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Targets to Improve Quality of Care for Patients with Hepatic Encephalopathy: Data from a Multi-Center Cohort

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Summary:

Background: Hepatic encephalopathy (HE) can adversely affect outcomes in both inpatients and outpatients with cirrhosis.

Aim: Define targets for improving quality of care in HE management in the multi-center North American Consortium for End-Stage Liver Disease (NACSELD) cohort.

Method: NACSELD inpatient cohort was analyzed for (a) medication-associated precipitants (b) aspiration pneumonia development (c) HE medication changes and (d) 90-day HE recurrence/

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readmissions. Comparisons were made between patients on no-therapy, lactulose only, rifaximin only or both. 90-day HE-readmission analysis was adjusted for MELD score.

Results: 2810 patients (1102 no-therapy, 659 lactulose, 154 rifaximin, 859 both) were included. HE on admission, and HE rates during hospitalization were highest in those on lactulose only or dual therapy compared to no-therapy or rifaximin only (p<0.001). Medications were the most prevalent precipitants (32%; 21% lactulose over/underuse, 5% benzodiazepines, 4% opioids, 1% rifaximin underuse, 1% hypnotics). Patients with medication-associated precipitants had a better prognosis compared to other precipitants. 23%(n=217) reached grade 3/4 HE, of which 16% developed HE-related aspiration pneumonia. 2420 patients were discharged alive without liver transplant (790 no-therapy, 639 lactulose, 136 rifaximin, 855 both); 12.5%(n=99) of no-therapy patients did not receive a discharge HE therapy renewal. 90-day HE-related readmissions were seen in 16% of patients (9% no-therapy, 9% rifaximin only, lactulose only 18%, dual 21%, <0.001), which persisted despite MELD adjustment (p=0.009).

Conclusion: Several targets to improve HE management were identified in a large cohort of hospitalized cirrhotic patients. Interventions to decrease medication-precipitated HE, prevention of aspiration pneumonia, and optimization of HE medications are warranted.

Keywords

Quality improvement; aspiration pneumonia; readmissions; precipitating factors

Introduction:

Hepatic encephalopathy (HE), is one of the leading causes of readmissions and healthcare expenditure in patients with cirrhosis in North America[1–3]. The expenditure and hospital discharges related to HE has been rising relentlessly over time[4, 5]. In addition to the disease-related expenditure, patients with HE also pose a major socio-economic burden on their caregivers[6, 7]. HE remains an independent predictor of inpatient mortality in cirrhosis and several HE precipitating factors could be related to medications[8–11]. Furthermore, at hospital discharge, patients may not receive appropriate prescriptions or counseling regarding the prevention of HE recurrence[12–14]. Therefore, there may be potential to improve the quality of inpatient and post-hospital discharge HE management[15]. The NACSELD (North American Consortium for the Study of End-Stage Liver Disease) patient cohort was generated from a 14-center hepatology consortium that prospectively recruited inpatients with cirrhosis and followed them for up to 90 days post-discharge[16].

The aim of the study was to use the NACSELD cohort to identify potential areas of quality improvement in: 1) the inpatient management of patients with cirrhosis admitted for or who develop HE during hospitalization and 2) their transition to the outpatient setting.

Materials and Methods:

NACSELD prospectively enrolled patients with cirrhosis who were hospitalized for non-elective reasons in 14 centers across North America from April 2013 through February 2017. Cirrhosis was confirmed by liver biopsy, signs of decompensation or endoscopic/radiological evidence of portal hypertension in patients with chronic liver disease. All

patients gave written informed consent. We excluded patients who were unable to consent, had an unclear diagnosis of cirrhosis, were HIV positive or had a prior organ transplant. After consent, patients were followed daily until discharge and subsequently for 90 days post-discharge to determine outcomes such as readmissions, transplant or death. Data collected prospectively at admission included demographics, reason for admission, prior admissions, concomitant medications and cirrhosis-related details.

For this study, we focused on data pertaining to HE quality of care in four specific areas: (a) HE admissions with medication related issues as precipitating factors, (b) aspiration pneumonia in patients with HE, (c) resumption/initiation of appropriate therapies for prevention of HE recurrence upon discharge and (d) readmissions for HE and their relationship with medication use.

Medication-related HE precipitating factors were defined as one or more of the following (a) non-adherence to HE-related medications such as lactulose or rifaximin, (b) overuse of HE-related medications, (c) opioids, (d) hypnotics (diphenhydramine and zolpidem), (e) benzodiazepines and (f) other psychoactive medications. Non-adherence or underuse was defined as not taking the medications in the prescribed manner and dose for at least 3 weeks prior to the hospitalization. Diarrhea leading to dehydration with >4 daily bowel movements/day was defined as lactulose overuse provided other causes of diarrhea were ruled out. Precipitating factors related to opioids, benzodiazepines and hypnotics were based on the PI's interpretation of the use of these medications vis-à-vis the HE episode.

The relative proportion of medication-associated HE was assessed with respect to other precipitating factors. We analyzed precipitating factors with medication-unrelated, medication-related only and those with medication-related plus another precipitating factor.

Precipitating factors were divided into those determined by each local PI as related to infection, , renal insufficiency, hyponatremia, or gastrointestinal bleeding. Precipitating factors were *a priori* defined and categorized when the NACSELD protocol was created, and occurred before the publication of the AASLD/EASL practice guidelines[13].

HE was defined as overt HE according to the clinically accepted West-Haven criteria based on the PI assessment (Grade II and beyond)[13, 17]. We studied patients who were on individual HE therapies on admission, which in North America are lactulose and rifaximin. We compared admission laboratory values, HE details and hospital course between groups based on HE therapies on admission. Specifically, for the HE details we studied the precipitating factors, grades of HE at admission and the maximum HE grade. The hospital course was studied with respect to length of stay (LOS), individual organ failures as defined by NACSELD, rate of ICU transfer, and rate of NACSELD-ACLF occurrence between the groups[16].

