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Trends, Predictors, and Outcomes of Hepatic Encephalopathy Treatment at a Quaternary Transplant Center From 2012-2022

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Abstract

Background: Hepatic encephalopathy (HE) is a devastating complication of cirrhosis that increases mortality. Many patients do not receive guideline recommended HE treatment.

Our aim is to evaluate trends in HE treatment over time, variables associated with receiving treatment, and outcomes based on the type of treatment received.

Methods: Retrospective single-center cohort study of hospitalized patients with HE from July 2012 – June 2022. HE treatment was defined as receiving lactulose, rifaximin, or combination therapy.

Results: A total of 1,683 unique patients were included, 72% of patients received HE treatment. Fewer HE patients received any treatment in 2022 (65.9%) compared to 2012 (72%). Predictors of receiving any treatment included: Medicare use ($p = 0.02$), increasing MELD-Na score ($p < 0.0001$), having portal hypertension ($p < 0.0001$), hepatocellular carcinoma ($p = 0.03$), alcohol-related cirrhosis ($p < 0.0001$), and being seen by gastroenterology/ hepatology ($p = 0.003$) or internal medicine ($p < 0.0001$). Predictors of receiving combination therapy included: having alcohol- related ($p = 0.002$), biliary ($p = 0.01$), or other cirrhosis ($p < 0.0001$), and portal hypertension ($p = 0.04$). Any HE treatment was associated with higher 30-day readmission ($p < 0.0001$) and 1-year mortality ($p = 0.0005$). Combination therapy was associated with a longer median length of stay (7.8 vs. 6.6 days, $p = 0.01$).

Conclusion: HE treatment rates decreased from 2012 to 2022, especially among patients of older age, with autoimmune cirrhosis, lower MELD-Na scores, and infection while hospitalized. Increasing access to care from gastroenterology/hepatology is a modifiable factor that may increase HE treatment.

Keywords

hepatic encephalopathy, rifaximin, lactulose, cirrhosis, hospitalization, mortality, readmission

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Abbreviations

HE – hepatic encephalopathy
US – United States
MELD-Na – Model for End-stage Liver Disease
AASLD – American Association for the Study of Liver Diseases
FDA – Food and Drug Administration
ICD - International Classification of Disease
NASH – non-alcoholic steatohepatitis
HCC – hepatocellular carcinoma
LOS – length of stay
SD – standard deviation
IQR – interquartile range
CI – confidence interval
AOR – adjusted odds ratio
ALD – alcohol-related liver disease

Introduction

Hepatic encephalopathy (HE) is a devastating complication of cirrhosis, presenting clinically as disturbances of consciousness, behavioral disorders, and coma.1 Clinically apparent or overt HE will occur in up to 40% of patients with cirrhosis.[1,2] Compared with variceal bleeding and ascites, HE alone is associated with the worst outcome, with 1-year mortality as high as 64%.1,3-6 HE is associated with more hospitalizations, falls, motor vehicle accidents, and poor quality of life for patients and is estimated to cost the United States (US) healthcare system over $7 billion annually.[2,3,5-10] Over 50% of admissions to the hospital related to HE are preventable.[5-7]

American Association for the Study of Liver Diseases (AASLD) guidelines recommend initiation of pharmacotherapy for patients with HE, as it reduces mortality.[2-7] Current US Food and Drug Administration (FDA) approved pharmacotherapies include lactulose and rifaximin. Recent analyses suggest that rifaximin combined with lactulose may be more efficacious than either drug alone.[11-16] Despite the compelling evidence for the use of these medications, only 50% of patients hospitalized with HE are discharged on pharmacotherapy.[17,18] Multiple factors may determine access to these medications, including cost, medication tolerance, and access to outpatient management.[18-20] Improving treatment rates could not only significantly improve the quality of life for patients and their caregivers but also reduce costs for healthcare systems.

Our aim is to evaluate 1) trends in HE treatment over time, 2) variables associated with an increased likelihood of receiving any HE treatment, 3) variables associated with receiving combination therapy with lactulose and rifaximin versus lactulose monotherapy, and 4) outcomes, including the length of stay, discharge disposition, 30-day readmission, along with inpatient, 30-day, and 1-year mortality based on the type of treatment received.

Methods

Study Design & Patient Selection

We performed a retrospective single-center cohort study of all hospitalized patients at the University of Nebraska Medical Center from July 1, 2012, to June 31, 2022, with a diagnosis of hepatic encephalopathy (HE). Patients were identified using the International Classification of Disease (ICD)-10 codes (Supplemental Table 1). To be included, patients had to be hospitalized for at least 48 hours, so there was sufficient opportunity to receive treatment. We included all patients 18 years of age or older. For the descriptive analysis of trends over time in prescribing practices, a patient's first hospitalization within each half-year period was included. Although a single patient may have contributed multiple data points over the study period, only one visit per half-year period was included. For the inferential analyses, only a patient's first visit within the entire study period was included. Thirty-day readmissions were only counted if the readmission was related to liver disease. This study was approved by the University of Nebraska Medical Center Institutional Review Board.

