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Hepatic Encephalopathy: Achieving Care Goals in the Acute Setting and Beyond

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Faculty

Robert Rahimi, MD
Transplant Hepatology
Baylor University Medical Center
Assistant Professor
Department of Medicine
Texas A&M Health Science Center
College of Medicine
Liver Consultants of Texas
Baylor Charles A. Sammons Cancer Center
Dallas, Texas

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Faculty Disclosures

- Advisory Board: Mallinckrodt
- Research: Mallinckrodt, Valeant Pharmaceuticals North America LLC

Learning Objectives

- Identify symptoms and risk factors of HE and approaches to diagnosis that are concordant with current guidelines recommendations
- Utilize available clinical and observational data to design effective acute and prophylactic treatment regimens for patients with HE
- Implement transitional and long-term care strategies to reduce rehospitalization in patients with HE

HE in the Hospital Setting

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Overview of HE

- Brain dysfunction caused by liver insufficiency and/or PSS
- Occurs in 30% to 45% of patients with cirrhosis and 10% to 50% of patients with TIPS
- Symptoms include neurological or psychiatric abnormalities ranging from subclinical alterations to coma
- Without successful treatment of the underlying liver disease, HE is associated with high risk of recurrence, diminished HRQOL, and poor survival

HRQOL, health-related quality of life; PSS, portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt.

Chacko KR, et al. *Hosp Pract*. 2013;41(3):48-59.Poordad FF. *Aliment Pharmacol Ther*. 2007;25(suppl 1):3-9.
2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

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HE Burden in the Hospital Setting

HE Inpatient Data	
Annual inpatient incidence	20,918-22,931
Length of hospital stay	Median: 8 days Maximum: 113 days 10.4% >30 days
Inpatient mortality	20.9%

Stepanova M, et al. *Clin Gastroenterol Hepatol*. 2012;10(9):1034-1041.e1031.

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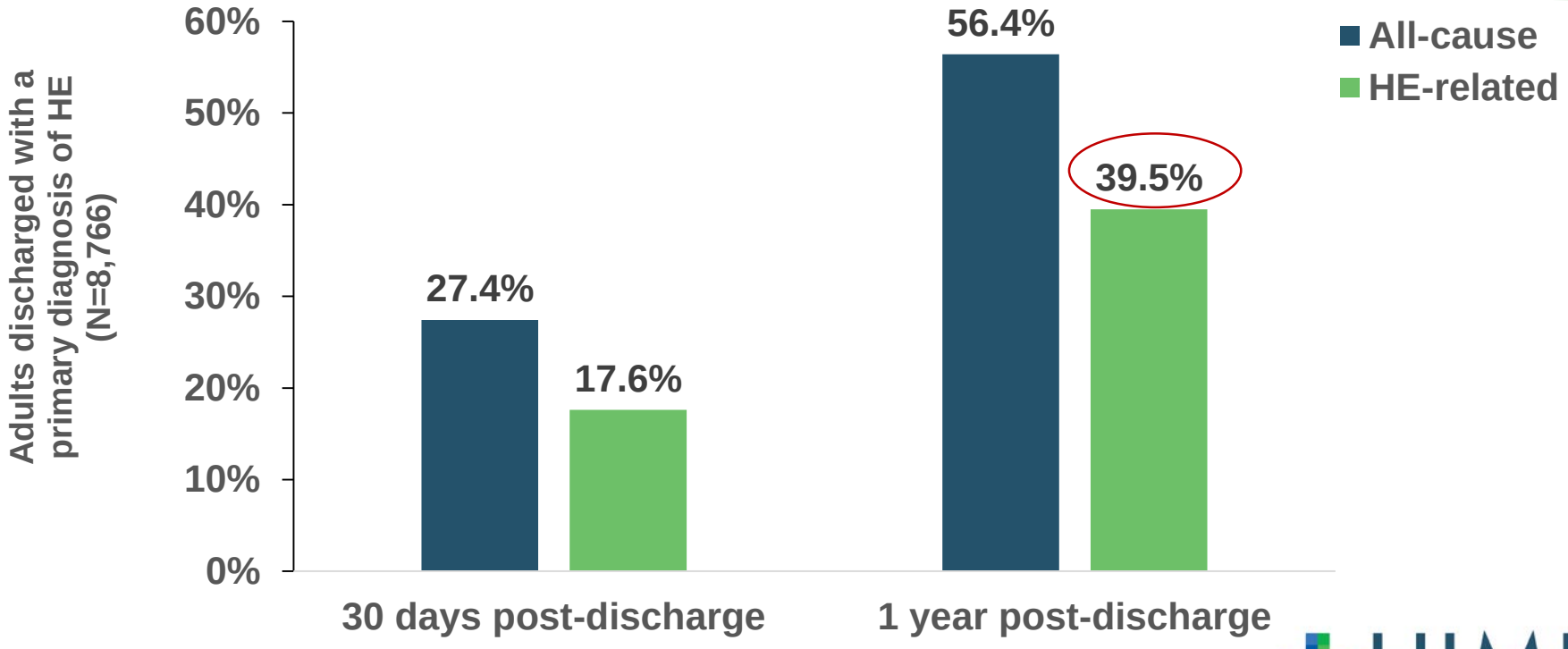
Readmission Rates Among Patients Hospitalized with HE



Neff G. *Hepatology*. 2013;58(S1):390A-391A.

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Factors Associated with a High Likelihood of HE Readmission

- Poor social support
- Failure to fill a prescription
- Lack of follow-up with a healthcare provider

Neff G. *Hepatology*. 2013;58(S1):390A-391A.

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Pathogenesis of HE

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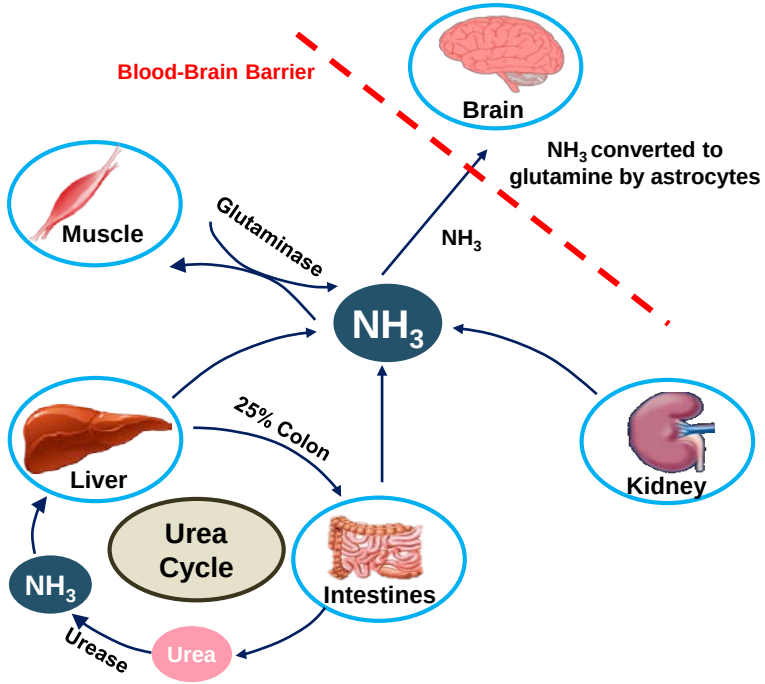
Ammonia (NH_3) is Primary Pathophysiologic Mechanism of HE



- NH_3 produced by bacterial metabolism of urea and proteins in gut and deamination of glutamine in small intestine
- Impaired hepatic metabolism of NH_3 and portal hypertension leads to shunting of NH3-rich portal blood to systemic circulation
- NH_3 crosses blood-brain barrier and is metabolized in the astrocytes to glutamine
- Glutamine accumulation leads to cerebral dysfunction in HE

Elwis S, Rahimi RS. *J Clin Transl Hepatol.* 2017;5(2):142-151. Swaminathan M, et al. *Hepatic Med.* 2018;10:1-11.

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Diagnosis of HE

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HE Types Based Upon Underlying Disease

Type	Underlying Disease
A	Acute liver failure
B	PSS or bypass
C	Cirrhosis

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West Haven Criteria Minimal and Grade I HE

WHC	Description	Operative Criteria
Unimpaired	• No encephalopathy, HE history	• Normal test results
Minimal	• Alterations in psychomotor speed/executive functions or on neurophysiological measures • No clinical evidence of mental change	• Abnormal results on psychometric or neurophysiological tests • No clinical manifestations
Grade I	• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	• Orientation in time and space • Cognitive/behavioral decay with respect to standard on clinical examination, or to caregivers

All conditions are required to be related to liver insufficiency and/or PSS.