While following the inpatient HE course, we also focused on the management of patients admitted with or those who developed grade 3/4 HE. Aspiration pneumonia was defined as radiological evidence of lower lobe infiltrates or pneumonitis. The occurrence of aspiration in these patients was recorded vis-à-vis its temporal relationship, where it occurred (the regular ward or in stepdown/ICU) and the consequences of this aspiration. Furthermore, the

initiation and withdrawal of HE-specific therapies were recorded during each patient's hospital admission.

Finally, transplant free survivers were followed for 90 days after discharge for all readmissions, with specific focus on HE-related readmissions; the cause of readmission was determined by the local PI. Groups were divided on the basis of HE therapy used at discharge and their readmission rates were compared. In order to account for the impact of cirrhosis severity on HE-related readmission, a binary logistic ANCOVA model studying HE therapy and discharge MELD was performed.

The protocol was approved by the IRBs at all participating centers.

Results:

Index admission:

HE details: We included 2810 patients in this analysis, of whom 1708 were on HE therapy at admission; specifically 695 were on lactulose alone, 154 were on rifaximin alone and 859 were on dual therapy. Compared to patients who were not taking any HE related medications, those on HE therapy had more advanced liver disease as measured by MELD score and more prior hepatic complications as they had higher prevalence of PPI use, nonselective beta-blockers use and SBP prophylaxis and a greater likelihood of past hospitalizations. Furthermore, patients on HE therapies were more likely to be admitted with infections. 460 patients' primary indication for admission was HE, of which 83 were on no therapy, 137 were on lactulose only, 15 on rifaximin only and 225 were on dual therapy. In all comers, the rate of HE on admission was significantly higher in patients on lactulose alone and those on dual therapy compared to those on rifaximin alone or those not being treated for HE prior to admission ($p<0.001$, table 1).

A further 453 patients diagnosed with HE during their index hospital stay, yielding a total of 913 patients with HE. Of these 189 were on no treatment, 282 were on lactulose only, 38 on rifaximin only, 404 were on dual therapy prior to admission. The proportion of patients developing HE during the hospitalization was also significantly higher in patients on lactulose and lactulose+rifaximin compared to those on rifaximin alone and those on no therapy (Table 1). Regardless of the HE-therapy status on admission, the initial HE grade distribution was similar between groups. However, reaching a maximum grade 3/4 HE, defined as brain failure according to NACSELD, was significantly higher in patients on lactulose+rifaximin compared to patients on rifaximin alone ($p=0.02$), patients on lactulose alone ($p=0.04$) and those admitted without any HE therapy ($p<0.001$ using Chi-square tests). The incidence of circulatory and respiratory failures was similar between groups, while the incidence of renal failure was higher in patients requiring therapy for HE pre-admission with rifaximin alone or dual therapy. The type of HE therapy did not affect the rates of development of NACSELD-ACLF.

LOS was highest in those admitted on lactulose monotherapy compared to the rest of the groups. 30-day mortality was higher in patients on any prior HE therapy, but in-hospital transplant was highest in those on both rifaximin and lactulose.

Precipitating factors: When all HE episodes were studied, the major precipitating factors were medication-related (32%) followed by acute kidney injury (18%), infections (17%), hyponatremia (16%) and other (17%). Of the 244 medication-related HE episodes, 146 (60%) had purely a medication-related factor, while the remaining 98 (40%) also had another precipitating factor. The majority of medication-related precipitants were lactulose non-adherence 20%, lactulose overuse 1%, rifaximin underuse in 3%, opioids 4%, benzodiazepines 5% and hypnotics 1% of the entire group.

The lactulose only group had the highest rate of non-adherence to HE medications followed by the other two HE-treatment groups. A similar pattern was seen for all medication-related precipitating factors and hyponatremia. Infections were significantly more frequent as precipitating factors in patients not admitted on HE therapy. This group, along with those on lactulose alone, also had a higher rate of renal dysfunction and GI bleeding as precipitating factors compared to those treated with rifaximin monotherapy.

When we compared patients with HE due to any medication-related precipitant compared to other precipitating factors (Table 2), important differences emerged. Patients with medication related HE had a greater proportion with HE as the cause of admission, lower likelihood of infections on admission and less frequent PPI use. These patients were also more likely be on lactulose alone compared to those with medication-unrelated precipitants. On the other hand, those admitted with medication-unrelated causes of HE had higher MELD scores and more frequently met SIRS criteria on admission than those admitted with medication-associated factors. This culminated in a longer LOS, higher rate of ICU transfer, more frequent diagnosis of NACSELD-ACLF, and a higher rate of mortality and liver transplant in this group compared to those with medication-related precipitating factors. When the 146 patients with medication-only precipitants were compared to the 98 patients had medication plus another precipitating factor (supplementary table 1), those with more than one precipitating factor had a lower serum albumin and sodium and had a worse prognosis overall.

Overall inpatient course and changes in medications:

During the hospital course, 281 patients died and 109 patients were transplanted.

Details of the medication changes during the hospitalization course vis-à-vis admission medications and discharge medications are shown in figure 1 with details in supplementary figure 1.

Continuation of HE therapy: A majority (81%) of these continued their pre-admission pattern of therapy at discharge (Figure 1 and Supplementary figure 1).

Addition of HE therapy: HE therapy was initiated in 311 patients (n=177 lactulose only, n=114, both and n=20 rifaximin only) during hospitalization. Of the 855 patients on dual therapy at discharge, 176 were started on dual therapy during the hospitalization. Of these, 114 had lactulose and rifaximin started together during the hospitalization, while 62 patients had rifaximin added to their pre-admission lactulose. None of the patients with dual therapy were changed to single therapy for HE at discharge. Withdrawal or lack of renewal of HE

therapy: Of the 790 patients who were discharged without HE therapy, 4%(n=99) were patients whose HE recurrence prevention therapy should have been resumed at discharge but was not.