Variables of Interest

HE Treatment Definition and Categorizations.

HE treatment was defined as receiving lactulose, rifaximin, or a combination of both while hospitalized, which was derived using pharmacy data from the patient's medical record. Two sets of analyses were run: the first comparing patients who received any drug (lactulose, rifaximin, or the combination of the two) versus no drug, and the second comparing patients who received lactulose monotherapy versus the combination of lactulose + rifaximin.

Non-Treatment Variables of Interest. Variables associated with HE treatment were divided into pre-hospitalization and in-hospital characteristics. Variables were obtained from data recorded in patients' charts during their index hospitalization. The model for End-Stage Liver Disease (MELD-Na) score was obtained using lab work on the date of hospitalization or the closest available lab work to this date within one year prior to hospitalization.

Pre-Hospitalization Characteristics. Pre-hospitalization characteristics included demographic variables (age, gender, ethnicity), etiology of liver cirrhosis [alcohol, autoimmune, biliary (including primary biliary cholangitis and primary sclerosing cholangitis), non-alcoholic steatohepatitis (NASH), or other], and presence of other liver-related decompensation (ascites, varices, hepatocellular carcinoma (HCC), sarcopenia, or portal hypertension).

In-Hospital Characteristics. In-hospital characteristics were evaluated to assess common precipitants of hospitalization among patients with HE, including infection (any), electrolyte derangements (hypokalemia, hyponatremia, and hypomagnesemia), intoxication (drugs, alcohol, sedatives), constipation, dehydration/hypovolemia, acute renal failure, gastrointestinal bleed, and anemia. For insurance status, if patients had multiple payers listed for a single visit, we categorized them based on this priority: private, Medicaid, Medicare, and self-pay.

We evaluated which inpatient medical teams were utilized for each hospitalization to determine potential care gaps that could be addressed with future prospective interventions.

Hospitalization Outcomes. We compared the length of stay (LOS), discharge disposition (against medical advice, home, home with nursing support, skilled nursing facility, or long-term care), and 30-day readmission, along with inpatient mortality, 30-day post-discharge and 1-year post-discharge mortality between treatment groups (any drug vs. no drug and lactulose monotherapy vs. combination therapy). Inpatient deaths were included in 30-day and 1-year mortality, and patients who died within 30 days of discharge were also included in 1-year mortality.

Statistical analysis

Categorical variables were summarized using counts and percentages, while continuous variables were summarized with means and standard deviations (SDs) for normally distributed variables (e.g., age, MELD-Na) or medians and interquartile ranges (IQRs) if the distribution was skewed. Associations between categorical variables and treatment type were assessed using Chi-square tests or Fisher's exact tests if expected cell sizes were low. Differences in age and MELD-Na were assessed using independent samples t-tests, and differences in LOS were assessed using Wilcoxon Rank Sum tests.

Variables that had a p-value less than 0.20 in the univariable analysis were entered into a logistic regression model, where any HE treatment (yes vs. no) was the outcome, to be able to calculate adjusted odds ratios (AORs) and associated 95% confidence intervals (CIs). Continuous variables could have non-linear associations with the outcome using restricted cubic splines. Given that AORs can vary across values of a given continuous variable, AORs are given for three example values for each continuous variable in the model results tables. Continuous variables that did not have an univariable p-value less than 0.20 were initially entered into the model (to assess for a possible non-linear association) but were removed if their overall p-value was greater than 0.10. A similar methodology was used when the outcome was lactulose monotherapy vs. combination therapy (lactulose + rifaximin). All analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Trends in HE Medication Prescribing

There were 1,683 unique patients included (**Figure 1**), of whom 57.7% were male, and the average age was 57.3 years (SD = 12.6). In the study population, 1,205 (71.5%) patients received any drug, and 478 (28.4%) received no drug. Among those who received any drug, 739 (61.3%) received combination therapy (lactulose + rifaximin), and 434 (36%) received lactulose monotherapy. The proportion of patients who did not receive any HE treatment went from 28.0% in 2012 to 34.1% in 2022. The proportion of patients receiving

