelling, oxidative stress, mitochondrial dysfunction, and changes in cell membrane potentials.⁵ Emerging data also support a role for microbiota–host interactions in the pathogenesis of HE.⁶ Treatment of HE includes treatment of acute episodes of HE and secondary prophylaxis for prevention of recurrence.⁷ Reducing the economic burden of HE may also require more proactive screening for HE. At least one study showed that over half (53%) of a cohort of cirrhotic patients without overt HE had covert HE when administered a cognitive battery test, and those patients had a higher risk of overt HE, hospitalization, and death in adjusted analyses.⁸

EMERGENCY DEPARTMENT VISITS AND HOSPITAL ADMISSIONS

HE is responsible for tens of thousands of emergency department (ED) visits in the United States each year. Data from the Healthcare Cost and Utilization Project reveal that there were 57,578 ED visits for HE in 2014, with an average cost per visit of \$2858.⁹ Moreover, the vast majority of patients presenting to the ED with HE require admission for ongoing treatment.^{9,10} Hospital admission increases the health care costs associated with an episode of HE.

It is estimated that HE accounts for 0.33% of all hospitalizations in the United States.¹¹ In 2014, there were 31,182 hospital admissions with HE, and from 2010 to 2014, total inpatient charges associated with HE increased by 46.0% (8.15 billion USD to 11.9 billion USD).¹² Despite reported declines in mortality and lengths of hospital stay for patients with decompensated cirrhosis from 2007 to 2017, related costs increased.¹³ The average length of stay for patients hospitalized with HE decreased from 6.2 days to 4.9 days, but the average cost per admission increased from \$38,897 to \$49,391.¹³

Unfortunately, the economic costs associated with HE often do not end with the index admission. Approximately 22.2% of patients admitted with HE are discharged to nursing homes or rehab facilities, and another 16.2% are discharged with home health care services.⁹ Skilled nursing facilities increase costs by an estimated \$11,073, whereas home health services increase charges by an estimated \$2,459.¹⁴

READMISSIONS

HE is a common reason for readmission for patients with decompensated cirrhosis,^{15,16} accounting for 47% of readmissions for cirrhosis-related complications in one study.¹⁷ In a single-center study of 402 cirrhotic patients, median time to readmission was 67 days, with 165 readmissions occurring within the first month after discharge.¹⁸ Because HE readmissions are often costly, a substantial amount of quality improvement efforts have been devoted toward decreasing them. One quality improvement study that used electronic medical records (EMR) checklists to prompt providers to provide goal-directed lactulose therapy and rifaximin for patients with overt HE reported a 38% lower risk of readmission and decreased length of stay (−1.34) with use of the checklist.¹⁹

Another quality improvement initiative encouraged patients to use a mobile phone app known as a “patient buddy” to track clinical data and prevent readmission.²⁰ Participating patients and caregivers entered information on daily medication adherence, sodium intake, and body weight, along with weekly cognitive and fall risk assessments.²⁰ Of the 40 patients using the “patient buddy” app, 17 had readmissions within 30 days, but none of the readmissions were for HE.²⁰ Efforts have also been undertaken

to better educate patients and caregivers on the pathophysiology of HE. One study examined the use of educational materials on patient outcomes.²¹ One group of patients received educational materials on HE pathophysiology and medications and the importance of regular bowel movements in preventing episodes of encephalopathy.²¹ Compared with standard of care, patients receiving the educational materials had a significant decrease in HE-related admissions (hazard ratio [HR] 0.14, CI 0.02 to 0.77).²¹

To improve transitions in care, some health systems have developed special post-discharge clinics for patients' admitted with HE.²² For example, a group of patients with alcohol-related cirrhosis with HE were scheduled for follow-up at a specialty rehabilitation clinic before discharge; at the rehabilitation clinic, patients' clinical, psychological, and social issues were identified and addressed.²² One-year survival was higher and alcohol consumption was lower in patients who followed up in the rehabilitation clinic compared with controls.²²