Management of grade 3/4 HE:

217 (23% of the total HE patients) patients were admitted with or developed grade 3 or 4 HE during their index hospitalization; only 67 of whom were intubated for HE. 34 (16% of 217) of these patients developed HE-related aspiration pneumonia, 14 of whom were on the regular wards and the remainder were admitted to an ICU without intubation. Of the 67 patients who were intubated, 60% had grade 3 while 40% had grade 4 HE. This aspiration pneumonia, according to the PI's judgement, could have been prevented by faster transfer to the ICU (n=13), earlier intubation (n=11) and changing the route of lactulose administration from oral to enema (n=10).

90-day outcomes:

We followed the patients who were discharged alive without transplant for 90 days. Of these, 790 were discharged without HE therapy, 639 on lactulose only, 136 on rifaximin only and 855 patients on dual therapy. At 90 days, readmissions among the entire discharge cohort of 2420 patients cohort occurred in 991 (41%) of these patients. The leading causes of readmissions were HE (16%), infection (10%), GI bleeding (8%) and renal/metabolic (8%) followed by others. The discharge MELD scores in all patients were lowest in those not on HE therapy (16.0±6.4) compared to the rest (lactulose only 17.6±6.7, rifaximin only 18.6±6.3 and lactulose+rifaximin 19.4±6.9, $p<0.0001$). However, when we compared the discharge MELD scores of patients in from this cohort from those who ultimately were readmitted there were no significant differences (No HE therapy 17.9±6.9, lactulose only 18.2±6.2, rifaximin only 19.1±5.9, lactulose+rifaximin 19.6±6.6, $p=0.07$).

The readmission rate, as expected, was lowest in those without HE therapy at discharge (34%, $p=0.001$) compared to the rest with HE therapy (lactulose only 43%, rifaximin only 42% and both 44%). However, the HE-related readmissions in the no-therapy and rifaximin only group (both 9%, figure 2) were significantly lower compared to lactulose only 18% vs both, 21%). To analyze the impact of MELD and HE therapy we fit a binary logistic ANCOVA model for patients who were readmitted at 90 days with HE compared to the other causes of readmission, and the predictors are HE discharge medication group and discharge MELD score, the overall group effect was still significant ($p = 0.009$) demonstrating that these medication changes were predictive despite the MELD score.

This potential decrease in HE also extended to the readmission course itself, where a total of 36% of all readmitted patients had HE during their course. The lowest rate of HE development was in the no-HE therapy group but within those who were readmitted on HE therapy, rifaximin only patients had the lowest rate of HE development compared to lactulose only or those on both therapies (Figure 2).

Discussion:

Hepatic encephalopathy represents a major burden on the healthcare system and quality improvement is needed to potentially improve the outcomes of affected patients[4, 18, 19] In our large cohort, we determined that there was potential for improvement in controlling medication-related precipitating factors, preventing aspiration pneumonia, and preventing readmissions by resuming and continuing appropriate HE medications on discharge.

The inpatient management of HE involves exclusion of other causes of altered mental status, initiation of empiric therapy, care of the unconscious patient, and identification and correction of precipitating factors[13, 14]. Identification of precipitating factors is paramount since their successful correction can reduce the progression of HE and potentially other organ failures[8, 9]. We found that HE-related medications, but also opioids, benzodiazepines and other psychoactive drugs were associated as major precipitants either alone or with other factors[20]. Medications can affect HE by modulating gut microbiota, altering neurotransmitters, affecting electrolyte levels and potentially lowering the threshold for mental status changes in response to other precipitants[21]. In the case of lactulose, over and underuse could precipitant HE. On the other hand, overuse of other medications such as opioids, benzodiazepines and hypnotics could precipitate HE. The contributions of these medications have been described but we extend them to a larger group of patients across multiple sites in North America[21–23]. Patients with HE precipitants unrelated to medications had a worse prognosis in terms of death, organ failure and transplant. This risk was lower if there was any medication involved as a precipitant and lowest if medications were the sole precipitants. These findings are likely because the major medication-associated precipitating factor was lactulose non-adherence, which is associated with a faster recovery time compared to other precipitants[11]. In addition to lactulose non-adherence, 1% of patients had HE due to lactulose overuse likely related to dehydration or alterations in electrolytes[24]. In addition, 3% had HE due to failure of rifaximin use. While the reasons for not taking rifaximin are unclear, its cost and potential reimbursement challenges could be relevant[25]. Even in patients presenting with HE who were not on HE medications on admission, 7% were judged to have HE due to medication non-adherence. This indicates that this subgroup was not adhering to previously prescribed HE medications. The data ultimately indicate that HE therapy monitoring is a continuous process that should not stop once the patient is discharged[19].

One-tenth of HE cases were judged to be related to benzodiazepines, opioids and hypnotics. These medications have varying effects on sensorium even independent of cirrhosis but can affect GABA metabolism, impair gut motility and worsen psychomotor coordination[21, 26, 27]. In cirrhotic outpatients, some of these medications, such as HE therapies and opioids, are associated with worse clinical and patient-reported outcomes, while in inpatients they are associated with varying degrees of gut dysbiosis and increased readmissions[21–23, 28]. These medications are frequently prescribed by practitioners other than hepatologists for chronic pain, anxiety, and insomnia that are prevalent in patients with cirrhosis[20]. Therefore, careful and repeated reassessment of their risk/benefit ratio in the outpatient and inpatient setting accompanying by communication with the prescribing team could provide alternatives to avoid potential HE precipitation[19, 20].