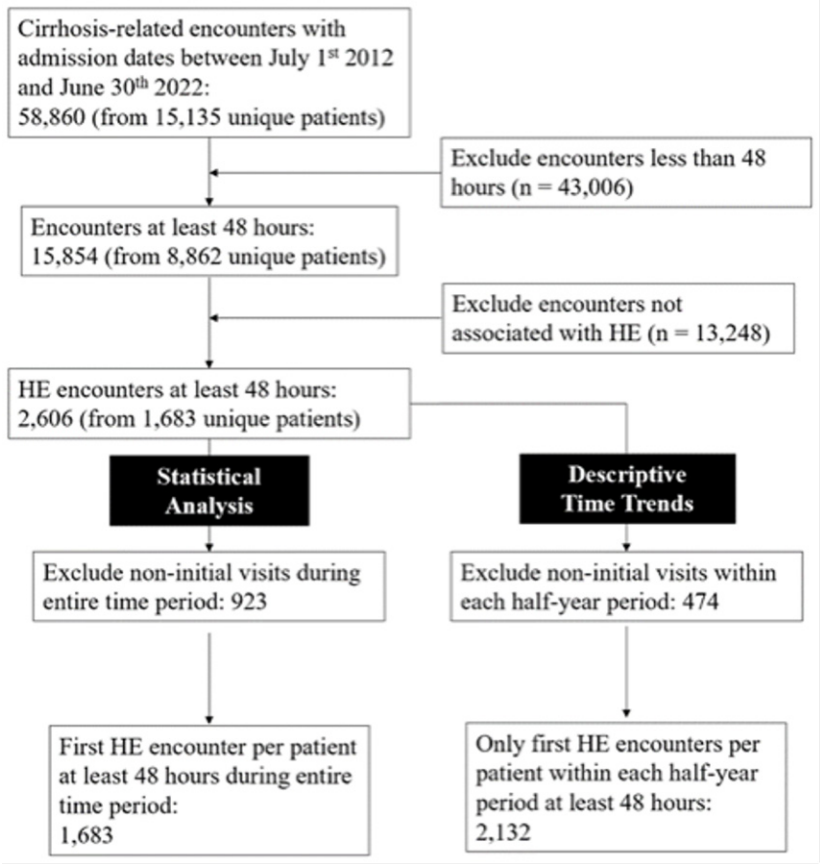

Figure 1. Criteria used to identify patients for the study.

combination therapy went from 38.3% in 2012 to 43.7% in 2022 (**Figure 2)**.

Variables Associated with Receiving Any HE Treatment

The distributions of variables between those who received any HE treatment and those who did not are displayed on the left side of **Table 1**. The logistic model results where the outcome was any HE treatment (yes vs. no) can be found in **Table 2**. Visualizations of the continuous variables, which were modeled using restricted cubic splines, can be seen in Supplemental Figure 1.

After adjusting for other variables in the model, predictors of receiving any HE treatment included: Medicare as primary insurance (AOR = 1.98, 95% CI: 1.05, 3.70), increasing MELD-Na scores (AOR (at MELD-Na = 30) = 1.07, 95% CI: 1.02, 1.12), having portal hypertension (AOR = 1.81, 95% CI: 1.37, 2.38), hepatocellular carcinoma (AOR = 1.58, 95% CI: 1.04, 2.38), or alcohol-related cirrhosis (AOR = 3.18, 95% CI: 2.25, 4.50), and consultation with gastroenterology/hepatology service (AOR = 3.39, 95% CI: 1.52, 7.55) or care from an internal medicine team (AOR = 1.77, 95% CI: 1.33, 2.36).

Variables associated with lower adjusted odds of receiving any treatment included: being hospitalized later in the study period (AOR (at year = 2021) = 0.67, 95% CI: 0.54, 0.82), having autoimmune cirrhosis (AOR = 0.46, 95% CI: 0.26, 0.81), and having infection while hospitalized (AOR = 0.72, 95% CI: 0.56, 0.94).

Variables Associated with Receiving Combination Treatment

In the subgroup analysis, comparisons were made between lactulose monotherapy and the combination of lactulose and rifaximin. The distribution of variables between these two treatment groups can be found on the right side of **Table 1**. AORs of receiving combination treatment versus lactulose monotherapy can be found in **Table 3**. Visualizations of the continuous variables, which were modeled using restricted cubic splines, can be found in Supplemental Figure 2.

After adjusting for other variables, predictors of receiving combination therapy included: having alcohol-related cirrhosis (AOR = 1.72, 95% CI: 1.21, 2.44), biliary cirrhosis (AOR = 3.43, 95% CI: 1.27, 9.22), other cirrhosis (AOR = 1.89, 95% CI: 1.43, 2.51), and portal hypertension (AOR = 1.35, 95% CI: 1.01, 1.80). Variables associated with lower odds of receiving combination therapy included increasing age (AOR (at age = 70 years) = 0.96, 95% CI: 0.93, 0.99), constipation (AOR = 0.43, 95% CI: 0.21, 0.87), and intoxication (AOR = 0.68, 95% CI: 0.48, 0.95).

