BREAKING BOUNDARIES in HEPATIC ENCEPHALOPATHY

EDUCATIONAL SERIES

This activity is jointly provided by Medical Education Resources and GHAPP.

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Learning Objectives

- Discuss the importance of adherence and compliance in the management of the hepatic encephalopathy (HE) patient
- Identify tools available to assist in reimbursement
- Demonstrate current strategies for successfully transitioning patients from inpatient HE care to outpatient HE care
- Discuss the current management guidelines and critical decision points that, if followed, will prevent disease recurrence and avoid hospital readmission

The Definition of Hepatic Encephalopathy

HEPATOLOGY

AASLD PRACTICE GUIDELINE

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

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The AASLD/EASL Practice Guideline Subcommittee on Hepatic Encephalopathy are: Jayant A. Talwalkar (Chair, AASLD), Hari S. Conjeevaram, Michael Porayko, Raphael B. Merriman, Peter L.M. Jansen, and Fabien Zoulim. This guideline has been approved by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver and represents the position of both associations.

Preamble

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic; (2) guideline policies covered by the American Association for the Study of Liver Diseases/European Association for the Study of the Liver (AASLD/EASL) Policy on the Joint Development and Use of Practice Guidelines; and (3) the experience of the authors in the specified topic.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information.

To more fully characterize the available evidence supporting the recommendations, the AASLD/EASL Practice Guidelines Subcommittee has adopted the classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup, with minor modifications (Table 1). The classifications and recommendations are based on three categories: the source of evidence in levels I through III; the quality of evidence designated by high (A), moderate (B), or low quality (C); and the strength of recommendations classified as strong (1) or weak (2).

Literature Review and Analysis

The literature databases and search strategies are outlined below. The resulting literature database was available to all members of the writing group (i.e., the authors).

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACLF, acute-on-chronic liver failure; ALD, alcoholic liver disease; ALF, acute liver failure; BCAA, branced-chain amino acids; CFF, Critical Flicker Frequency; CHE, overt HE; CLD, chronic liver disease; CRT, Continuous Reaction Time; CT, computed tomography; DM, diabetes mellitus; EASL, European Association for the Study of the Liver; EEG, electroencephalography; GI, gastrointestinal; GRADE, the Grading of Recommendation Assessment, Development, and Evaluation; GCS, Glasgow Coma Scale; GPB, glycerol phenylbutyrate; HCV, hepatitis C virus; HE, hepatic encephalopathy; HM, hepatic myelopathy; ICT, Inhibitory Control Test; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; IV, intravenous; LOLA, L-ornithine L-aspartate; LT, Liver transplantation; MHE, minimal HE; MR, magnetic resonance; OHE, overt HE; PH, portal hypertension; PHES, Psychometric Hepatic Encephalopathy Score; PP, portal pressure; PSE, portosystemic encephalopathy; PSS, portosystemic shunting; RCT, randomized, controlled trial; TIPS, transjugular intrahepatic portosystemic shunt; VB, variceal bleeding; WHC, West Haven Criteria; WM, working memory.

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†Deceased.