Another critical aspect of inpatient care is to protect the airway in HE, which is relevant to patients with grades 3 and 4 HE primarily[13]. Despite almost a quarter of HE patients developing these high grades, only sixty-seven patients were intubated and aspiration pneumonia was seen in 16% of these patients. Aspiration pneumonia carries a uniformly poor prognosis in cirrhosis and is a major preventable cause of organ failure that can lead to ACLF[29, 30]. Therefore, a greater awareness of this fast devolving HE grades with prompt transfer and intubation and conversion from oral lactulose to enema is needed to prevent these complications and reduce length of stay and mortality rates[31].

A major challenge related to HE patients at discharge is the prevention of recurrence that can lead to readmission[13] that may need a multi-disciplinary approach involving caregivers as well[32, 33]. Indeed, studies ensuring medication adherence, enhanced outpatient services, greater communication with the clinical team and dedicated protocols have shown benefit in readmissions for HE[34, 35]. An important quality component is to ensure that patients are discharged on the approved therapies to prevent HE recurrence[15]. These include lactulose and/or rifaximin at discharge based on the number of prior HE episodes[13]. Our data demonstrate that HE therapy was not resumed in a substantial proportion of patients at discharge. Neither the guidelines nor any participating institutional policy recommend stopping therapy to prevent HE recurrence[13]. Therefore, patients in whom therapy was not resumed after discharge would be a quality improvement target to potentially reduce HE recurrence.

The 90-day readmission rate was more than 40%, with HE being the leading cause, similar to prior studies[1, 3]. Rates of 90-day HE readmissions were highest in lactulose users compared to other groups despite current practice dictating that rifaximin be reserved for patients who fail or cannot tolerate lactulose[13]. This pattern was significant despite adjusting for the discharge MELD scores. While the reasons for lactulose-using groups experiencing a higher recurrence are unclear, we can speculate that the adverse events or non-adherence related to lactulose could contribute. In the Bass et al trial, the protection from rifaximin was similar regardless of concomitant lactulose use but only 9% of patients were without lactulose[36]. This relative protection from recurrence was maintained during open-label rifaximin follow-up consisting of newer cohorts and continuation of the same cohort[37, 38]. The reduction in hospitalizations and better outcomes were found in other studies as well[39–41]. However, these findings need to be carefully considered because the subgroup on rifaximin alone was much smaller compared to the remaining groups and the use of rifaximin or lactulose did not differentially impact the 60% of readmissions that were not related to HE within 90 days. Therefore, while the data suggest that rifaximin alone could be better than lactulose alone or lactulose+rifaximin, this would only extend to HE-related readmissions and would require a larger confirmatory study.

The study is limited by enrollment of patients in large, tertiary-care centers who are not representative of the general population. Also, a convenience sample of patients and their relatives who were able and willing to consent were included, which could have excluded some patients with more advanced HE. Regardless, more than a quarter of our patients had grade 3 or 4 HE. The adjudication of precipitating factors was performed by the local PI, which could cause errors due to subjectivity. Given that the data collection was started

before AASLD/EASL guidelines were published, precipitating factors were not completely concordant with these guidelines. We combined several medication groups together to increase the ease of understanding but many of these, such as opioids and benzodiazepines, can worsen sensorium even in inpatients without cirrhosis. Prior HE history was reflected in the pattern of HE-related medication use typical of North America (no therapy for patients with prior HE, lactulose after first episode, additional rifaximin after the second episode and only rifaximin in those with severe lactulose intolerance) but the exact number of prior episodes were not accounted for specifically. We focused on selected areas related to HE as potential targets for quality improvement, but there also remain other aspects of HE care such as caregiver input that need further analysis. However, the data entry was performed after the hospitalization was complete, which gave the PI greater insight into the hospital course and followed current clinical practice.

We conclude that hepatic encephalopathy remains a major reason for admission and readmission in cirrhosis. Judicious use of psychoactive medications, careful monitoring of adherence on previously prescribed HE medications, continued monitoring to prevent aspiration pneumonia and optimization of HE therapy at discharge, are important areas to focus on in order to improve the quality of care for patients with HE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of Interests

1. Authors' declaration of personal interests:

i. JSB has served as an advisory board member for Valeant, Norgine and institutions of NACSELD members have received research funding from Grifols and Valeant Pharmaceuticals as part of investigator-initiated grants.

2. Declaration of funding interests:

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ii. The writing and preparation, data analysis and decision to publish were performed by the authors without input from any funding

References:

1. Tapper EB, Halbert B, Mellinger J. Rates of and Reasons for Hospital Readmissions in Patients With Cirrhosis: A Multistate Population-based Cohort Study. Clin Gastroenterol Hepatol 2016;14(8):1181–1188 e2. [PubMed: 27085758]
2. Volk ML, Tocco RS, Bazick J, Rakoski MO, Lok AS. Hospital readmissions among patients with decompensated cirrhosis. Am J Gastroenterol 2012;107(2):247–52. [PubMed: 21931378]