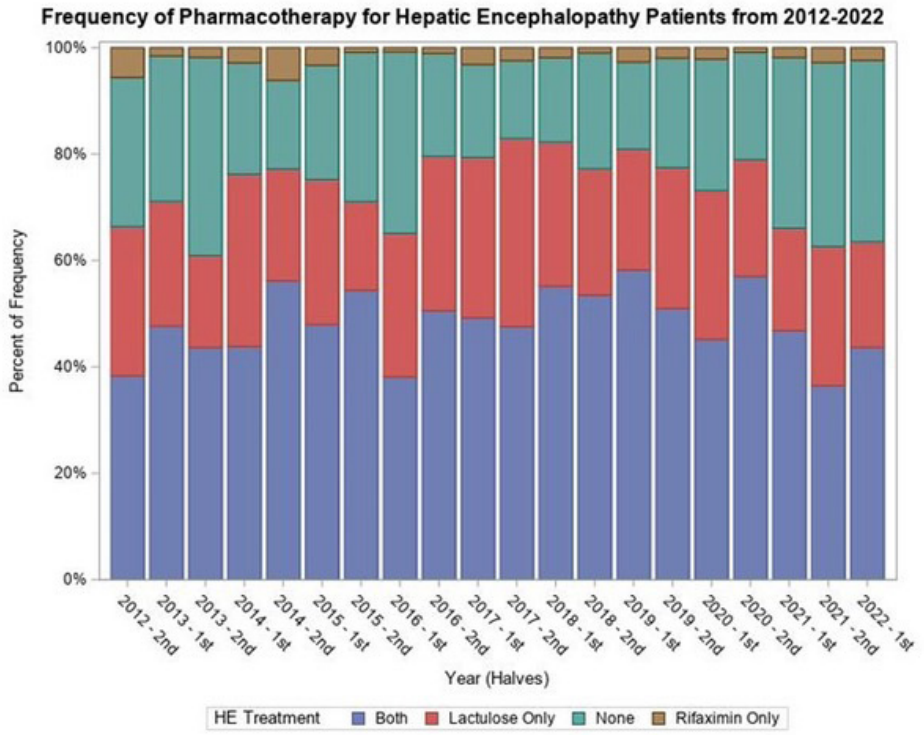

Figure 2. Frequency of pharmacotherapy for hepatic encephalopathy from 2012-2022.

Hospitalization Outcomes

Any HE Treatment. Differences in outcomes between any HE treatment and no HE treatment groups can be found on the left side of **Table 4**. Treatment with any drug was associated with higher 30-day re-admission for liver-disease-related hospitalizations (37.0% vs. 25.7%, $p < 0.0001$) and 1-year mortality (39.2% vs. 30.1%, $p = 0.0005$).

Combination Treatment. Differences in outcomes between patients who received lactulose monotherapy and those who received combination therapy can be found on the right side of **Table 4**. The median LOS was significantly longer for combination therapy (LOS 7.8 (IQR: 4.1, 14.8)) compared to lactulose monotherapy (LOS 6.6 (IQR: 3.6, 12.6), $p = 0.01$).

Discussion

Despite the impact of HE on patients[17,21,22] and reported benefits of HE medications,[23-32] only 71.6% of patients with HE hospitalized for at least 48 hours at our institution received pharmacotherapy. In addition, the proportion of patients receiving treatment has declined over time. There are several hypotheses regarding why treatment is less common now than 10 years ago. First, although lactulose is inexpensive (10 g/15 mL solution costs $0.05-0.17 U.S. dollars per mL) and typically well-tolerated, it typically works best in the acute setting, as rates of recurrent HE on maintenance lactulose are high.[31] It also has gastrointestinal side effects and is not tolerated by some patients.[2,30,22] Second, although effective in treating HE and well tolerated, treatment with rifaximin has been limited by cost ($126.40 U.S. dollars per day).[2,23,33] Some data suggests that long-term rifaximin therapy is associated with a 20% higher risk of *Clostridium difficile colitis* and *Candida albicans* infection, along with the selection of resistant mutants of gram-negative and positive bacteria in the gastrointestinal tract. Rifaximin can cause electrolyte derangements and may interfere with vitamin K production, which could potentiate coagulopathy in patients with cirrhosis.[33] Third, it is suspected that knowledge gaps among providers regarding the application of HE treatments could contribute to the observed trends in HE treatment over time.[34]

Variables associated with HE Treatment

Demographic. Younger age has been previously associated with improved survival in patients with HE.[17] Younger age was associated with increased treatment rates in our study. Older age is typically associated with greater comorbidities and medication burden, along with the risk of electrolyte disturbances,

Table 1. Demographic and clinical characteristics by receipt of any drug and drug type (for those who received lactulose).