2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

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West Haven Criteria Grades II, III, and IV HE

WHC	Description	Suggested Operative Criteria
Grade II	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	• Disoriented for time (≥3 of the following errors: day of month or week, month, season, or year) • ± Other symptoms
Grade III	• Somnolence to semi stupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	• Disoriented for space (≥3 of the following errors: country, state [or region], city, or place) • ± Other symptoms
Grade IV	• Coma	• Does not respond even to painful stimuli

All conditions are required to be related to liver insufficiency and/or PSS.

2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

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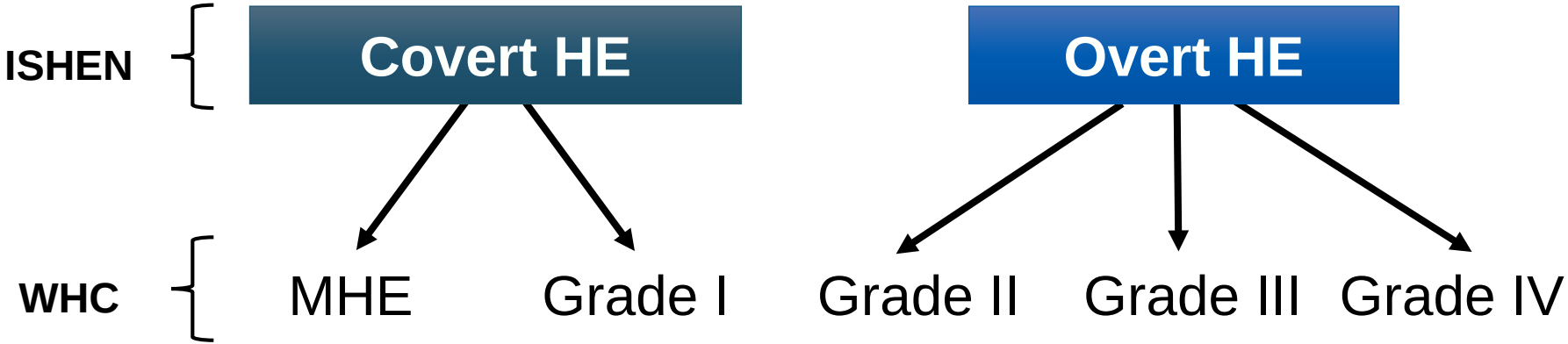
Covert vs Overt HE



ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism;
MHE, minimal HE (covert HE).

2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

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Approach to the Diagnosis of HE

- Overt HE diagnosis is based primarily on clinical examination
  - Disorientation and asterixis are reliable overt HE markers
  - Mild hypokinesia, psychomotor slowing, and lack of attention are easily overlooked in clinical examination
- Specific quantitative tests are only needed in study settings
- The West Haven Criteria (WHC) is the gold standard for staging disease severity

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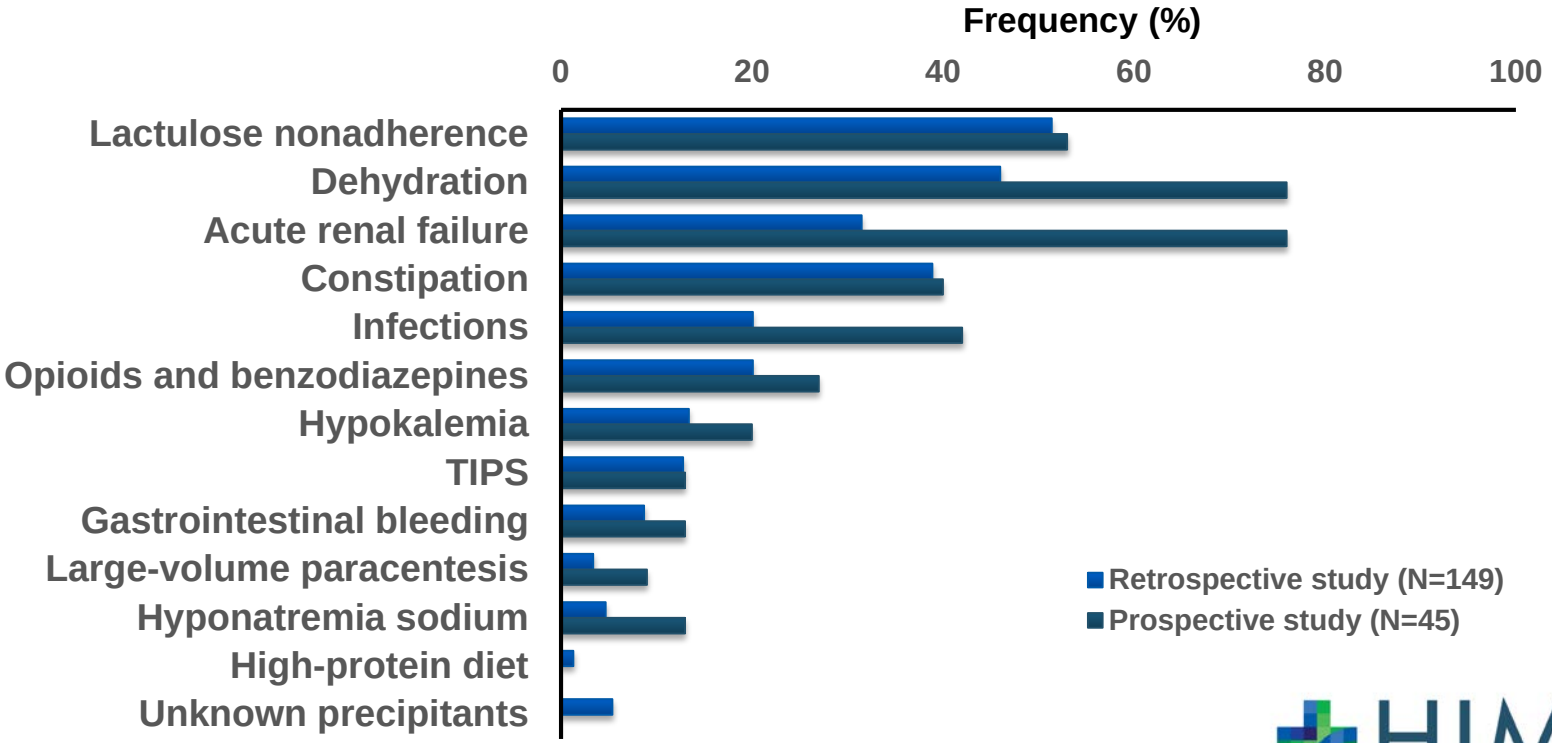
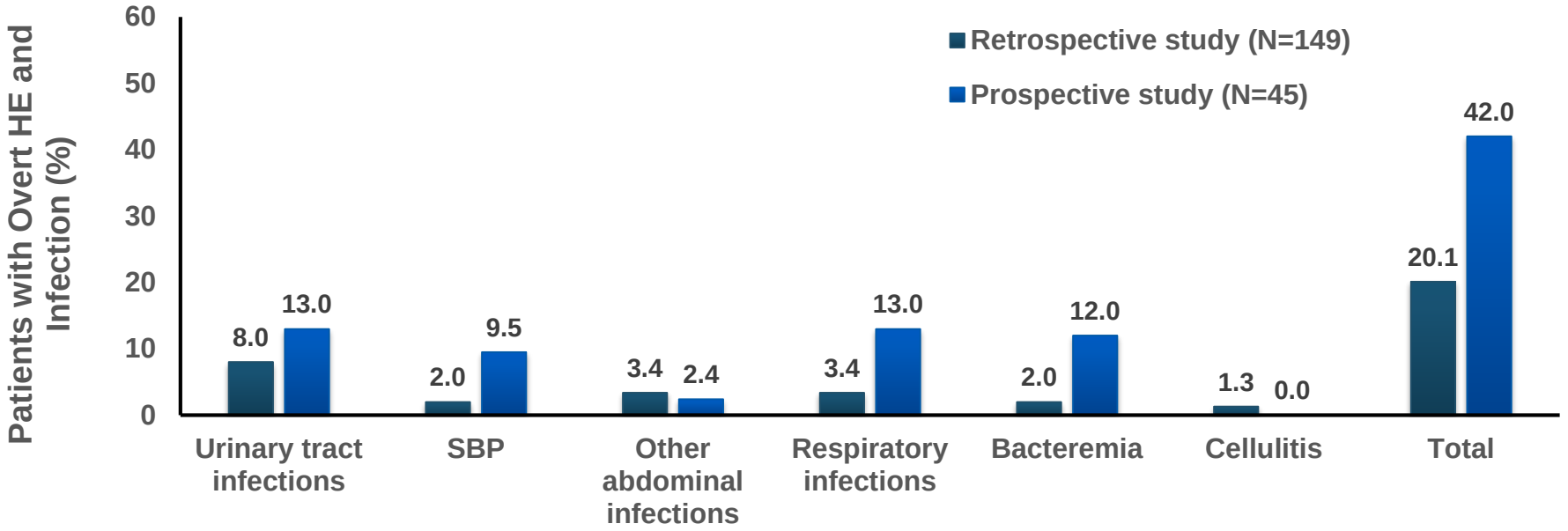
Precipitating Factors for Overt HE



Pantham, et al. *Dig Dis Sci.* 2017;62:2166-2173.