3. Bajaj JS, Reddy KR, Tandon P, et al. The 3-month readmission rate remains unacceptably high in a large North American cohort of patients with cirrhosis. Hepatology 2016;64(1):200–8. [PubMed: 26690389]
4. Stepanova M, Mishra A, Venkatesan C, Younossi ZM. In-hospital mortality and economic burden associated with hepatic encephalopathy in the United States from 2005 to 2009. Clin Gastroenterol Hepatol 2012;10(9):1034–41 e1. [PubMed: 22642955]
5. Allen AM, Kim WR, Moriarty JP, Shah ND, Larson JJ, Kamath PS. Time trends in the health care burden and mortality of acute on chronic liver failure in the United States. Hepatology 2016;64(6): 2165–2172. [PubMed: 27696493]
6. Rakoski MO, McCammon RJ, Piette JD, et al. Burden of cirrhosis on older Americans and their families: analysis of the health and retirement study. Hepatology 2012;55(1):184–91. [PubMed: 21858847]
7. Bajaj JS, Wade JB, Gibson DP, et al. The multi-dimensional burden of cirrhosis and hepatic encephalopathy on patients and caregivers. Am J Gastroenterol 2011;106(9):1646–53. [PubMed: 21556040]
8. Bajaj JS, O'Leary JG, Tandon P, et al. Hepatic Encephalopathy Is Associated With Mortality in Patients With Cirrhosis Independent of Other Extrahepatic Organ Failures. Clin Gastroenterol Hepatol 2017;15(4):565–574 e4. [PubMed: 27720916]
9. Cordoba J, Ventura-Cots M, Simon-Talero M, et al. Characteristics, risk factors, and mortality of cirrhotic patients hospitalized for hepatic encephalopathy with and without acute-on-chronic liver failure (ACLF). J Hepatol 2014;60(2):275–81. [PubMed: 24128414]
10. Pantham G, Post A, Venkat D, Einstadter D, Mullen KD. A New Look at Precipitants of Overt Hepatic Encephalopathy in Cirrhosis. Dig Dis Sci 2017;62(8):2166–2173. [PubMed: 28560484]
11. Salam M, Matherly S, Farooq IS, et al. Modified-orientation log to assess hepatic encephalopathy. Aliment Pharmacol Ther 2012;35(8):913–20. [PubMed: 22348593]
12. Neff G Factors affecting compliance and persistence with treatment for hepatic encephalopathy. Pharmacotherapy 2010;30(5 Pt 2):22S–7S. [PubMed: 20412037]
13. Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60(2):715–35. [PubMed: 25042402]
14. Bajaj JS, Cordoba J, Mullen KD, et al. Review article: the design of clinical trials in hepatic encephalopathy--an International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) consensus statement. Aliment Pharmacol Ther 2011;33(7):739–47. [PubMed: 21306407]
15. Kanwal F, Tapper EB, Ho C, et al. Development of Quality Measures in Cirrhosis by the Practice Metrics Committee of the American Association for the Study of Liver Diseases. Hepatology 2018.
16. O'Leary JG, Reddy KR, Garcia-Tsao G, et al. NACSELD Acute-on-Chronic Liver Failure (NACSELD-ACLF) Score Predicts 30-Day Survival in Hospitalized Patients with Cirrhosis. Hepatology 2018.
17. Shawcross DL, Dunk AA, Jalan R, et al. How to diagnose and manage hepatic encephalopathy: a consensus statement on roles and responsibilities beyond the liver specialist. Eur J Gastroenterol Hepatol 2016;28(2):146–52. [PubMed: 26600154]
18. Stepanova M, De Avila L, Afendy M, et al. Direct and Indirect Economic Burden of Chronic Liver Disease in the United States. Clin Gastroenterol Hepatol 2016.
19. Thomson MJ, Tapper EB, Lok ASF. Dos and Don'ts in the Management of Cirrhosis: A View from the 21st Century. Am J Gastroenterol 2018.
20. Lewis JH, Stine JG. Review article: prescribing medications in patients with cirrhosis - a practical guide. Aliment Pharmacol Ther 2013;37(12):1132–56. [PubMed: 23638982]
21. Acharya C, Betrapally NS, Gillevet PM, et al. Chronic opioid use is associated with altered gut microbiota and predicts readmissions in patients with cirrhosis. Aliment Pharmacol Ther 2017;45(2):319–331. [PubMed: 27868217]
22. Gronbaek L, Watson H, Vilstrup H, Jepsen P. Benzodiazepines and risk for hepatic encephalopathy in patients with cirrhosis and ascites. United European Gastroenterol J 2018;6(3):407–412.