	Any Drug Administration (Lactulose, Rifaximin, or Both)			**Drug Type for Patients Who Received a Drug†**		
	No (n=478) n (%)	Yes (n=1205) n (%)	P-value	Lactulose + Rifaximin (n=739) n (%)	Lactulose Only (n=434) n (%)	P-value
Patient Characteristics						
Age at Visit (years)			0.0172[1]			0.3552[1]
Mean (SD)	58.5 (13.78)	56.8 (12.05)		56.6 (11.67)	57.3 (12.64)	
Median (IQR)	59.0 (51.0, 67.0)	57.0 (50.0, 65.0)		57.0 (50.0, 64.0)	57.0 (49.0, 65.0)	
Sex, n (%)			0.4582[2]			0.6301[2]
Female	209 (29.4%)	503 (70.6%)		312 (63.8%)	177 (36.2%)	
Male	269 (27.7%)	702 (72.3%)		427 (62.4%)	257 (37.6%)	
Ethnicity, n (%)			0.5961[2]			1.0000[4]
Hispanic or Latino	33 (27.7%)	86 (72.3%)		54 (63.5%)	31 (36.5%)	
Not Hispanic or Latino	444 (28.5%)	1112 (71.5%)		680 (62.9%)	401 (37.1%)	
Unknown	1 (12.5%)	7 (87.5%)		5 (71.4%)	2 (28.6%)	
Insurance, n (%)			0.0343[2]			0.1332[2]
Medicaid	18 (19.1%)	76 (80.9%)		47 (64.4%)	26 (35.6%)	
Medicare	176 (31.5%)	382 (68.5%)		234 (63.6%)	134 (36.4%)	
Private	228 (26.7%)	625 (73.3%)		393 (64.4%)	217 (35.6%)	
Self-Pay	56 (31.5%)	122 (68.5%)		65 (53.3%)	57 (46.7%)	
MELD			<.0001[3]			0.0043[3]
Mean (SD)	18.7 (8.22)	23.0 (8.70)		23.6 (8.80)	22.1 (8.37)	
Median (IQR)	18.5 (11.0, 24.1)	23.0 (16.0, 29.1)		23.2 (16.7, 30.3)	22.3 (16.0, 27.9)	
Visit Department^						
Family Medicine, n (%)	73 (30.4%)	167 (69.6%)	0.4547[2]	102 (62.2%)	62 (37.8%)	0.8178[2]
Gastroenterology/Hepatology, n (%)	8 (8.9%)	82 (91.1%)	<.0001[2]	79 (97.5%)	2 (2.5%)	<0.0001[2]
Internal Medicine, n (%)	216 (23.8%)	692 (76.2%)	<.0001[2]	418 (61.4%)	263 (38.6%)	0.1762[2]
Surgery, n (%)	28 (57.1%)	21 (42.9%)	<.0001[2]	10 (55.6%)	8 (44.4%)	0.5097[2]
Liver/Intestine Transplantation, n (%)	54 (36.5%)	94 (63.5%)	0.0224[2]	60 (72.3%)	23 (27.7%)	0.0690[2]
Etiology of Cirrhosis^						
Alcoholic, n (%)	188 (18.3%)	840 (81.7%)	<.0001[2]	539 (66.0%)	278 (34.0%)	0.0014[2]
Autoimmune, n (%)	143 (19.7%)	583 (80.3%)	<.0001[2]	388 (68.8%)	176 (31.2%)	<.0001[2]
Biliary, n (%)	13 (28.3%)	33 (71.7%)	0.9829[2]	26 (81.3%)	6 (18.8%)	0.0302[2]
NASH, n (%)	145 (19.3%)	608 (80.7%)	<.0001[2]	406 (68.9%)	183 (31.1%)	<.0001[2]
Failure, n (%)	241 (22.9%)	811 (77.1%)	<.0001[2]	532 (67.6%)	255 (32.4%)	<.0001[2]
Symptoms^						
Ascites, n (%)	148 (19.9%)	597 (80.1%)	<.0001[2]	383 (65.9%)	198 (34.1%)	0.0402[2]
HCC, n (%)	75 (18.8%)	324 (81.2%)	<.0001[2]	207 (66.8%)	103 (33.2%)	0.1087[2]
Portal Hypertension, n (%)	255 (23.0%)	854 (77.0%)	<.0001[2]	541 (65.1%)	290 (34.9%)	0.0201[2]
Sarcopenia, n (%)	140 (27.2%)	374 (72.8%)	0.4825[2]	240 (65.8%)	125 (34.2%)	0.1894[2]
Varices, n (%)	45 (18.5%)	198 (81.5%)	0.0002[2]	132 (69.1%)	59 (30.9%)	0.0560[2]
Comorbid Conditions^						
Acute Renal Failure, n (%)	156 (27.0%)	422 (73.0%)	0.3529[2]	264 (64.1%)	148 (35.9%)	0.5741[2]
Anemia, n (%)	10 (20.8%)	38 (79.2%)	0.2381[2]	28 (73.7%)	10 (26.3%)	0.1655[2]
Constipation, n (%)	12 (23.1%)	40 (76.9%)	0.3871[2]	15 (40.5%)	22 (59.5%)	0.0040[2]
Dehydration, n (%)	63 (32.8%)	129 (67.2%)	0.1499[2]	81 (65.3%)	43 (34.7%)	0.5712[2]
Electrolyte Issues, n (%)	167 (30.1%)	387 (69.9%)	0.2667[2]	235 (62.8%)	139 (37.2%)	0.9355[2]
GI Bleed, n (%)	48 (22.0%)	170 (78.0%)	0.0251[2]	106 (63.9%)	60 (36.1%)	0.8056[2]
Infection, n (%)	225 (32.1%)	477 (67.9%)	0.0050[2]	284 (61.5%)	178 (38.5%)	0.3819[2]
Intoxication, n (%)	91 (29.8%)	214 (70.2%)	0.5393[2]	113 (53.8%)	97 (46.2%)	0.0023[2]