Guidelines recommend lactulose as first-line therapy for HE and rifaximin in combination with lactulose for reducing the risk of HE recurrence.⁷ Lactulose is a nonabsorbable disaccharide which acidifies the bowel milieu and increases intestinal transit and excretion of ammonia.³ The dosing of lactulose is usually 15 to 20 mL titrated to 3 to 4 soft bowel movements per day.³ Standard dosing of lactulose has been associated with a decrease in HE severity and mortality.²³ Unfortunately, the titratable nature of this medication can lead to lactulose ineffectiveness due to factors such as patient nonadherence or inadequate titration. Rifaximin is a non-aminoglycoside which acts against gram positive and gram negative aerobic and anaerobic enteric bacteria.³ In a study of 299 patients who were in remission from recurrent HE, rifaximin significantly reduced the risk of an episode of HE when compared with placebo over a 6-month period (HR 0.42 95% CI 0.28–0.64).²⁴ Furthermore, in a double-blind randomized controlled trial, patients receiving lactulose and rifaximin had a shorter length of hospitalization (5.8 days vs 8.2 days) when compared with patients receiving lactulose alone.²⁵

Inability to Work and Operate Heavy Machinery

In addition to the health care costs associated with HE hospitalizations, HE also creates a large economic burden due to missed work and disability claims. HE can impact job performance through decreased attention span, increased fatigue, and inability to operate work-related machinery. In a German study of 110 patients with cirrhosis, rates of HE were higher in blue-collar works (drivers, carpenters, factory workers) rather than white-collar workers (doctors, lawyers, academicians)²⁶; 60% of blue-collar employees were deemed unfit for work by the German social security system compared with 20% of white-collar employees.²⁶

One US study of 104 cirrhotic (44% with a history of HE) patients examined a variety of impacts of HE on patients' employment and personal finances.²⁷ Following the diagnosis of cirrhosis, 53% of patients decreased their work hours and 44% stopped working completely.²⁷ Patients with a history of HE had an unemployment rate of 87% compared with 19% in patients with no history of HE.²⁷ With decreased work hours, 56% of families stopped saving, 46% of families incurred debt, and 7% of families filed for bankruptcy.²⁷ The negative economic effects of HE may make it challenging for patients to afford medications and can lead to medication nonadherence.²⁷ This can create a cycle where medication nonadherence leads to hospital admissions, which increases the economic burden on patients and then promotes further nonadherence.

HE may impact the ability to safely drive and operate heavy machinery.²⁸ In a driving simulator study of 100 patients with cirrhosis and 67 controls, rates of collisions,

speeding, and center line crossings were higher in patients with HE.²⁹ In addition, patients with HE were more likely to report fatigue after driving compared with controls.²⁹ Another study of 205 patients with cirrhosis categorized drivers as “safe” or “unsafe” based on crashes and violations reported on official driving records; 16% of patients with HE were characterized as unsafe compared with 7% of patients without HE.³⁰ Recognition of the deleterious effects HE can have on driver safety has led to recognition that hepatologists should ask patients with HE about driving safety and should recommend driving restrictions in patients with HE and prior poor driving history.^{31,32}

Risks of Falls

In addition to increased risks of driving accidents, patients with HE are also prone to other injuries. Rates of falls are significantly higher in patients with cirrhosis and HE compared with patients with cirrhosis without cognitive issues.³³ Patients with cirrhosis who present to the ED with falls often have more severe injuries compared with patients without cirrhosis; rates of intracranial hemorrhage, skull fractures, and pelvic fractures are higher in patients with cirrhosis who present with falls.³⁴ The mean length of hospitalization for patients with cirrhosis following a fall is 7.25 days compared with 5.12 days in patients without cirrhosis.³⁴ Furthermore, the mean inpatient charges associated with a fall are higher in patients with cirrhosis (\$61,808) compared with patients without cirrhosis (\$43,106).³⁴

Effects on Caregiver Quality of Life

In addition to the effects on patients themselves, there are significant psychological and financial costs associated with being a primary caregiver for a patient with HE. Caregivers report a sense of entrapment and a negative impact on their personal schedules and health compared with caregivers for patients without HE.²⁷ This is likely due to the detailed level of care required by patients with HE. In one study, 18% of care givers reported mild depression, 5% reported moderate depression, and 5% reported severe depression.²⁷ The patient's cognitive performance and model for end-stage liver disease (MELD) score were correlated with employment status and caregiver burden.²⁷ Patients with higher MELD scores and worse cognitive performance often require more detailed care making meaningful employment challenging and placing a larger psychological and financial strain on caregivers.