23. Lee PC, Yang YY, Lin MW, et al. Benzodiazepine-associated hepatic encephalopathy significantly increased healthcare utilization and medical costs of Chinese cirrhotic patients: 7-year experience. Dig Dis Sci 2014;59(7):1603–16. [PubMed: 24482035]
24. Bajaj JS, Sanyal AJ, Bell D, Gilles H, Heuman DM. Predictors of the recurrence of hepatic encephalopathy in lactulose-treated patients. Aliment Pharmacol Ther 2010;31(9):1012–7. [PubMed: 20136802]
25. Bajaj JS, Riggio O. Drug therapy: rifaximin. Hepatology 2010;52(4):1484–8. [PubMed: 20814894]
26. Jones EA. Ammonia, the GABA neurotransmitter system, and hepatic encephalopathy. Metab Brain Dis 2002;17(4):275–81. [PubMed: 12602504]
27. Jones EA, Mullen KD. Theories of the pathogenesis of hepatic encephalopathy. Clin Liver Dis 2012;16(1):7–26. [PubMed: 22321462]
28. Bajaj JS, Thacker LR, Heuman DM, et al. Cognitive performance as a predictor of hepatic encephalopathy in pretransplant patients with cirrhosis receiving psychoactive medications: a prospective study. Liver Transpl 2012;18(10):1179–87. [PubMed: 22674517]
29. Bajaj JS, O'Leary JG, Reddy KR, et al. Second infections independently increase mortality in hospitalized patients with cirrhosis: the North American consortium for the study of end-stage liver disease (NACSELD) experience. Hepatology 2012;56(6):2328–35. [PubMed: 22806618]
30. Merli M, Lucidi C, Giannelli V, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. Clin Gastroenterol Hepatol 2010;8(11):979–85. [PubMed: 20621200]
31. Acharya C, Bajaj JS. Current Management of Hepatic Encephalopathy. Am J Gastroenterol 2018.
32. Tapper EB. Challenge accepted: Confronting readmissions for our patients with cirrhosis. Hepatology 2016;64(1):26–8. [PubMed: 26806609]
33. Tapper EB, Volk M. Strategies to Reduce 30-Day Readmissions in Patients with Cirrhosis. Curr Gastroenterol Rep 2017;19(1):1. [PubMed: 28101791]
34. Tapper EB, Finkelstein D, Mittleman MA, Piatkowski G, Chang M, Lai M. A Quality Improvement Initiative Reduces 30-Day Rate of Readmission for Patients With Cirrhosis. Clin Gastroenterol Hepatol 2016;14(5):753–9. [PubMed: 26407750]
35. Ganapathy D, Acharya C, Lachar J, et al. The Patient Buddy App Can Potentially Prevent Hepatic Encephalopathy-Related Readmissions. Liver Int 2017.
36. Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362(12):1071–81. [PubMed: 20335583]
37. Mullen KD, Sanyal AJ, Bass NM, et al. Rifaximin Is Safe and Well Tolerated for Long-term Maintenance of Remission From Overt Hepatic Encephalopathy. Clin Gastroenterol Hepatol 2013.
38. Bajaj JS, Barrett AC, Bortey E, Paterson C, Forbes WP. Prolonged remission from hepatic encephalopathy with rifaximin: results of a placebo crossover analysis. Aliment Pharmacol Ther 2015;41(1):39–45. [PubMed: 25339518]
39. Orr JG, Currie CJ, Berni E, et al. The impact on hospital resource utilisation of treatment of hepatic encephalopathy with rifaximin-alpha. Liver Int 2016;36(9):1295–303. [PubMed: 26950766]
40. Kang SH, Lee YB, Lee JH, et al. Rifaximin treatment is associated with reduced risk of cirrhotic complications and prolonged overall survival in patients experiencing hepatic encephalopathy. Aliment Pharmacol Ther 2017;46(9):845–855. [PubMed: 28836723]
41. Kimer N, Krag A, Moller S, Bendtsen F, Gluud LL. Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy. Aliment Pharmacol Ther 2014;40(2):123–32. [PubMed: 24849268]

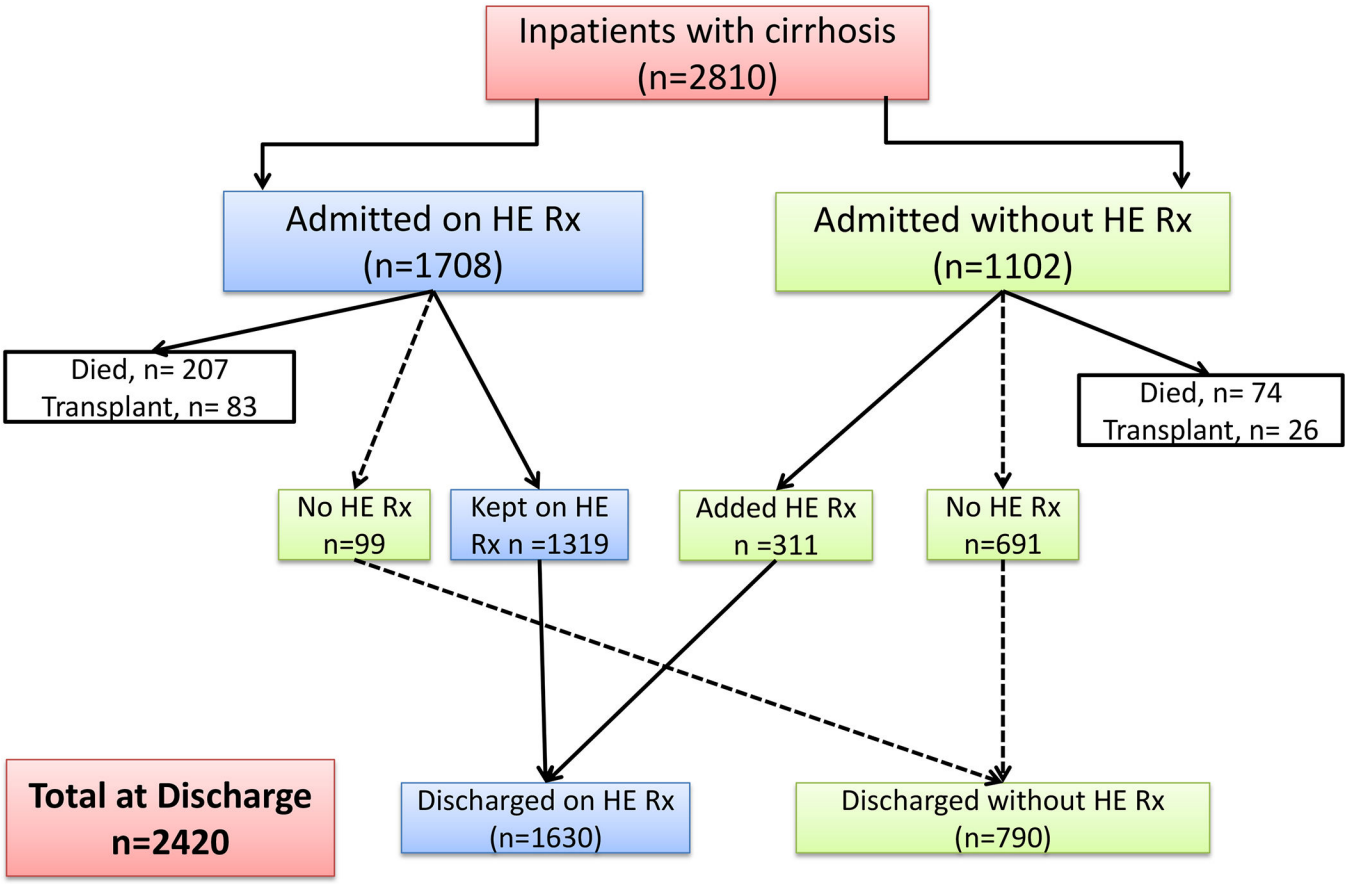

Figure 1:
Flow of patients on hepatic encephalopathy medications or not in the index admission, on discharge and during the 90-day post-discharge period