†Patients on Rifaximin only were excluded from this analysis; [1]Unequal variance two sample t-test; [2]Chi-Square p-value; [3]Equal variance two sample t-test; [4]Fisher Exact p-value; ^Patients may have had more than one department, etiology of cirrhosis, symptom, and comorbid condition associated with their visit.

Table 2. Outcomes by receipt of any drug and drug type (for those who received lactulose).

	Any Drug Administration (Lactulose, Rifaximin, or Both)			Drug Type for Patients Who Received a Drug†		
	No (n=478) n (%)	Yes (n=1205) n (%)	P-value	Lactulose + Rifaximin (n=739) n (%)	Lactulose Only (n=434) n (%)	P-value
Length of Stay (Days)			0.2191[1]			0.0050[1]
Mean (SD)	15.2 (31.81)	12.3 (17.82)		12.9 (18.37)	11.3 (17.28)	
Median (IQR)	7.8 (3.9, 16.1)	7.2 (4.0, 13.8)		7.8 (4.1, 14.8)	6.6 (3.6, 12.6)	
Disposition			0.1946[2]			
Expired	68 (14.2%)	179 (14.9%)		115 (15.6%)	58 (13.4%)	
Home	170 (35.6%)	410 (34.0%)		242 (32.7%)	162 (37.3%)	
Home with Home Health	88 (18.4%)	280 (23.2%)		176 (23.8%)	92 (21.2%)	
LAMA	4 (0.8%)	6 (0.5%)		5 (0.7%)	0 (0.0%)	
LTAC	47 (9.8%)	98 (8.1%)		53 (7.2%)	42 (9.7%)	
Other	9 (1.9%)	11 (0.9%)		4 (0.5%)	7 (1.6%)	
SNF	92 (19.2%)	221 (18.3%)		144 (19.5%)	73 (16.8%)	
30-day Readmission	123 (25.7%)	446 (37.0%)	<.0001[2]	279 (37.8%)	156 (35.9%)	0.5357[2]
30-day Mortality	96 (20.1%)	287 (23.8%)	0.0995[2]	176 (23.8%)	104 (24.0%)	0.9545[2]
1-year Mortality	144 (30.1%)	472 (39.2%)	0.0005[2]	289 (39.1%)	171 (39.4%)	0.9207[2]

[1]Wilcoxon rank sum p-value; [2]Chi-Square p-value; *For the Lactulose vs. Lactulose + Rifaxmin disposition groups, LAMA was excluded from the Chi-Square test due to small sample size.

which could precipitate HE and result in lower treatment rates.

There were statistically significant differences in the rates of treatment depending on insurance type. Patients using Medicare had higher adjusted odds of receiving any HE treatment relative to self-pay patients. This is suspected to be related to insurance coverage, as patients using Medicare Part D have 100% coverage of rifaximin. This low/no-cost barrier is alleged to improve treatment rates for those with insurance coverage but also provide a financial barrier to those without insurance coverage for rifaximin.

Prior studies have found no significant differences in HE treatment based on gender or ethnicity, which is consistent with our findings.

Variables Associated with Liver Disease. Prior studies indicate that alcohol-related liver disease (ALD) has a strong association with HE-related hospitalizations and morbidity.[7,17] Patients with ALD had higher adjusted odds of receiving any HE treatment (compared to patients without this diagnosis) in our study, which has not been previously reported. Patients with ALD have been shown to have a higher prevalence of private insurance and a high burden of hospitalizations and readmissions among patients with cirrhosis.[35] Increased healthcare contact could explain why a higher proportion of patients with ALD receive HE treatment. Higher usage of private insurance could explain why more patients with ALD received combination therapy, although this interaction was not directly evaluated in our study.

Patients with autoimmune cirrhosis and hepatic encephalopathy often present with acute liver failure, whose management is unique to those with chronic HE from other etiologies of cirrhosis.[36] This difference may explain why HE treatment rates were lower in patients with autoimmune cirrhosis in our cohort.