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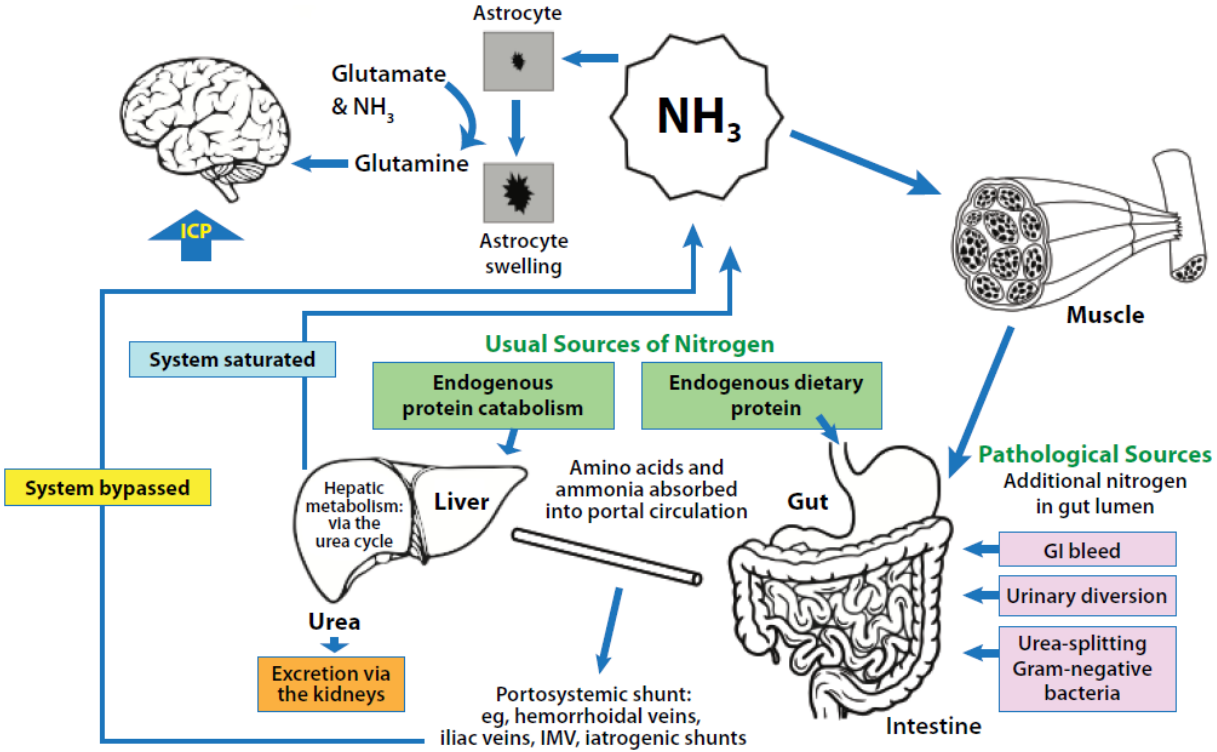
Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and portal systemic shunt

It manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma

Vilstrup H et al. *Hepatology*. 2014;60(2):714-735.

The Pathophysiology of HE: A Multifactorial Process

Understanding the various factors that contribute to HE pathophysiology clarifies the diagnosis and management