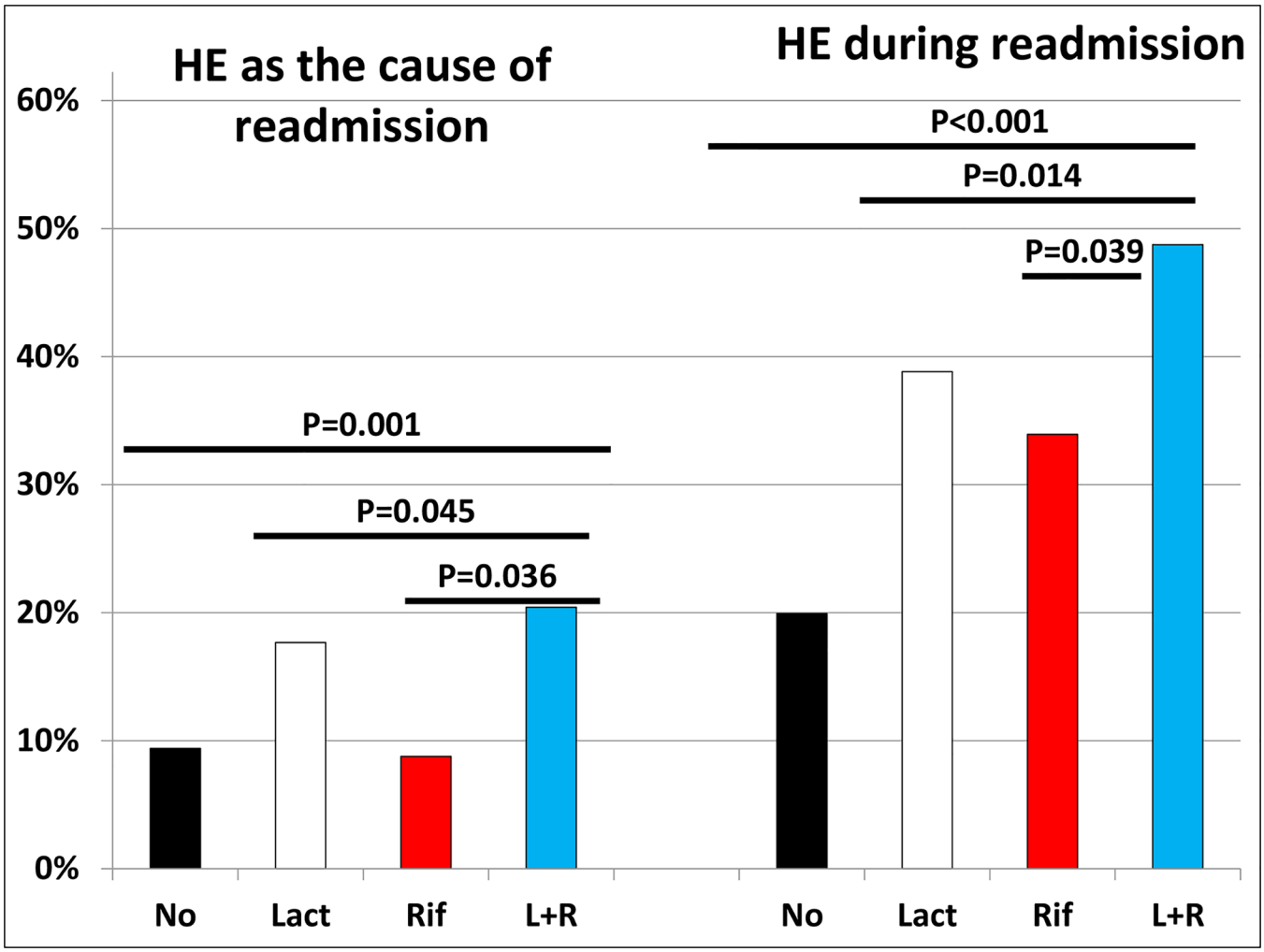

Figure 2:

90-day hepatic encephalopathy (HE)-related readmission rates and rates of HE during that particular readmission between groups based on discharge HE therapy. No= discharged without HE therapy, Lact=discharged on lactulose only, Rif=discharged on rifaximin only and L+R=discharged on lactulose and rifaximin.

Table 1:

Patient Characteristics During The Index Admission

	Admission None *n* = 1102	**Admission Lactulose Only *n* = 695**	**Admission Rifaximin Only *n* = 154**	**Admission Lactulose & Rifaximin *n* = 859**	***p*-value**
Demographics					
Age (years)	57.21 (12.03)	57.23 (10.11)	57.22 (11.28)	57.30 (9.42)	0.82
Gender - Male	63%	62%	56%	62%	0.46
Etiology					<0.0001
Alcoholic cirrhosis	30%	37%	23%	29%	
HCV	20%	19%	23%	22%	
HCV + alcoholic cirrhosis	13%	15%	9%	15%	
NASH	21%	17%	25%	24%	
Other	17%	12%	20%	11%	
Diabetes	32%	32%	33%	39%	0.008
Admission characteristics					
Ascites	54%	74%	82%	84%	<0.0001
Reason for Admission					
GI Bleeding	22%	17%	10%	9%	<0.0001
HE	8%	20%	10%	26%	<0.0001
Renal dysfunction	8%	9%	18%	15%	<0.0001
Electrolyte Dysfunction	3%	3%	6%	5%	0.03
Anasarca	11%	10%	8%	10%	0.57
Non-liver related	7%	5%	8%	5%	0.08
Infection	23%	28%	32%	29%	0.001
Other	40%	36%	36%	32%	0.09
Medication on admission:					
PPI	43%	60%	56%	67%	<0.0001
Beta-Blockers	36%	40%	43%	45%	0.002
SBP prophylaxis	8%	23%	20%	26%	<0.0001
Hospitalization in Past 6 months	56%	71%	70%	80%	<0.0001
Admission Values					