Higher MELD-Na scores, portal hypertension, and hepatocellular carcinoma were all associated with a higher likelihood of receiving any HE treatment. Patients with portal hypertension are more likely to develop HE in their lifetime and be under the care of a gastroenterologist, which could explain higher treatment rates in this sub-group, although the treating medical team was adjusted for in this analysis.[17]

Sarcopenic or frail patients have been historically shown to have higher HE rates compared to non-frail patients,[37] but our study found no significant difference in treatment rates among patients with sarcopenia.

In-hospital diagnoses. Current guidelines recommend identifying and correcting precipitating factors of HE.[2-4] We evaluated the most common precipitating factors for HE, and while we found that patients with gastrointestinal (GI) bleeding were more likely to receive pharmacotherapy in the unadjusted analyses, it was not significant in the adjusted analyses. GI bleeding is a commonly recognized complication of liver disease. As a result, providers may recognize GI bleeding from cirrhosis and are cued to treat other forms of decompensation, including HE. It is also likely that patients hospitalized with GI bleeding received consultation from gastroenterology/hepatology, which could lead to higher treatment rates.[38]

We found that patients with infection were less likely to receive any HE treatment. These patients could be receiving other antibiotics for infection and, therefore, not receive rifaximin. Infection can lead to multiorgan dysfunction, shock, and hypovolemia, so administering medications that could potentiate dehydration may be intentionally avoided.

Patients with constipation or intoxication were significantly less likely to receive combination therapy compared to lactulose monotherapy. Those with constipation were more likely to receive lactulose, and those who were dehydrated/hypovolemic were less likely to receive lactulose. Although these findings were not statistically significant, they make intuitive clinical sense as constipation would be treated with lactulose, and those already hypovolemic would not want to have fluid losses from the therapeutic use of lactulose.

Primary inpatient service. Gastroenterology/hepatology care has been associated with improved treatment rates and survival in HE.[7] Our study found that gastroenterology/hepatology consultation resulted in significantly greater rates of HE treatment.

Patients cared for on a primary internal medicine service were more likely to receive any HE treatment, but their patients did not have greater odds of receiving combination therapy. This could relate to a lack of access to resources that help providers minimize patient costs (e.g., pharmacy discount programs).

These findings suggest that patients with cirrhosis and either persistent or incident HE would benefit from gastroenterology/hepatology consultation to maximize the likelihood of receiving HE treatment.

Hospitalization Outcomes

Any HE treatment has been associated with shorter LOS in historical cohorts,[34] which is not consistent with our study, which found that combination therapy was associated with

Table 3. Results of logistic regression with combination therapy (lactulose + rifaximin) versus lactulose monotherapy as the outcome.

	Adjusted Odds Ratio	95% Confidence Interval		
Age (in years)				0.13
40	1.03	1.004	1.07	
55	0.97	0.94	1.00	
70	1.00	0.98	1.03	
MELD				<.0001
10	1.06	1.002	1.12	
20	1.04	0.995	1.09	
30	1.07	1.02	1.12	
Year				<.0001
2013	1.14	0.91	1.44	
2017	1.06	0.93	1.21	
2021	0.67	0.54	0.82	
Insurance				0.02
Medicaid	1.31	0.57	3.00	
Medicare	1.15	0.77	1.72	
Self-Pay	0.58	0.33	1.03	
Private	1.00	Reference		
Department				
hs_gastro (Yes vs. No)	3.39	1.52	7.55	0.003
hs_internal (Yes vs. No)	1.77	1.33	2.36	<.0001
hs_surg (Yes vs. No)	0.55	0.27	1.11	0.09
hs_transp (Yes vs. No)	0.69	0.44	1.09	0.11
Etiology				
any_alc_cirr (Yes vs. No)	3.18	2.25	4.50	<.0001
Auto_cirr (Yes vs. No)	0.46	0.26	0.81	0.01
NASH_cirr (Yes vs. No)	1.32	0.76	2.29	0.32
cdx_fail (Yes vs. No)	2.50	1.90	3.30	<.0001
Symptoms				
Ascites (Yes vs. No)	1.00	0.73	1.36	0.99
hep_carc (Yes vs. No)	1.58	1.04	2.38	0.03
cdx_port_HTN (Yes vs. No)	1.81	1.37	2.38	<.0001
varices (Yes vs. No)	1.19	0.75	1.89	0.47
Comorbidities				
dehyd (Yes vs. No)	0.73	0.50	1.09	0.12
GI_bleed (Yes vs. No)	1.20	0.80	1.80	0.37
infect (Yes vs. No)	0.72	0.56	0.94	0.01

Note: Age, MELD score, and year are modeled as cubic restricted splines to allow for non-linear associations. As such, three example values for each variable were chosen to show how the adjusted odds ratio may differ over the range of values. Patients can have more than one department, etiology, symptom, or comorbid condition. Confidence intervals for the insurance variable were Bonferroni adjusted for all possible pairwise comparisons; the only significant adjusted comparison was that Medicare had a higher odds of receiving any drug relative to self-pay (AOR: 1.98; 95% CI: 1.05, 3.70).