Site of Infection in Patients with Overt HE



SBP, spontaneous bacterial peritonitis.

Pantham, et al. *Dig Dis Sci.* 2017;62:2166-2173.

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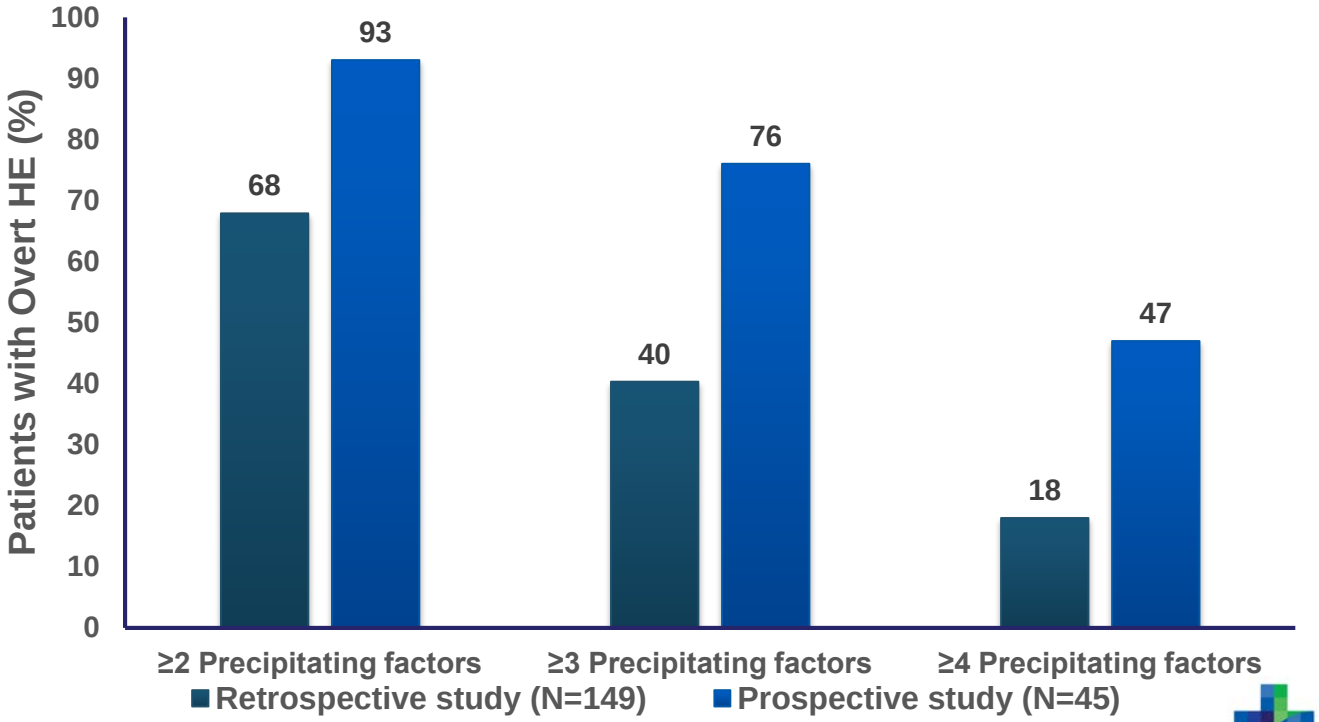
Patients with Overt HE and Multiple Precipitating Factors



Pantham, et al. *Dig Dis Sci.* 2017;62:2166-2173.

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Diagnostic Tests

- CBC, CMP
- Blood cultures
- Urine analysis and culture
- Chest x-ray
- Paracentesis
- Alcohol level/drug screen if suspicion arises based on history

CBC, complete blood count; CMP, comprehensive metabolic panel.

Differential Diagnosis of HE

Overt HE or Acute Confusional State

- Diabetes
- Alcohol
- Drugs
- Neuroinfections
- Electrolyte disorders
- Nonconvulsive epilepsy
- Psychiatric disorders
- Intracranial bleeding and stroke
- Severe medical stress

Other Presentations

- Dementia
- Brain lesions
- Obstructive sleep apnea

2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

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Treatment of Acute Overt HE

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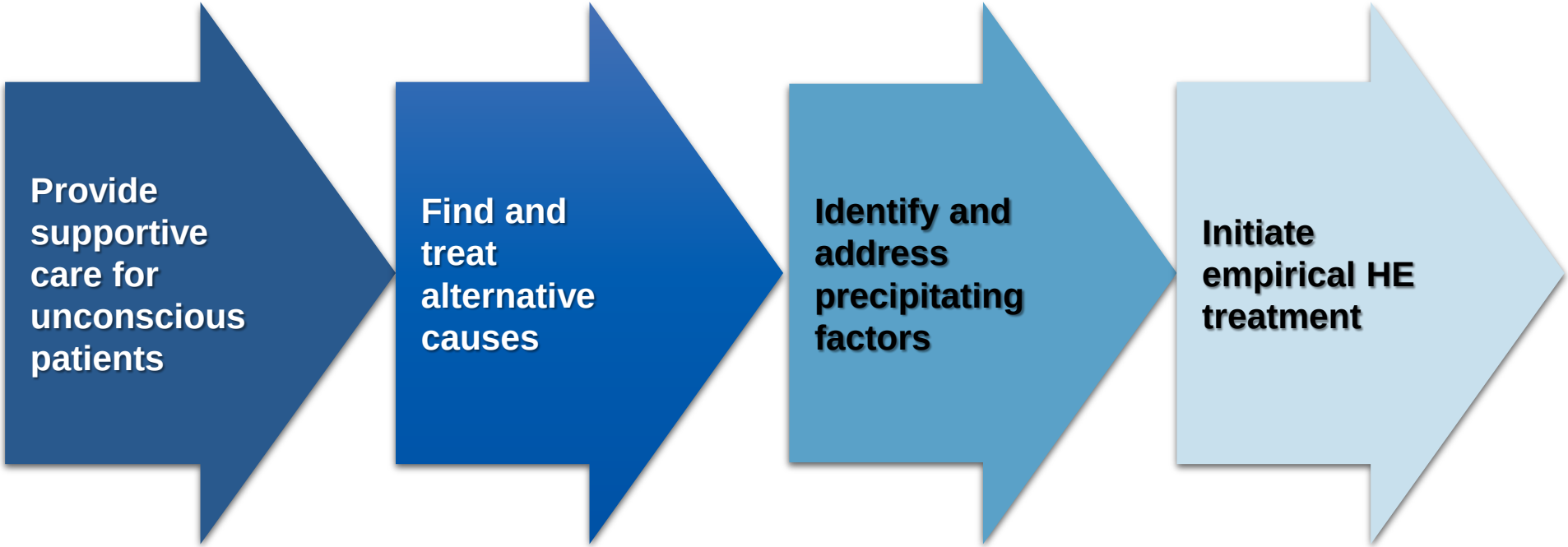
A Four-Pronged Approach to the Management of Overt HE



2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

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Available Therapies for the Treatment of Acute Overt HE

First-line Therapy

Agent	Mechanism of Action/Comments
Nonabsorbable disaccharides	Promotes conversion of NH3 to NH4+ in the colon, shifting colonic flora from urease- to non-urease-producing bacteria; has a cathartic effect
Rifaximin	Thought to reduce ammonia production by eliminating ammonia-producing colonic bacteria; indicated for reducing risk of overt HE recurrence in adults

Adjunctive Therapy

Agent	Mechanism of Action/Comments
Zinc	Enhances urea formation from ammonia and amino acids
BCAAs	Source of glutamate, which helps to metabolize ammonia in skeletal muscle
MARS	Removes non–protein-bound ammonia that accumulates in liver failure; primarily used in research
Percutaneous embolization of PSSs	Rescue treatment for patients with persistent or recurrent HE despite optimal medical management

NH3, ammonia; NH4, ammonium; BCAAs, branched chain amino acids; MARS, molecular adsorbent recirculating system.