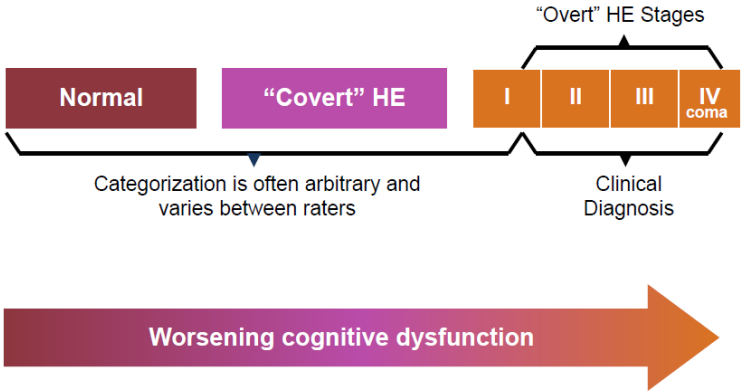


Reau et al. *Gastro and Hep* 2016;12(12):S5

Characterization of HE Stages

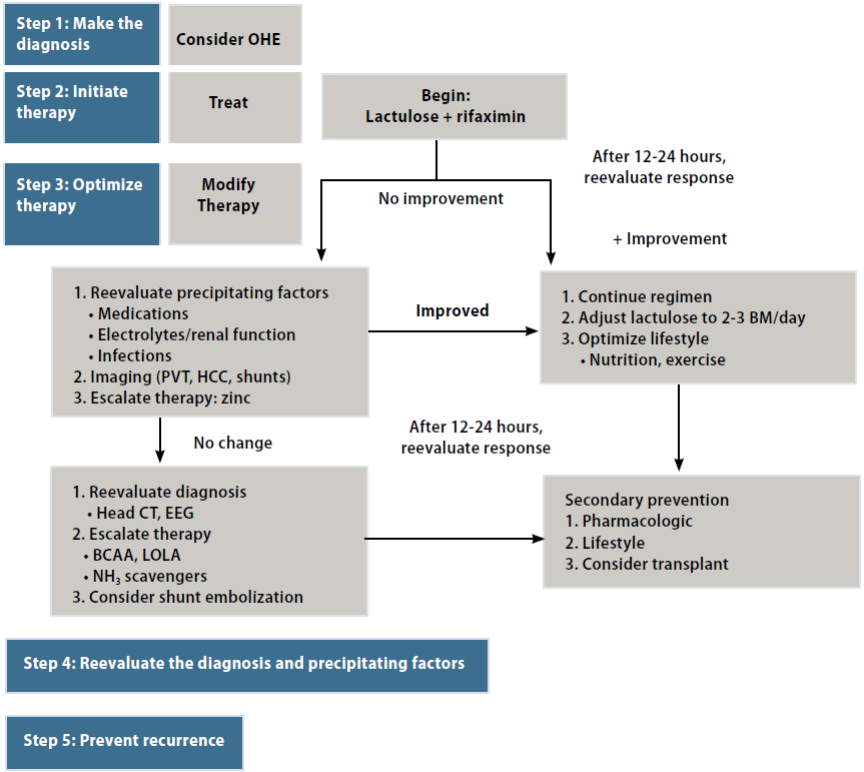
- Covert HE:
  - Minimal HE (MHE):
    - Tests indicate psychometric or neuropsychological alterations
    - No clinical evidence of mental change
  - Grade I HE:
    - Trivial lack of awareness
    - Euphoria or anxiety
    - Shortened attention span
    - Impairment of addition or subtraction
    - Altered sleep rhythm

- Overt HE (OHE)
  - Fully symptomatic
  - Defines the decompensated phase of the disease
  - ***At this time, only OHE is routinely treated***



Vilstrup H et al. *Hepatology*. 2014;60(2):714-735.

Algorithm for the Diagnosis and Management of Overt Hepatic Encephalopathy



Reau et al. *Gastro and Hep* 2016;12(12):S5

Clinical Practice Gaps in HE

- Lack of recommendations for risk stratification prior to the first HE episode
- Poor adherence to treatment
- High treatment costs and reimbursement challenges
- Disruptions in the continuity of care when transitioning from inpatient HE to outpatient HE care
- High rate of hospital readmissions

Risk Stratification for HE: What are the formal recommendations?

- ***There are not any formal AASLD recommendations on risk stratification for HE***
- The AASLD guidance states that “the recognition of precipitating factors for HE (e.g., infection, bleeding, and constipation) supports the diagnosis of HE”
- The guidelines *do not* address:
  - Identifying patients at risk for HE *before* an episode occurs
  - Early intervention prior to a first episode of HE in patients at risk

Vilstrup H et al. *Hepatology*. 2014;60(2):714-735.

Risk Stratification for HE: How can this be improved in clinical practice?

- ***All patients with cirrhosis are at risk for HE and need to be educated on how to recognize early signs and symptoms of HE***
- During the first few office visits, educate the patient on
  - The natural history of cirrhosis and associated complications (e.g., HE, varices)
  - Recognizing the signs and symptoms of HE
  - Understanding the importance of preventing constipation, among other risk factors and HE precipitants
- During cirrhosis follow-up visits, ask the patient about any signs of potential HE

Targeted History to Assess for HE

Examples of Questions to Ask Patients with Cirrhosis and/or Family Members

Changes in handwriting
Difficulty doing everyday tasks (e.g. taking care of the finances)
Forgetfulness
Difficulty with finding items (e.g., lost keys)
Walking into a room and forgetting why you came into it
Losing your place on a page in a book
Changes in personality (not just confusion)
Insomnia at night
Daytime drowsiness