Table 4: Outcomes by receipt of any HE treatment versus none and combination therapy (lactulose + rifaximin) versus lactulose monotherapy.

	Adjusted Odds Ratio	95% Confidence Interval		
Age (in years)				0.04
40	0.98	0.95	1.02	
55	1.02	0.99	1.06	
70	0.96	0.93	0.99	
MELD				0.03
10	1.02	0.96	1.09	
20	0.99	0.95	1.03	
30	1.05	1.01	1.09	
Insurance				0.09
Medicaid	0.99	0.48	2.03	
Medicare	1.14	0.75	1.74	
Self-Pay	0.61	0.34	1.09	
Private				
Department				
hs_internal (Yes vs. No)	0.91	0.69	1.20	0.52
hs_transp (Yes vs. No)	1.27	0.73	2.22	0.40
Etiology				
any_alc_cirr (Yes vs. No)	1.72	1.21	2.44	0.002
Auto_cirr (Yes vs. No)	0.72	0.39	1.32	0.28
cdx_bil_cirr (Yes vs. No)	3.43	1.27	9.22	0.01
NASH_cirr (Yes vs. No)	1.69	0.95	3.02	0.07
cdx_fail (Yes vs. No)	1.89	1.43	2.51	<.0001
Symptoms				
Ascites (Yes vs. No)	0.88	0.64	1.23	0.45
hep_carc (Yes vs. No)	0.84	0.60	1.19	0.33
cdx_port_HTN (Yes vs. No)	1.35	1.01	1.80	0.04
sarco (Yes vs. No)	0.92	0.66	1.29	0.62
varices (Yes vs. No)	1.41	0.93	2.14	0.10
Comorbidities				
Anemia (Yes vs. No)	1.28	0.59	2.75	0.54
Constipation (Yes vs. No)	0.43	0.21	0.87	0.02
intox (Yes vs. No)	0.68	0.48	0.95	0.02

Note: Age and MELD scores are modeled as cubic restricted splines to allow for non-linear associations. As such, three example values for each variable were chosen to show how the adjusted odds ratio may differ over the range of values. Patients can have more than one department, etiology, symptom, or comorbid conditions. The gastro/hepatology department variable was excluded from this model given the limited variability in it (97.5% of patients who were seen in that department received L+R). Confidence intervals for the insurance variable were Bonferroni adjusted for all possible pairwise comparisons.

a longer LOS and higher rates of mortality compared to lactulose monotherapy or no treatment. This is suspected to be a result of greater comorbid illness and higher grades of HE that are more difficult to treat in the combination therapy group, although this correlation was not directly evaluated in our study. It is also possible that a longer LOS would provide more opportunities to identify, prescribe, and obtain coverage for rifaximin for the combination therapy group.

Prior studies have highlighted the benefits of combination therapy on patient-related outcomes and improving quality of life.[5] Although our study shows that providing medical treatment may not significantly improve outcomes such as readmission and mortality, its ability to improve quality-of-life factors, such as social functioning, communication, sleep, and mobility, are essential patient-related outcomes that pharmacotherapy can provide in HE.[5]

Strengths

Our study presents a large cohort of data relating to HE treatment, variables associated with treatment, and outcomes in patients hospitalized with HE over the last decade. This study provides important implications regarding gaps in HE treatment. Our results add to the findings of prior studies and provide new insights into patient and provider population subsets that could benefit from interventions to increase treatment access.

Contextual Factors

Our data is from a single medical center, so it may not represent trends across the United States or the world. Retrospective data carries inherent limitations with diagnostic coding and verifying medication adherence. We did not subclassify patients based on type or severity of HE, department visit, more than one etiology of liver disease, or assess for the presence of portosystemic shunts. We did not assess for important outcomes such as quality-of-life measures, cost, or number of days in intensive care. We could not determine if patients with alcohol-associated cirrhosis were actively drinking at the time of hospitalization. No patients in our study received any other therapies for HE (e.g., sodium benzoate, L-ornithine-L-aspartate, or others), and no patients underwent treatment with artificial liver support devices, both of which may have impacted outcomes, including length of stay.

Conclusion

The proportion of patients receiving any HE treatment in 2022 has declined from 2012 at our institution. Older patients, those with autoimmune cirrhosis and infection while hospitalized, are less likely to receive treatment. Patients with ALD and who are seen by gastroenterology/hepatology are more likely to receive treatment. Further efforts are needed to improve treatment access through multidisciplinary care, reducing cost barriers, and educating providers on HE management.[39-42] Our results suggest that expanding access to gastroenterology/hepatology care is a modifiable factor that may increase HE treatment rates. ■

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Conflict of Interest

All authors report no conflicts of interest. All authors had access to data and had an equal role in writing and revising the manuscript.

Ethical Approval

This study was approved by the University of Nebraska Medical Center Institutional Review Board.

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