Leise MD, et al. *Mayo Clin Proc*. 2014;89(2):241-253; Flamm SL. *Ther Adv Gastroenterol*. 2011;4(3):199-206; Lynn AM, et al. *Liver Transpl*. 2016 Jun;22(6):723-31.

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Emerging Ammonia-Lowering Agents

Agent	Mechanism of Action/Byproduct
Glycerol phenylbutyrate	• Nitrogen removal in the form of urinary PAGN
Polyethylene glycol 3350-electrolyte solution	• Purgative; causes water to be retained in the colon and produces a watery stool
Ornithine phenylacetate	• Nitrogen removal in the form of urinary PAGN

PAGN, Phenylacetylglutamine.

Elwir S, et al. *J Clin Transl Hepatol*. 2017;5(2):142-151.

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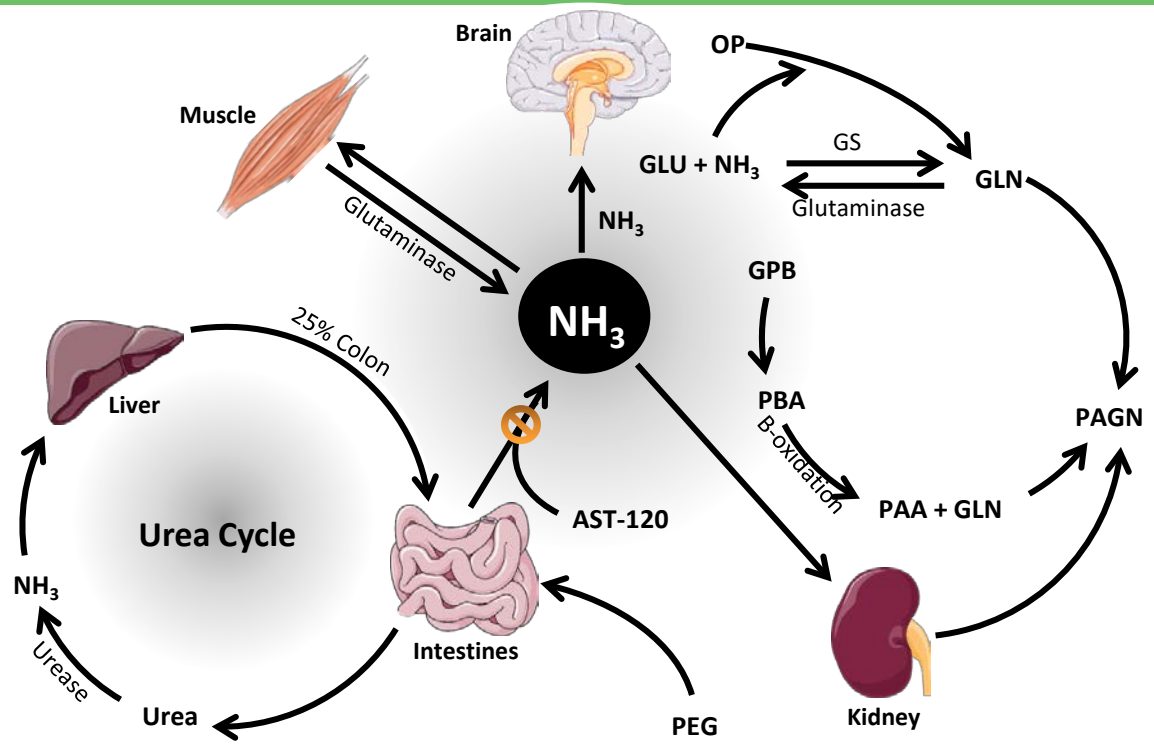
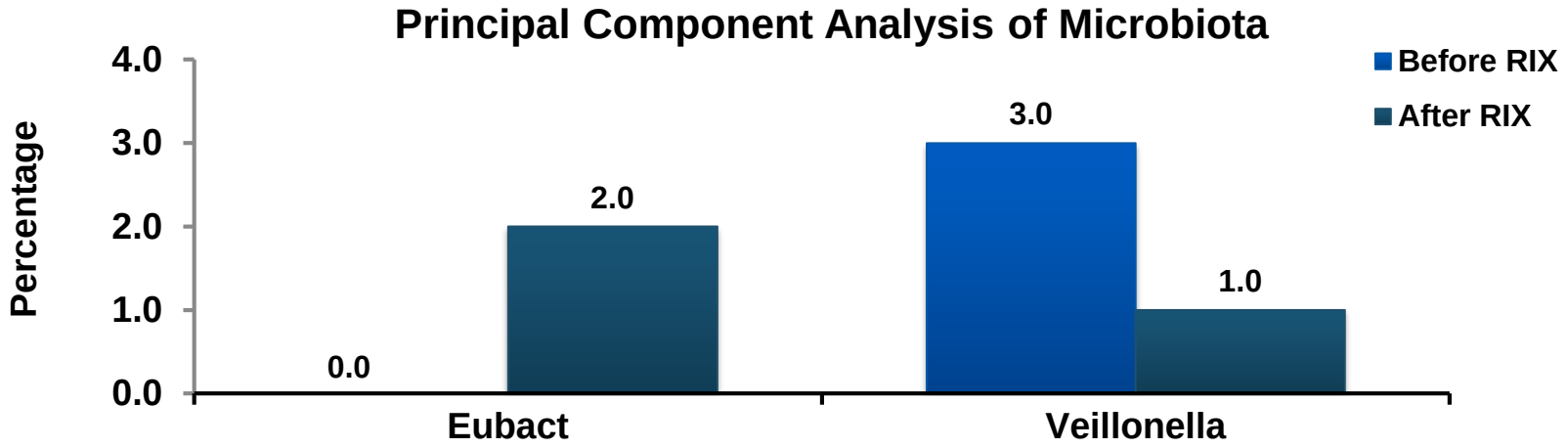
Pathways Targeted by Specific Ammonia-Lowering Medications



Elwir S, et al. *J Clin Transl Hepatol*. 2017;5(2):142-151.

Microbiota Changes Associated with RIX Therapy



A significant decrease in *Veillonellaceae* and increase in *Eubacteriaceae* abundance were observed after RIX therapy.*

*No significant change in the principle component of microbiota was observed.

Bajaj JS, et al. *PLoS One*. 2013;8(4):e60042.

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Adverse Effects of Lactulose

- Aspiration
- Dehydration
- Hypernatremia
- Severe perianal skin irritation
- Precipitation of HE with overuse

Note: Data for precise frequency of AEs are not available.

AE, adverse effects.

2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.
Enulose® [package insert]. Baltimore, MD: Actavis Mid Atlantic LLC; 2006.

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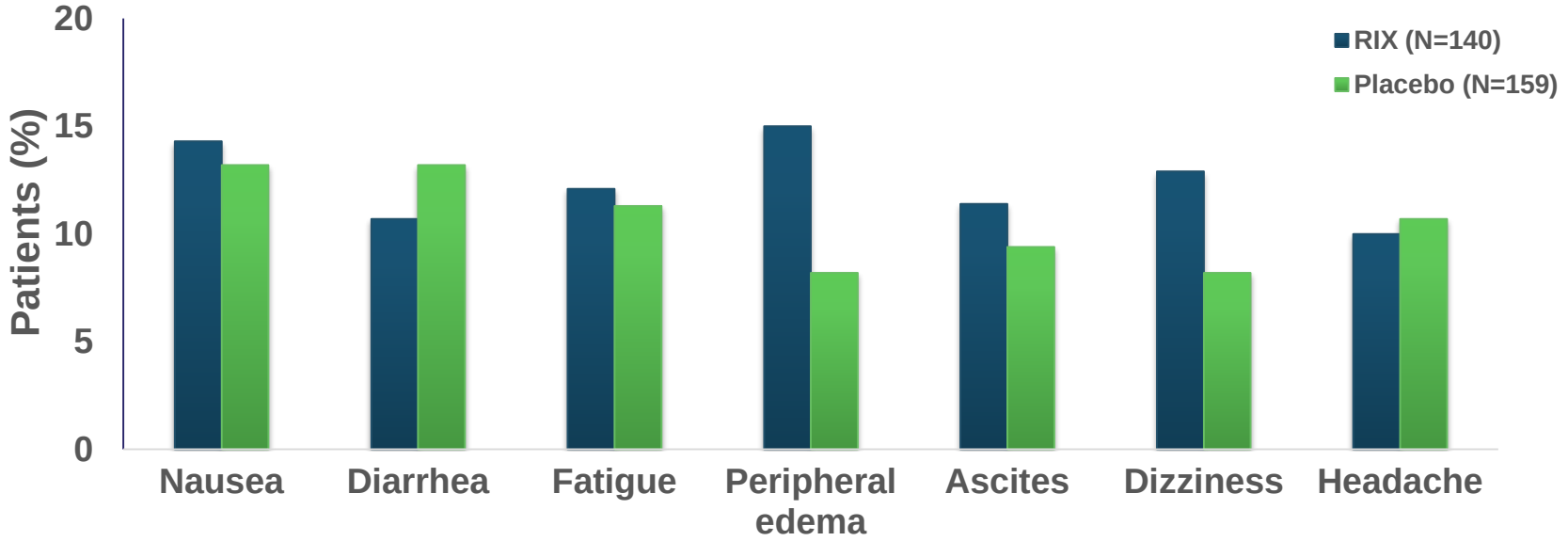
Common AEs Observed with Rifaximin Treatment*



The incidence of AEs did not differ significantly between groups.