Case Study: Overview

- A 62 year old female with NASH cirrhosis, T2DM and HTN is presenting at her regular (6-month interval) monitoring appointment
- She has no history of HE
- At her prior visit, she stated that she was grieving the loss of her mother while handling the cleaning and moving of her possessions. She was having trouble falling asleep and feeling overwhelmed. She was tired but not napping during the day or falling asleep when she should not.
- For this visit, she is accompanied by her spouse, who normally does not attend appointments. He has noticed depression, withdrawal, mistakes doing the family finances and has started driving the patient where needed.
- She normally has a bowel movement once a day but sometimes just every other day. She cannot recall her last bowel movement with questioning today.

Case Study: Physical Exam

- General appearance: quiet, speaks only when requested, alert to person but not place or time, cooperative
- BP: 100/60 HR: 80 Temp: 98.9F R: 20
- Eyes: anicteric
- Lungs: clear to auscultation bilaterally
- Heart: regular rate and rhythm, S1, S2 normal
- Abdomen: soft, non-tender; bowel sounds normal; no masses, no organomegaly
- Bedside ultrasound shows no ascites
- Extremities: mild LE edema of feet bilaterally
- Skin: no rashes or lesions
- Lymph nodes: cervical, supraclavicular, and axillary nodes normal.
- Neurologic: grossly normal, + asterixis

Case Study: Labs

- WBC 3500, Hgb 11.5, Platelets 160,000
- AST 60, ALT 75, ALP134, t bili 1.2
- Albumin 3.4, creatinine 1.2, K 4.0, Na 132
- Urinalysis: negative for LE, nitrates or blood
- PCP had performed TSH in the past 6 months and normal.
- Hemoglobin A1C 7.2%

Case Study: What would *you* do?

- *What is your differential diagnosis?*
- *Do you consider this patient at risk for HE? Why or why not?*
- *What about this patient case supports being at risk for HE?*
- *What would are your recommended next steps?*

Case Study: Next Steps and Outcome

- Normal exam except the presence of asterixis, and no signs of infection by urinalysis, normal blood sugar, diagnosis is new onset HE
- Lactulose 20 grams/30 mL, 30 mL TID or until passing at least 3 stools per day, is prescribed
- Spouse is directed to take her to the ED if her mental status worsens or if she will not/cannot take lactulose and to return to see you the next day.
- You discuss possible precipitating factors for HE.
- On return, she is able to converse and is her baseline from prior visits

Diagnosis of HE: What are the formal recommendations?

- The AASLD recommends that the diagnosis of overt OHE be based on a clinical examination and a clinical decision[1]
- Effective October 2022, ***K76.82***, a billable/specific *ICD-10-CM code* for HE became available and can be used to indicate an HE diagnosis for reimbursement purposes[2]
  - Applies to HE, not otherwise specified, HE without coma, hepatocerebral intoxication and portal-systemic encephalopathy
- West Haven criteria is the gold standard to analyze HE severity[1]
- Additional tests* are available to aid in this analysis; use requires skilled examiners[1]

*e.g., Stroop Test, Continuous Reaction Time Test, Inhibitory Control Test

1. Vilstrup H et al. *Hepatology*. 2014;60(2):714-735; 2. 2023 ICD-10-CM Diagnosis Code K76.82 Hepatic Encephalopathy. Available at: https://www.icd10data.com/ICD10CM/Codes/K00-K95/K70-K77/K76-/K76.82#:~:text=2023%20ICD%2D10%2DCM%20Diagnosis,82%3A%20Hepatic%20encephalopathy.

Diagnosis of HE:
How can this be improved in clinical practice?

- These tests can be ineffective given the inconsistencies of what a patient with potential HE will present like on any given day
- It is recommended that a skilled examiner perform these tests on more than one visit

Diagnosis of HE:
How do *you* practice?

- *How do you approach analysis of HE severity in your practice?*

Treatment and Prevention of HE: What are the formal recommendations?