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	Admission None *n* = 1102	**Admission Lactulose Only *n* = 695**	**Admission Rifaximin Only *n* = 154**	**Admission Lactulose & Rifaximin *n* = 859**	***p*-value**
Albumin (g/dl)	2.85 (0.68)	2.82 (0.68)	2.80 (0.65)	2.86 (0.68)	0.54
Serum Na (mmol/L)	134.83 (7.95)	133.83 (6.32)	133.03 (6.32)	133.82 (6.23)	<0.0001
Child-Pugh score	8.88 (2.18)	9.86 (2.08)	9.97 (1.93)	10.24 (1.97)	<0.0001
MELD score	18.03 (7.50)	19.41 (7.65)	20.15 (7.33)	21.30 (7.66)	<0.0001
SIRS (n, %)	29%	22%	27%	24%	0.005
HE details					
HE as the reason for Admission	8%	20%	10%	26%	<0.0001
HE During the Admission	17%	41%	25%	47%	<0.0001
Grade 3/4 HE on initial presentation	28%	30%	30%	31%	0.57
Leading Precipitating factors					
Infections	26%	15%	11%	17%	0.01
Renal insufficiency	21%	20%	11%	15%	0.09
Hyponatremia	12%	24%	13%	14%	0.0005
GI Bleed	16%	13%	8%	7%	0.005
Medication-related	17%	38%	28%	32%	0.0001
Non-adherence to HE medications	7%	29%	18%	21%	<0.0001
Grade 3/4 HE maximum grade (brain failure)	7%	18%	14%	22%	<0.0001
Hospital course and Outcomes					
LOS (days)	10.54 (12.32)	13.22 (15.76)	12.78 (14.73)	12.82 (15.00)	<0.0001
ICU	21%	22%	25%	28%	0.0020
Renal Failure	6%	7%	12%	10%	0.0003
Respiratory Failure	12%	13%	13%	14%	0.50
Circulatory Failure	8%	9%	12%	10%	0.35
NACSELD-ACLF	8%	11%	12%	13%	0.002
In-hospital mortality	5%	8%	8%	6%	0.02
In-hospital transplant	3%	4%	3%	6%	0.003

Data are presented as mean(SD) unless mentioned otherwise. Comparisons performed using Kruskal-Wallis or ANOVA as appropriate

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Table 2

Patients with any medication-related vs other precipitants

	HE due to any medication-related precipitants (*n* = 244)	**HE due to other precipitants (*n* = 545)**	***p*-value**
Demographics and cirrhosis details			
Age (years)	57.92 (8.40)	57.37 (9.77)	0.61
Gender - Male	61%	64%	0.57
Etiology			0.41
Alcoholic cirrhosis	31%	33%	
HCV	22%	19%	
HCV + alcoholic cirrhosis	19%	15%	
NASH	19%	22%	
Other	9%	11%	
Diabetes	43%	39%	0.28
Ascites	77%	79%	0.50
Reason for Admission			
GI Bleeding	7%	13%	0.017
HE	61%	35%	<0.0001
Renal dysfunction	9%	17%	0.004
Electrolyte Dysfunction	2%	5%	0.07
Anasarca	7%	8%	0.54
Non-liver related	2%	2%	1.0
Infection	25%	34%	0.02
Other	32%	35%	0.52
Medication on admission:			
PPI	70%	55%	0.0003
Beta-Blockers	41%	43%	0.58
SBP prophylaxis	18%	23%	0.21
Hospitalization in Past 6 months	72%	73%	0.85
Admission Values			
Albumin (g/dl)	2.84 (0.66)	2.79 (0.72)	0.19

	HE due to any medication-related precipitants (*n* = 244)	HE due to other precipitants (*n* = 545)	*p*-value
Serum Na (mmol/L)	134.98 (5.51)	133.40 (6.78)	0.001
Child-Pugh score	10.33 (2.01)	10.61 (1.99)	0.07
MELD score	18.97 (7.15)	22.31 (8.08)	<0.0001
SIRS	20%	28%	0.01
HE details			
HE medications on admission			0.0001
None	11%	24%	
Lactulose only	41%	30%	
Rifaximin only	3%	4%	
Lactulose+Rifaximin	44%	43%	
Grade 3/4 HE on admission	37%	28%	0.08
Leading Precipitating factors			
Non-Adherence to HE Meds	78%	0%	<0.0001
Other	9%	26%	<0.0001
Renal Failure	9%	26%	<0.0001
Hyponatremia	13%	22%	0.0015
GI Bleed	6%	16%	<0.0001
Grade 3/4 HE maximum grade (brain failure)	48%	43%	0.14
Hospital course and Outcomes			
LOS (days)	12.36 (15.41)	17.59 (18.71)	<0.0001
ICU	21%	41%	<0.0001
Renal Failure	5%	17%	<0.0001
Respiratory Failure	11%	26%	<0.0001
Circulatory Failure	5%	21%	<0.0001
NACSELD-ACLF	12%	29%	<0.0001
In-hospital Mortality	4%	16%	<0.0001
In-hospital transplant	3%	6%	0.040

Data are presented as mean(SD) unless mentioned otherwise. Comparisons performed using Mann-Whitney or unpaired t-test as appropriate. Of the 244 patients with any medication-related precipitants, 146 had only medication-related precipitants while 98 had a medication-related precipitant and another precipitating factor.

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