*AEs occurring at an incidence rate of 10% or higher in the rifaximin group.

Bass NM, et al. *N Engl J Med*. 2010;362(12):1071-1081.

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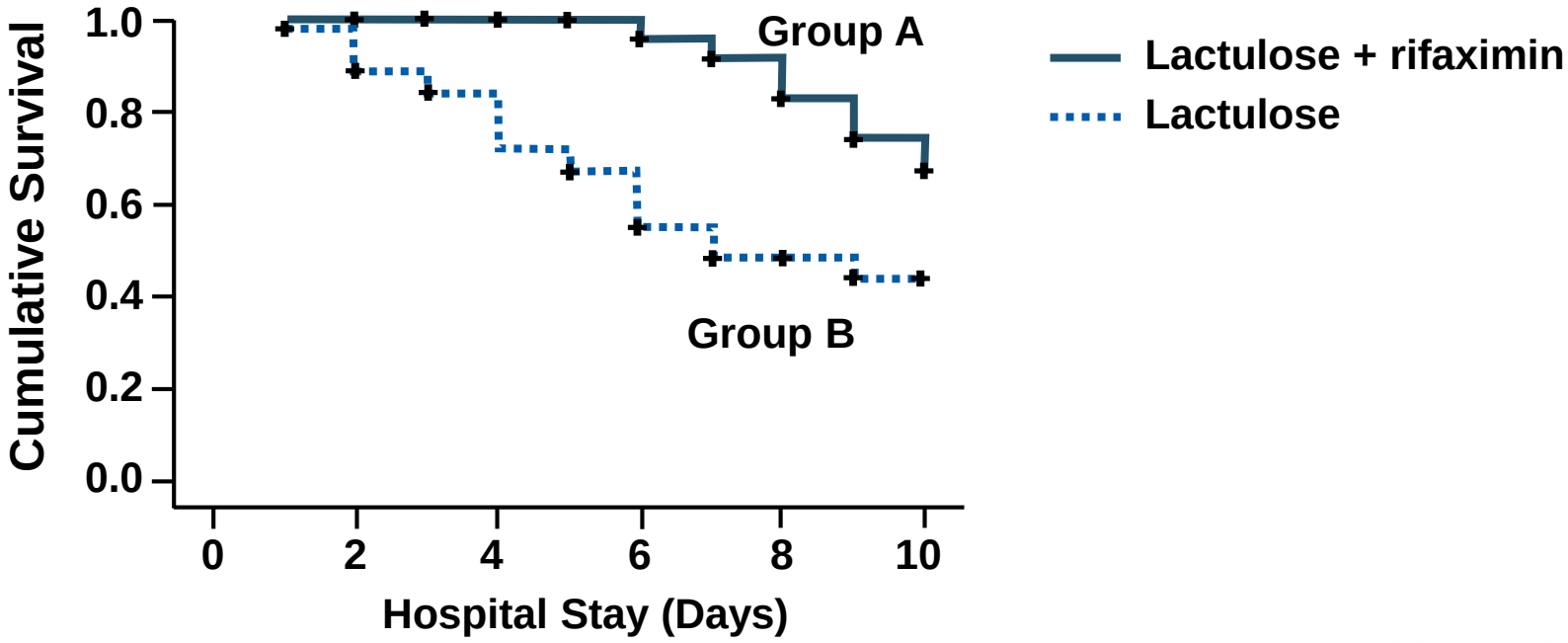
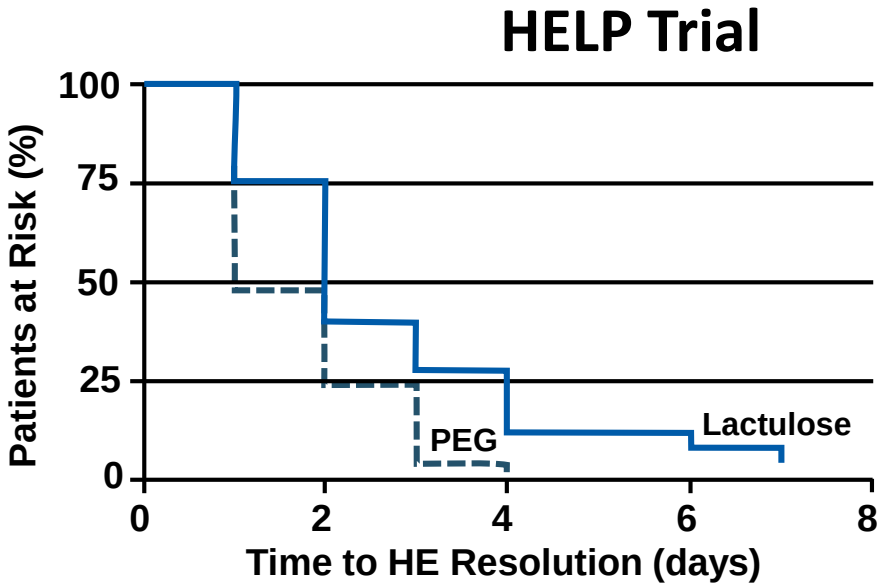
RIX Added on to Lactulose in the Treatment of Acute Overt HE



Sharma BC, et al. *Am J Gastroenterol*. 2013;108(9):1458-1463.

PEG Treatment in Patients with Cirrhosis Hospitalized for HE



PEG vs standard lactulose therapy:

- ⬆ % of patients with a **HESA score improvement ≥1***
- ⬆ Mean **change in HESA score at 24h**†
- ⬆ **Rate of HE resolution**‡ (graph)

*P<.01; †P=.002; ‡P=.01

PEG, polyethylene glycol 3350-electrolyte solution; HESA, hepatic encephalopathy scoring algorithm.

Rahimi RS, et al. *JAMA Internal Medicine*. 2014;174(11):1727-1733.

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Causes of Persistent Overt HE

PSS

- 71% of patients with persistent overt HE show patent, large PSSs vs 14% of those without
- Interventional radiologic embolization or coiling may improve symptoms

TIPS

- A minority of patients develop persistent overt HE after TIPS
- Radiological interventions (eg, ballooning) may be required to occlude the TIPS shunt

Other causes

- Undiscovered source of sepsis (eg, abscesses)
- Inability to tolerate medications prescribed for overt HE

Bajaj JS. *Aliment Pharmacol Ther*. 2010;31(5):537-547.

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Liver Transplantation

- Indication:
  - HE cannot be improved despite maximal medical therapy
  - HE severely compromises HRQOL
  - Only for HE associated with poor liver function
- Considerations:
  - Large PSSs may cause neurological disturbances and persistent HE, even after LT
  - Shunts should be identified and embolization should be considered before or during transplantation

LT, liver transplant.