- The AASLD recommends that an episode of OHE be actively treated with lactulose
  - 25 mL q 1-2 hours is recommended until at least 2 soft or loose bowel movements/day are produced
  - Subsequently titrate to maintain 2-3 bowel movements/day
- Secondary prophylaxis is recommended after the first OHE episode
  - Rifaximin 550 mg BID is an effective add-on therapy to lactulose for prevention of OHE recurrence

Vilstrup H et al. *Hepatology* 2014;60:715-35.
Xifanan [Package Insert], Bridgewater, NJ: Salix Pharmaceuticals, Inc. 2022.

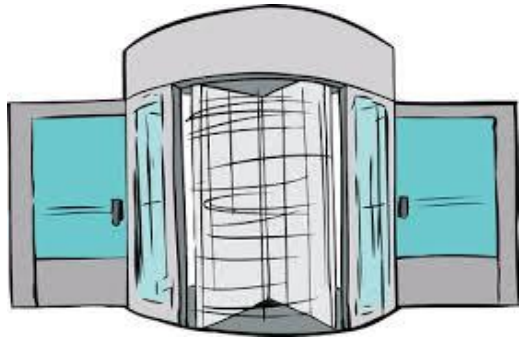
The “Revolving Door”: Poor Compliance Leads to HE Recurrences and Hospital Readmissions

Study Methods	Results
Retrospective chart review of 402 patients with decompensated cirrhosis[1]	34% of first admissions were for HE; 314 ***(78%) readmitted*** during follow-up; median time to first readmission was 67 days
Analysis of 119,722 unique index admissions with cirrhosis[2]	The 30- and 90-day rates of readmission were 12.9% and 21.2%; ***HE was most strongly associated with readmission*** within 30 and 90 days; OR, 1.77 for each
One-year retrospective chart review. 139 patients admitted with a complication related to liver cirrhosis (36% with HE)[3]	31% of patients overall were readmitted within 30 days; 47% of these cases were attributed to HE ***HE was the most common cause of readmission*** within 30 days

1. Volk ML et al. *Am J Gastroenterol* 2012;107:247-52; 2. Tapper EB et al. *Clin Gastroenterol Hepatol* 2016;14:1181-8.e2; 3. Masadeh MM et al. *Gastroenterology* 2014;146:S986.

Reasons for the “Revolving Door”

- Lactulose noncompliance secondary to adverse events and issues with titration
- Access to rifaximin secondary to high treatment costs and reimbursement challenges
- Disruptions in the continuity of care when transitioning from inpatient to outpatient HE care



Lack of Compliance with Lactulose: Misuse and Unwanted Adverse Events

- Lactulose administration requires patients self-titrate to achieve 2-3 bowel movements per day
- Poor self-titration results in over-use, subsequent dehydration and hyponatremia, which potentially worsens or precipitates HE
- Unwanted AEs associated with lactulose include diarrhea (most common), nausea, bloating, and flatulence
- One study found that 40% of HE recurrences were due to lactulose noncompliance and 8% were due to lactulose overuse

Flamm SL. *Am J Manag Care*. 2018;24(4 Suppl):S51-S61.

Lack of Compliance with Rifaximin: Direct Patient Costs and Insurance Coverage

- Treatment compliance is improved with rifaximin
  - Data indicates that rifaximin compliance is ~80-90%[1-3]
  - In a retrospective chart review of 145 HE patients, rates of adherence (i.e. taking ≥ 75% of prescribed doses), were significantly higher in the rifaximin group vs. the lactulose group (92% vs 31%; *P* <.001)[3,4]
- High patient costs and reimbursement challenges impact rifaximin compliance
  - Reimbursement requires prior authorization
  - Medicaid data from 2019 indicates the average cost paid by payers for a two-week course of rifaximin* in the US is $1,250.76, when covered by insurance[5]