Treatment Options

Given the negative effects that HE has on quality of life for patients and caregivers, emphasis is placed on preventing and treating episodes of HE. Guidelines from the American Association for the Study of Liver Diseases (AASLD) recommend identifying and treating precipitating factors for HE, such as infections, GI bleeding, constipation, dehydration, and electrolyte derangements.⁷ The AASLD also recommends therapies for HE including lactulose and rifaximin.⁷ A recent meta-analysis of 16 studies demonstrated that lactulose and rifaximin improve several patient-reported outcomes in HE.³⁵ Lactulose and rifaximin also improved overall health-related quality of life, social activity, communication, and sleep in patients with HE.³⁵ A systematic review published in 2018 suggested the use of lactulose plus rifaximin reduces hospital readmissions and has a cost savings of \$25–\$49 million per year in the United States, compared with lactulose monotherapy.³⁶ There are increasing data that rifaximin is a cost-effective therapy for HE, both when used in conjunction with lactulose and used as a monotherapy. A large database analysis of 13,515 patients treated with rifaximin monotherapy and 9,946 patients with lactulose monotherapy revealed hospital admissions decreased by 33% when patients were treated with rifaximin versus

lactulose alone.³⁷ Although higher pharmacy costs were associated with rifaximin, these costs were negated by the cost-saving effects on hospital admission rates and lengths of stay.³⁷ Similarly, a recent meta-analysis of 11 studies demonstrated rifaximin used as an add-on treatment with lactulose or as a monotherapy is a cost-effective treatment for HE when compared with lactulose alone.³⁸

Despite the effectiveness of lactulose and rifaximin, HE continues to be a significant issue for patients with cirrhosis. A current research is focused on developing novel therapies for patients with HE. Enteric bacteria play a significant role in ammonia production; therefore, many future therapies for HE focus on altering gut bacteria composition.⁶ Fecal microbial transplantation (FMT) has been proposed for treating HE.³⁹ In a study of patients with recurrent HE on lactulose plus rifaximin, 10 patients were randomized to receive FMT from the same donor, whereas 10 patients were randomized to receive standard of care.⁴⁰ No additional episodes of HE were experienced in the FMT group through 150 days compared with 6 episodes of HE in the standard of care group.⁴⁰ Further large-scale randomized studies are needed to evaluate the efficacy of FMT for patients with refractory HE. Studies have also investigated other novel therapies for HE including flumazenil, glycerol phenylbutyrate, L-ornithine L-aspartate, polyethylene glycol, and probiotics.⁴¹ As our understanding of HE improves, it is likely novel therapeutic targets will continue to be identified.⁴¹

Role of Liver Transplantation

When considering the economic burden of HE, it is also important to consider costs associated with liver transplant, which is the definitive treatment of patients with decompensated cirrhosis. Although the presence of HE does not influence position on the transplant waitlist, the condition improves following liver transplantation, based on both cognitive function evaluations and neurologic imaging studies.⁴² Costs associated with liver transplantation have risen substantially in the past decade, increasing from \$577,100 in 2011 to \$812,500 in 2017 (+41%).⁴³ Moreover, these numbers do not include the costs associated with the long-term immunosuppressive treatment that patients require posttransplant for the rest of their lives.

SUMMARY

As the prevalence of chronic liver disease increases throughout the United States, the health care burden of HE will continue to grow. HE results in direct health care costs through health care utilization and hospital admissions. Furthermore, HE creates indirect costs for patients and caregivers by affecting ability to work and quality of life. Current quality improvement initiatives are focused on improving transitions of care for patients with HE and decreasing hospital readmissions. There is also ongoing research focused on developing novel therapies for patients with refractory HE to improve quality of life for patients and caregivers. Continued efforts will be required to decrease the health care burden of HE.

CLINICS CARE POINTS

- Hepatic encephalopathy (HE) is a common complication of cirrhosis that affects survival and frequently results in hospital admissions.
- Beside the health care costs associated with hepatic encephalopathy, patients face economic burden from missed workdays and disability. Individuals with HE should be assessed for fall risk and driving safety.

- Identifying and treating precipitating factors for HE such as infections, GI bleeding and dehydration can shorten the duration of these episodes. Patients' and caregivers' education can reduce hospitalizations.

DISCLOSURE

No disclosures to report.

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