Prophylaxis of Recurrent Overt HE

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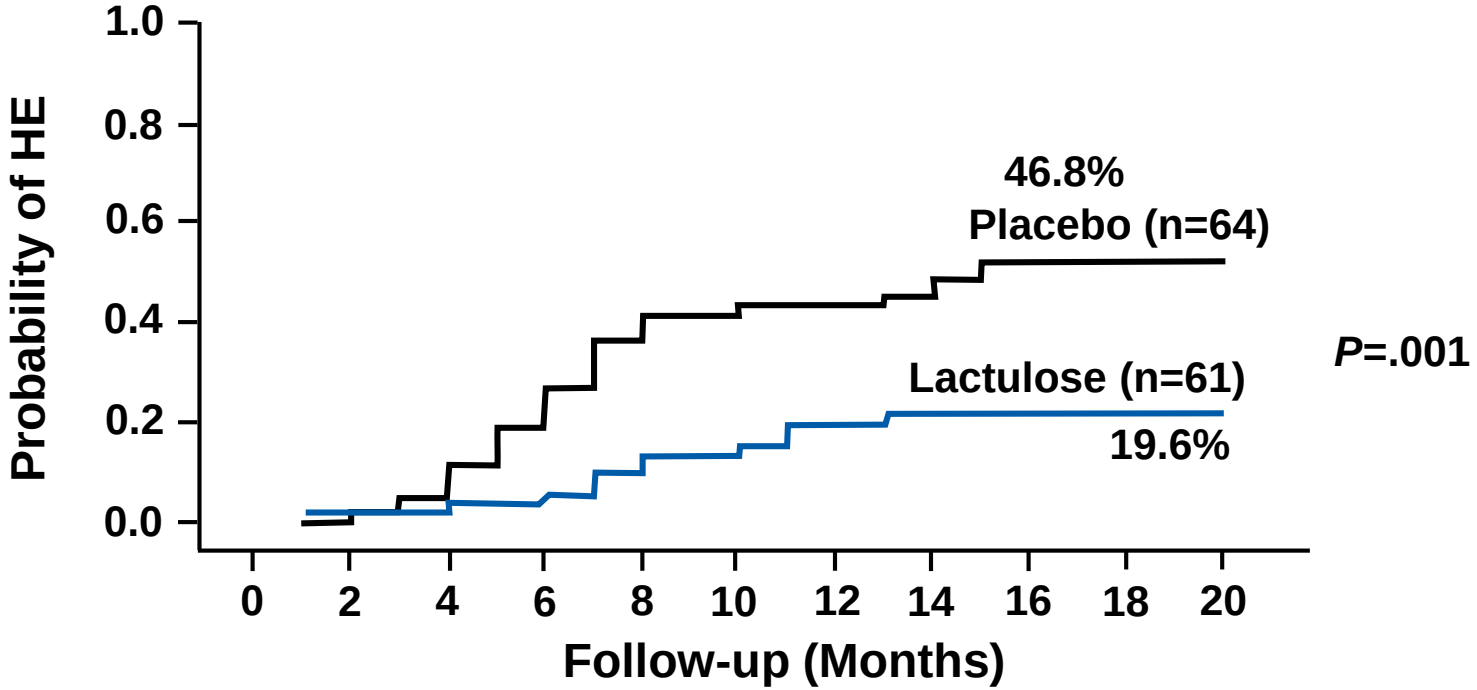
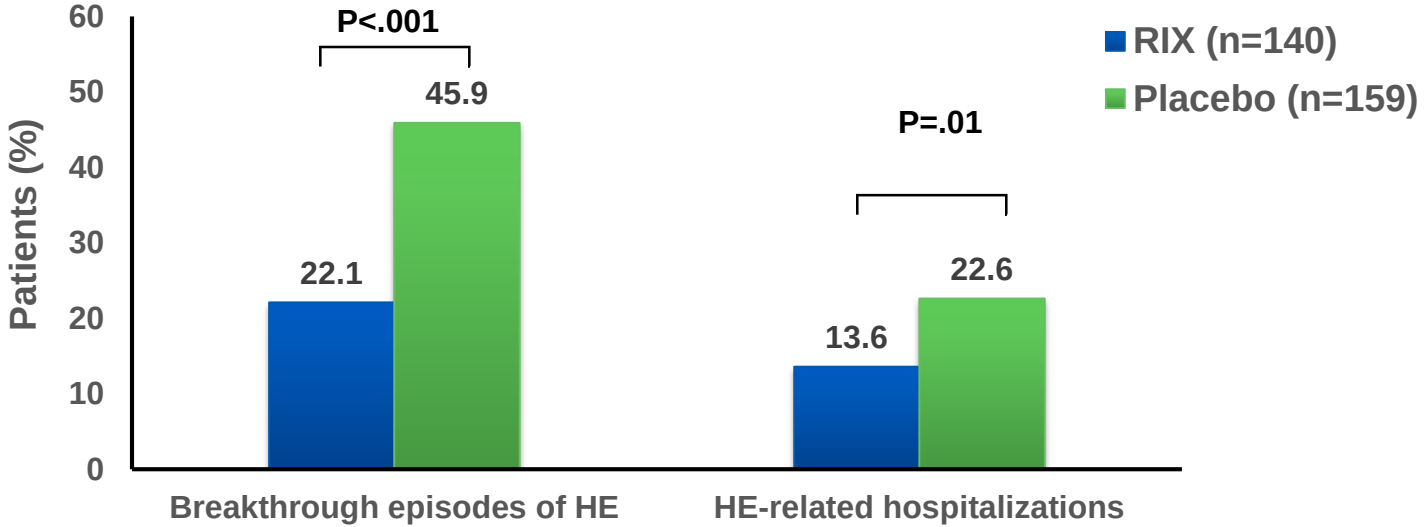
Lactulose Prevents Recurrence of HE in Patients with Cirrhosis



Sharma BC, et al. *Gastroenterology*. 2009;137(3):885-891.e881.

Effect of RIX Treatment on Breakthrough HE Episodes and HE-related Hospitalizations



Over a 6-month period, treatment with RIX resulted in a greater proportion of patients maintaining remission vs placebo.

Note: >90% of patients received concomitant lactulose during the study period.

Bass NM, et al. *N Engl J Med*. 2010;362(12):1071-1081.

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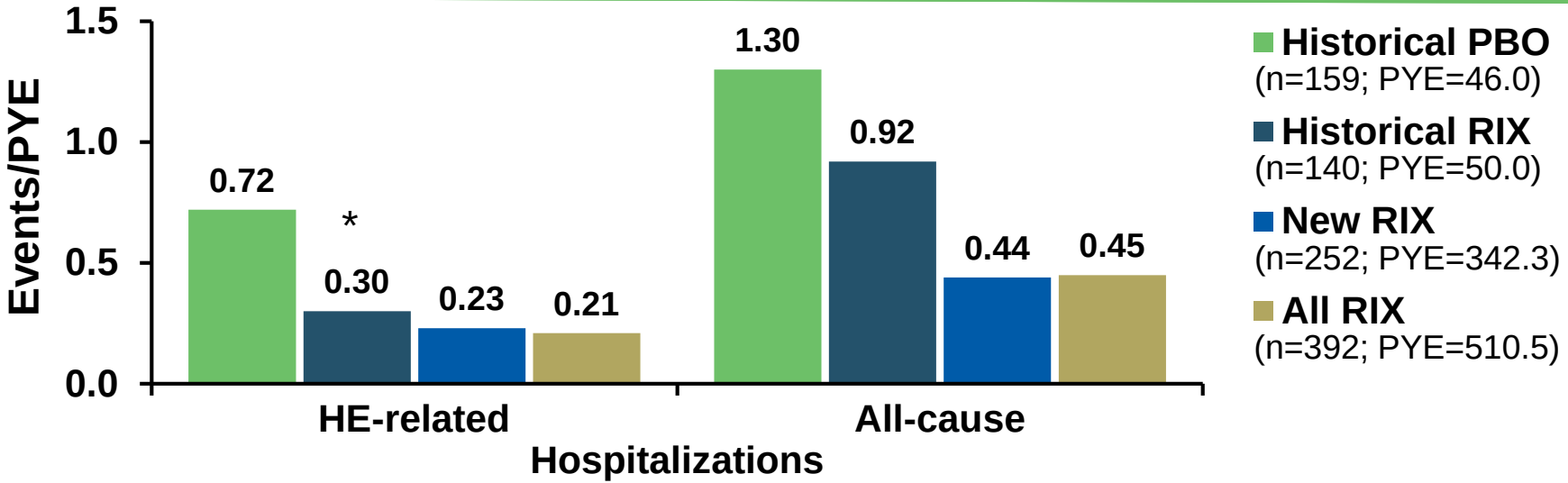
Long-term Maintenance of Remission From Overt HE with RIX



Treatment with RIX (550 mg bid) for ≥2 years reduced the rate of HE-related and all-cause hospitalization, without increasing the rate of adverse events.

**P*<.001 vs PBO.

PYE, person-years of exposure; bid, twice a day; PBO, placebo.

Mullen KD, et al. *Clin Gastroenterol Hepatol*. 2014;12(8):1390-1397.e1392.