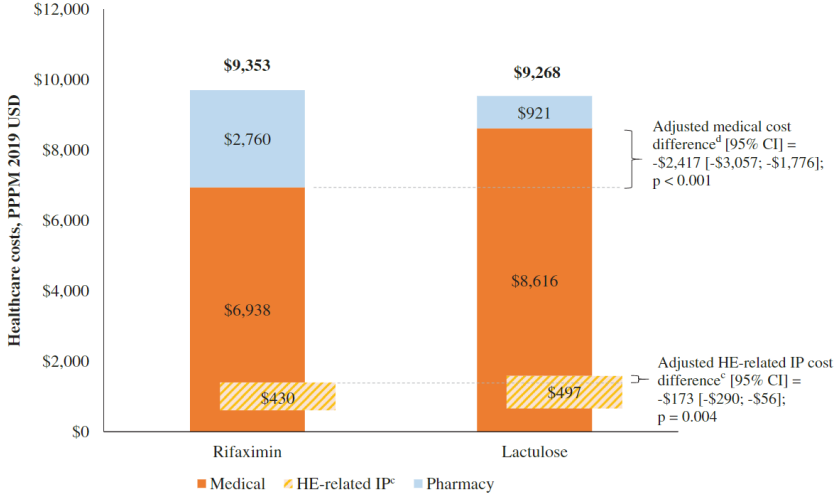
*IBS-D data

1. Bass NM et al. *NEJM* 2010;362:1071-1081. 2. 2. Bajaj JS et al. *Gastroenterology* 2011;140:478-487. 3. Flamm SL. *Am J Manag Care*. 2018;24(4 Suppl):S51-S61. 4. Leevy CB et al. Dig Dis Sci. 2007;52:737-741. 5. Medicaid National Average Drug Acquisition Cost (NADAC) Database. Https:// Data.Medicaid.Gov/.

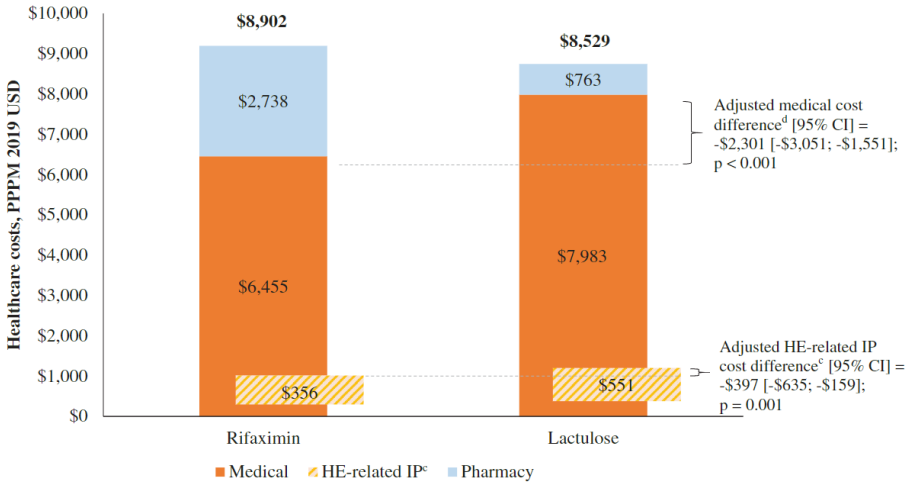
Healthcare Costs and Hospitalization Rates with Rifaximin vs Lactulose

- Two claims databases were analyzed to assess healthcare costs and hospitalization rates in at-risk HE patients
- The study compared rifaximin to lactulose therapy

Marketscan Database



Optum Database



IP, in-patient

Volk ML et al. *J Med Econ.* 2021;24(1):202-211. .

Healthcare Costs and Hospitalization Rates with Rifaximin vs Lactulose (cont'd)

- Patients incurred significantly lower rates of HE-related and all-cause hospitalizations during rifaximin vs lactulose episodes
- As a result, lower facility and professional costs were observed
- ***Cost savings may be possible if rifaximin adherence is improved in HE patients***

Volk ML et al. *J Med Econ.* 2021;24(1):202-211. .