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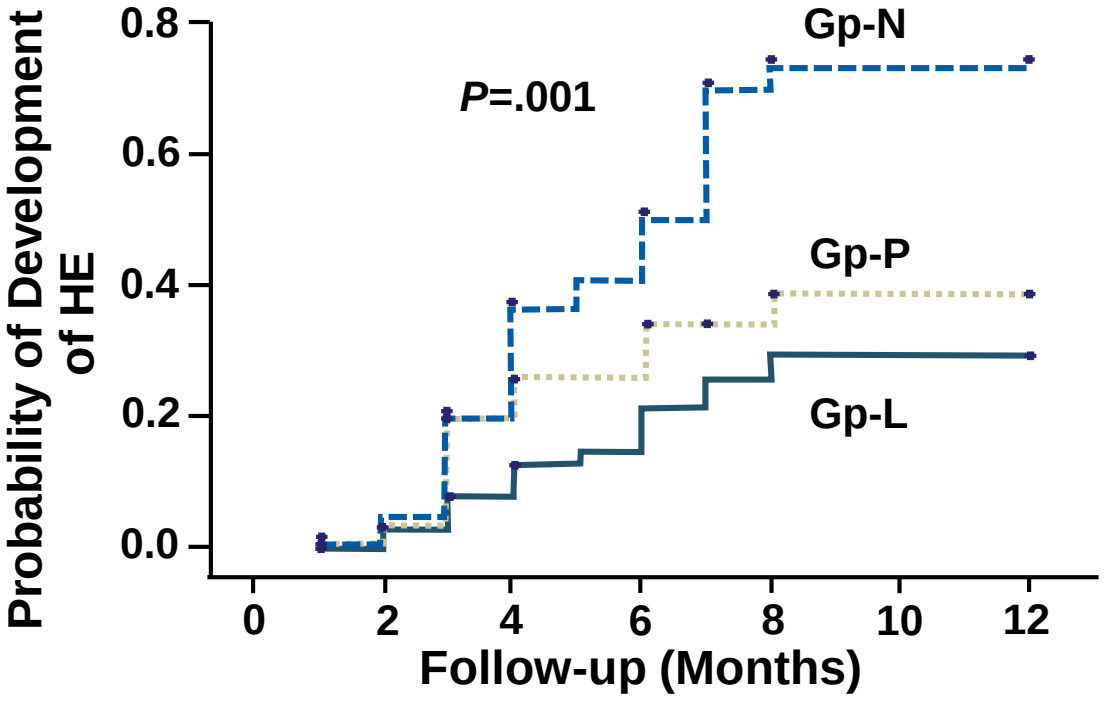
Comparison of Lactulose and Probiotics vs PBO for the Prevention of HE Recurrence



Gp-N: No therapy

Gp-P: Probiotics

Gp-L: Lactulose

Agrawal A, et al. *Am J Gastroenterol*. 2012;107(7):1043-1050.

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Additional Considerations for Treatment Selection

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RIX vs Lactulose: Impact on Hospitalization Outcomes

	Lactulose-treated patients*	RIX-treated patients*
Mean number of hospitalizations	1.6	0.5
Mean days per hospitalization	7.3	2.5
Total time hospitalized	1.8 weeks	0.4 weeks
Estimated hospitalization charges per patient (per 6-month period)**	$56,635	$14,222

*Greater than 6 months of treatment

**Hospitalization charges were estimated based on average cost per hospital day in 2005 US dollars

Leevy CB, et al. *Dig Dis Sci*. 2007;52(3):737-741.

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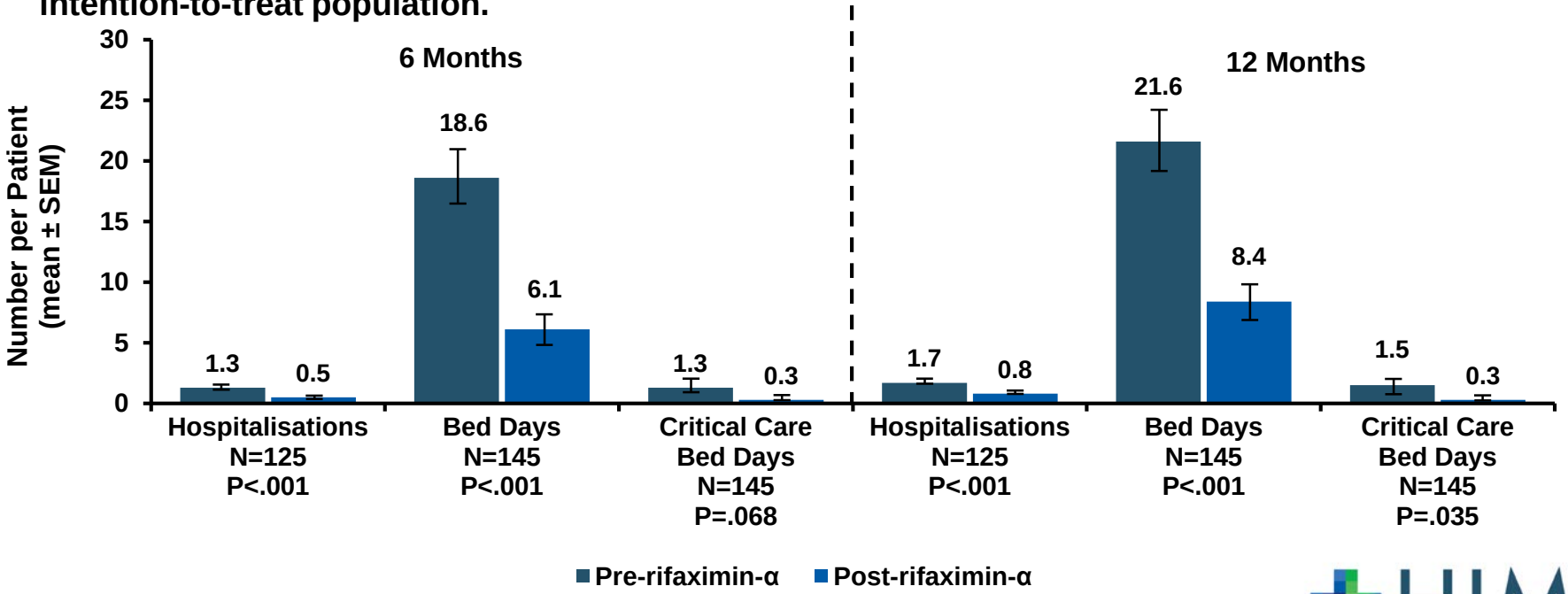
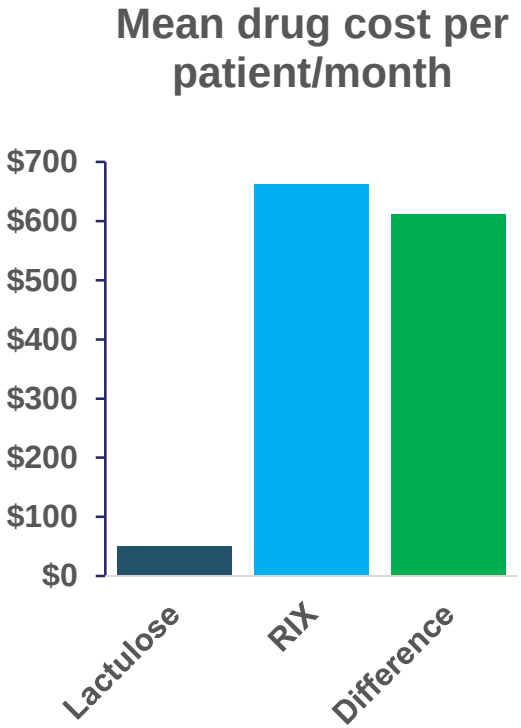
Impact of RIX Treatment of HE on Liver-related Healthcare Utilization

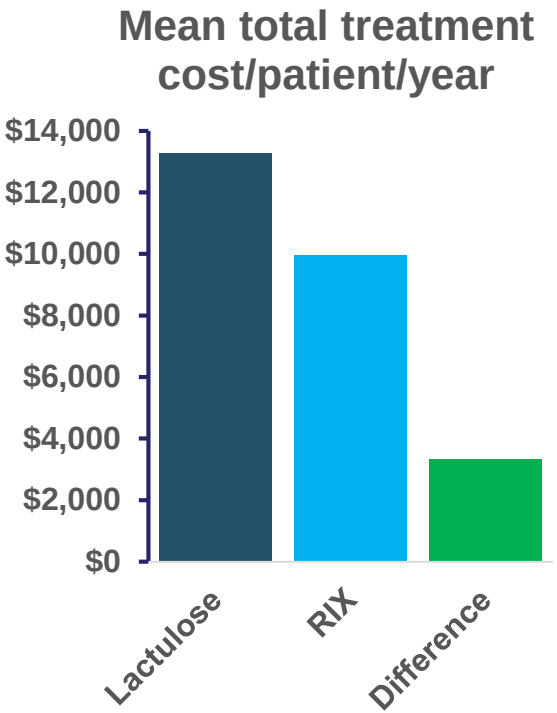
Liver-related resource use in the 6 and 12 months pre-rifaximin-α and post-rifaximin-α initiation—intention-to-treat population.

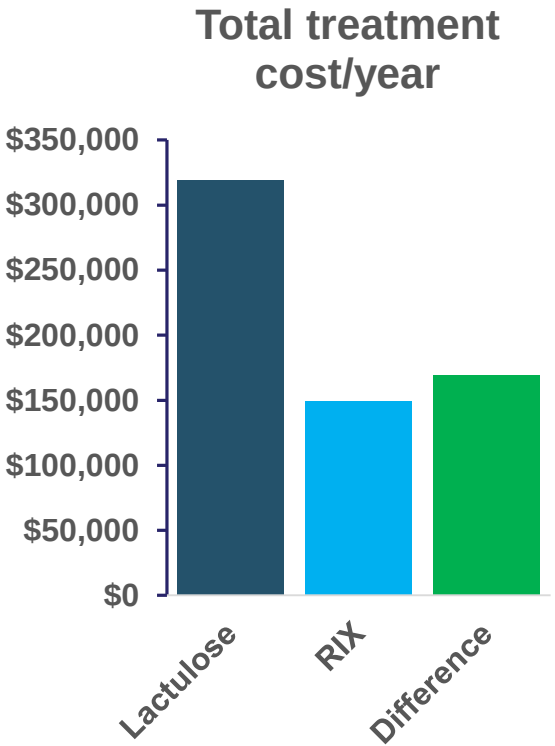


Hudson M, et al. *Frontline Gastroenterol.* 2017;8:243–251.

Comparison of Costs Associated with RIX vs Lactulose Treatment of Patients with Overt HE







Flamm SL, et al. *Am J Manag Care*. 2018;24:S51-S61.

Long-term Management of HE

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ISHEN/AASLD Recommendations: Energy and Protein Requirements

	Optimal Daily Intake Per Kg Ideal Body Weight
Energy	35 kcal-40 kcal
Protein	1.2 g-1.5 g

- Small meals throughout the day and a late-night snack of complex carbohydrate (to minimize protein utilization)
- Diet rich in vegetable and dairy protein
- BCAA supplementation may allow attainment/maintenance of recommended nitrogen intake in patients intolerant of dietary protein

BCAA, branched-chain amino acid.

2013 ISHEN Consensus Statement. *Hepatology*. 2013;58(1):325-336.
2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

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ISHEN Recommendations: Fiber and Micronutrient Provision

- Prebiotics
  - 25 g to 45 g of fiber daily
- Micronutrients
  - 2-week multivitamin course in patients with decompensated cirrhosis or those at risk for malnutrition
  - Specific treatment of clinically apparent vitamin deficiencies
  - Slow correction of hyponatremia
  - Avoidance of long-term treatment with manganese-containing nutritional formulations

2013 ISHEN Consensus Statement. *Hepatology*. 2013;58(1):325-336.

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Real-world Driving Ability in Patients Diagnosed with HE

- Patients' ability was evaluated by a professional driving instructor on being fit to drive
- Minimal HE and HE were associated with significantly reduced rates of driving fitness

Group	N	Fit to Drive
Control	48	87%
No HE	10	75%
Minimal HE	27	48%
Grade I HE	14	3%

Kircheis G, et al. *Gastroenterology*. 2009;137(5):1706-1715.e1701-1709.

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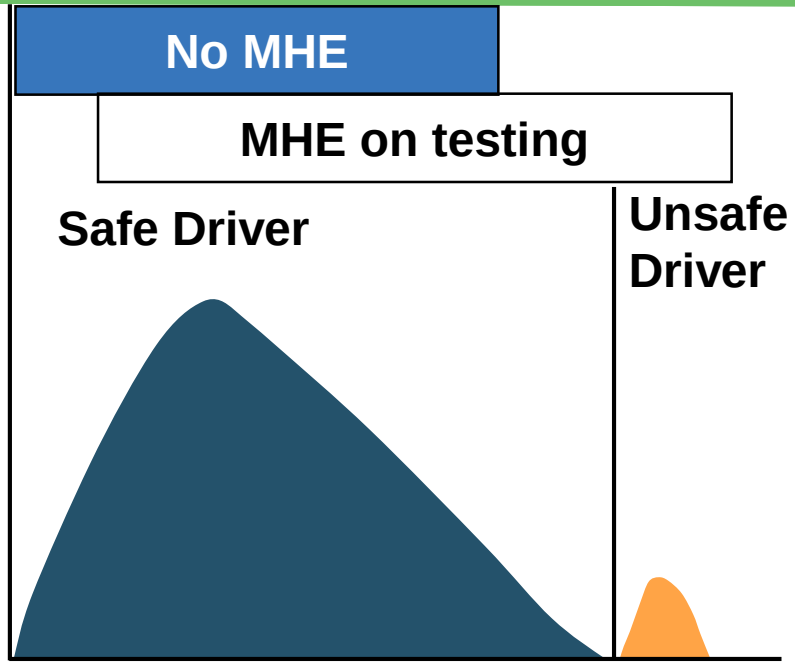
Challenges in Evaluating Driving Ability in Patients with MHE



MHE, minimal HE (covert HE).

Shaw, et al. *J Clin Gastroenterol*. 2017;51(2):118-126.

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Planning for Patient Discharge

Neurological Status

- Confirm status
- Assess other contributing causes
- Inform caregivers of potential changes after acute illness resolution and need for monitoring

Precipitating Factors

- Identify and discuss with patient and caregivers
- Plan for future clinical management

Postdischarge Follow-up

- Ensure patients follow-up with PCPs who can:
  - Adjust prophylactic treatment
  - Advise on avoiding precipitating factors
  - Act as liaison between patient's family, caregivers, and other HCPs

HCP, healthcare provider; PCP, primary care provider.

2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

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Case Evaluations

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Case Evaluation #1: Patient Description

A 61-year-old man presents with noticeable confusion, disorientation, and asterixis. He appears to know where he is, but is confused about how long he has been at the hospital. His wife reports that “he has not been himself lately” and has recently shown signs of increased fatigue, somnolence, and diminished ability to communicate. His medical history includes HCV-related cirrhosis, asthma, and allergic rhinitis. During the previous year, he was treated for an episode of overt HE, but was discharged without maintenance therapy.

Case Evaluation #1: Discussion Question 1

Based on his history and current symptoms, you determine that the patient is experiencing an episode of HE. How would you classify this patient?

A. West Haven Criteria Grade I

B. <u>West Haven Criteria Grade II</u>

C. West Haven Criteria Grade III

Case Evaluation #1: Discussion Question 2

What type of additional testing, if any, would be most appropriate for the patient?

A. Ammonia levels

B. <u>Serum electrolytes</u>

C. Computed tomography or magnetic resonance imaging

Case Evaluation #1: Discussion Question 3

What recommendation would you make for this patient after resolution of the current overt HE episode and prior to discharge?

A. Limit exposure to precipitating factors
B. Involve family and caregivers in HE management
C. Pharmacologic prophylaxis

Case Evaluation #2: Patient Description

A 72-year-old woman presents with symptoms consistent with an acute overt HE episode. Her daughter reports that she is currently on lactulose maintenance therapy, but is only sporadically adherent. She explains that her mother's medication makes her feel nauseous and bloated, and that she tends to stop taking it when she has not had an acute episode for several weeks.

Case Evaluation #2: Discussion Question

What type of intervention would you recommend to improve the patient's adherence?

A. Provide education on the importance of medication adherence
B. Adjust the patient's dose of lactulose
C. Prescribe rifaximin as an alternative maintenance treatment

Summary

- HE is a major complication of liver disease that represents a substantial healthcare burden in the hospital setting
- Management goals include active treatment of acute episodes, prevention of recurrence, and evaluation for surgical intervention
- Several agents have shown good efficacy when administered as acute treatment or secondary prophylaxis
- Following an acute episode of HE, prophylaxis and patient education are crucial for preventing unnecessary recurrence and hospitalization, as well as improving health outcomes

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Clinical Pearls

- For patients with decompensated liver disease, obtain a thorough history of mental status changes, administer tests to rule out other causes of neurological disturbances, and evaluate the need for HE treatment
- Treatment of acute overt HE should incorporate complementary strategies for ammonia reduction, supportive care, and nutritional support
- Consider secondary prophylaxis with lactulose and/or rifaximin in patients with previous overt HE episodes and at high risk for rehospitalization
- Assess the nutrition of all patients with cirrhosis and HE, and encourage an individualized plan for maintaining adequate intake of calories, fiber, and micronutrients

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Thank You!

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