Pitfalls in Transitioning from Inpatient to Outpatient HE Care from the Patient's Perspective

Patients……

- Have the misconception that HE medications are for treating constipation
- Cannot access the medication at discharge because the reimbursement process was delayed
- Reject prescriptions at the pharmacy because the cost is a surprise
- Are advised to follow up with their physician 6 weeks post-discharge
- Are not aware the medicine is waiting for them at the pharmacy

Closing the Revolving Door: How can processes be improved in clinical practice?

Coordinate care *upon admission*

- Order discharge medications upon admission so that the pharmacist can begin the approval process

Reinforce patient education *in the hospital*

- While patients are still in the hospital, advise them about discharge prescriptions
- Teach them that these medications "keep [their] brain clear" and how to use them
- Recommend engaging a support person or a team approach to taking the medication

Improve communication on *medication costs*

- Refer patients to the rifaximin "patient savings program"*
- Communicate costs to the patient prior to discharge

Promote *timely* post-discharge follow-up

- Schedule a patient follow-up appointment for 2 weeks after discharge
- Document the appointment in the patient chart

*https://xifaxan.copaysavingsprogram.com/ or 1-866-XIFAXAN

Case Study: Overview

- A 45 year old male presents to the ED with ETOH associated cirrhosis, complicated by ascites and HE, awaiting liver transplantation
- Current medications include spironolactone, furosemide, ciprofloxacin daily for SBP prophylaxis and lactulose 20 grams/30 mL BID
- HE was diagnosed one month ago during an admission for SBP
- He presents to your ED after his family called 911 when they found him unarousable at home.
- You are called for a consult. By the time you are able to see the patient, he has been given a lactulose enema and subsequently produced two semi-solid stools. He is arousable to stimuli but not engaging otherwise.

Case Study: Physical Exam

- General appearance: cachectic, arousable but somnolent
- BP 90/50 HR: 90 R: 16 Temp 97.8F
- Eyes: icteric
- Lungs: decreased air movement, bilateral crackles at bases
- Heart: rate and rhythm, S1, S2 normal
- Abdomen: minimally distended, liver not palpable, spleen palpable at left costal margin, reducible umbilical hernia with 3 cm deficit
- Bedside ultrasound + ascites
- Extremities: mild LE edema of feet bilaterally
- Skin: spider angiomata chest and face
- Lymph nodes: cervical, supraclavicular, and axillary nodes normal.
- Neurologic: grossly normal, + asterixis

Case Study: Labs

- WBC 2500, Hgb 10.2, Platelets 75,000, PT 14.5, INR 1.5
- AST 60, ALT 75, ALP134, t bili 7.0
- Albumin 3.0, creatinine 1.9, K 4.0, Na 129
- Urinalysis: negative for LE, nitrates or blood
- CXR: Cardiac silhouette and mediastinal contours within normal limits. No pleural effusion or pneumothorax. No acute airspace process.

Case Study: Next Steps

- You recommend diagnostic paracentesis with cell count and culture
- As he now able to protect airway, administer oral lactulose 20 grams/30 mL once every hour until 3 stools are passed, then BID baseline with titration to achieve 3 stools daily
- Start rifaximin 550 mg BID

Case Study: What would *you* do?

- *Since the patient is now on a preventative treatment regimen, what steps would you take to facilitate a smooth transition from inpatient to outpatient care? Specifically:*
  - *Patient education and communication*
  - *Prior authorization*
  - *Medication costs*
  - *Discharge instructions*

Key Takeaways

- All patients with cirrhosis are at risk of HE and should be educated as such
- Prior to the first episode of HE, it is recommended that providers question the patient at every visit about any signs of potential HE
- Tests are available to diagnose and grade HE and, in the correct setting with a skilled examiner, they offer some utility
- Prevention involves strategies to enhance patient education, communication and coordination of care and ameliorate prescription drug costs
- ***The most important goal in HE management is prevention of episodes in order to avoid brain injury and coma***