

Strategies for Improving Long-term Management of Hepatic Encephalopathy: Assessing Therapies for Secondary Prophylaxis



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Faculty Disclosures

- Alpesh Amin, MD, has no real or apparent conflicts of interest to report.

Learning Objectives

- Describe the burden and need to prevent recurrence and rehospitalizations for overt hepatic encephalopathy (HE)
- Evaluate the efficacy and safety of available and emerging agents for secondary prophylaxis of HE
- Develop a multidimensional long-term management plan that includes pharmacologic and nonpharmacologic strategies to care for patients with HE

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

PSS, portosystemic shunt; TIPS, transjugular intrahepatic portosystemic shunt; HRQOL, health-related quality of life; AASLD, American Association for the Study of Liver Disease; EASL, European Association for the Study of Liver Disease.

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.

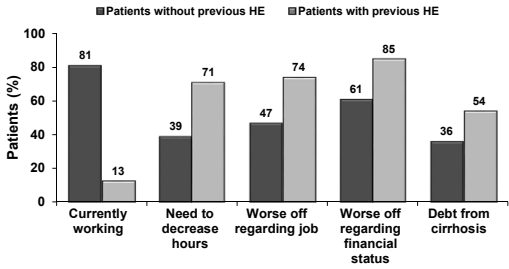
Impact of HE on HRQOL

Individual SF-36 Domain/Summary Component	No HE	Subclinical HE	Overt HE	P value
Physical functioning	61.5	52	44.2	.01
Role limitations (due to physical health issues)	44.4	25	22.9	.02
Bodily pain	52.3	51.4	42	NS
General health perceptions	41.4	37	31.7	.03
Vitality	40.4	37.6	30.3	NS
Social functioning	73.5	58.6	50	.002
Role limitations (due to emotional health issues)	70	52.3	53	.03
General mental health	75	63	64.1	.03
Physical component summary	35.6	33.2	29.3	.02
Mental component summary	50	42.4	44	.03

SF-36, Short Form-36 questionnaire; NS, not significant.

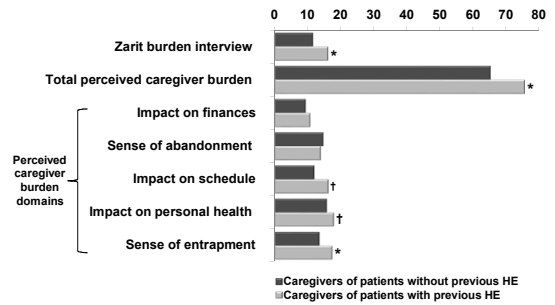
Arguedas MR, et al. *Dig Dis Sci*. 2003;48(8):1622-1626.

Effect of HE on Employment and Financial Status



Bajaj JS, et al. *Am J Gastroenterol.* 2011;106(9):1646-1653.

Burden of HE on Caregivers



*P<.05; †P<.01

Bajaj JS, et al. *Am J Gastroenterol.* 2011;106(9):1646-1653.

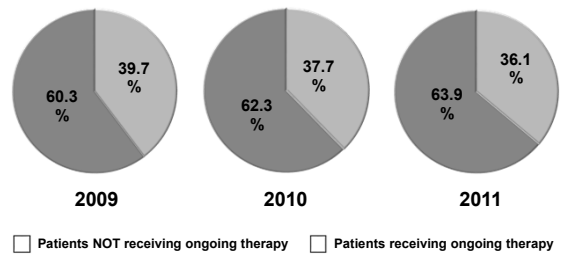
Readmission Rates Among Patients Hospitalized with HE

- Retrospective analysis of >500 US hospitals
- Adults discharged with a primary diagnosis of HE (N=8,766)

Reason for Readmission	30-day	1-year
All-cause	27.4%	56.4%
HE-related	17.6%	39.5%

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

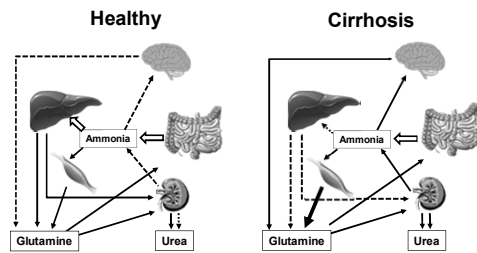
Majority of Patients with HE do not Receive Maintenance Therapy at or After Discharge



Volk ML, et al. *Am J Gastroenterol.* 2012;107(2):247-252.

Pathogenesis of HE

Role of Ammonia in HE



Morgan MY, et al. *Int J Clin Rev.* 2011;02:04.

Neurotoxic Effects of Ammonia



Impairment of amino acid metabolism and energy utilization in the brain



Alteration in the transport of amino acids, water, and electrolytes across astrocytes and neurons



Inhibition of excitatory and inhibitory postsynaptic potentials

Recognition and Diagnosis of HE



Case Study #1: Background

- 66-year-old man is brought to the hospital noticeably confused and disoriented, accompanied by his wife and son
- Social history:
 - Former smoker with 30 pack-year history
 - Retired general contractor
 - Lives with his wife
- Medical history:
 - COPD (gets very winded when walking)
 - Cirrhosis
 - HE

COPD, chronic obstructive pulmonary disease.



Case Study #1: Background and Physical Exam

- Additional clinical history provided by family
 - Incoherent late-night phone calls
 - Family often unable to communicate with him
 - Sometimes forgets where he is
 - Suffers from panic attacks
 - Fell and hit his head a few days ago (severity of the injury is unclear because he was home alone)
- Physical exam
 - Ascites
 - Edema



Case Study #1: Discussion

- What type of testing would be appropriate for further evaluation of this patient?
 - Paracentesis
 - CT scan

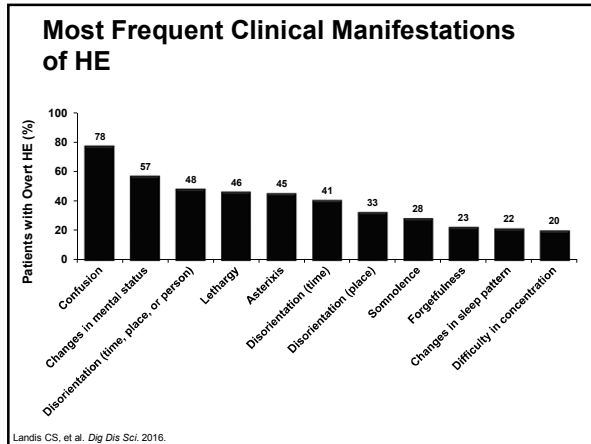
CT, computed tomography.

Approach to the Diagnosis of HE

- Diagnosis is based primarily on clinical examination
 - Disorientation and asterixis are reliable markers
 - Mild hypokinesia, psychomotor slowing, and lack of attention are easily overlooked
- The West Haven Criteria is the gold standard for staging severity
- Specific quantitative tests are not routinely recommended for practice settings*

*Recommendations about the place of quantitative testing for diagnosis continue to evolve.

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



Clinical Findings Associated with HE Classifications

ISHEN Classification	West Haven Grade	Neurologic Changes	Asterixis
Covert HE	0	None (detection requires specialized psychometric testing)	—
	1	Decreased attention span, hypersomnia/insomnia	Detectable
Overt HE	2	Lethargy, disorientation for time	Obvious
	3	Semistupor or stupor, disorientation for space	—
	4	Coma	—

ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism.
Adapted from: Sweigart JR, et al. *J Hosp Med*. 2016.

West Haven Criteria (Minimal and Grade I HE)

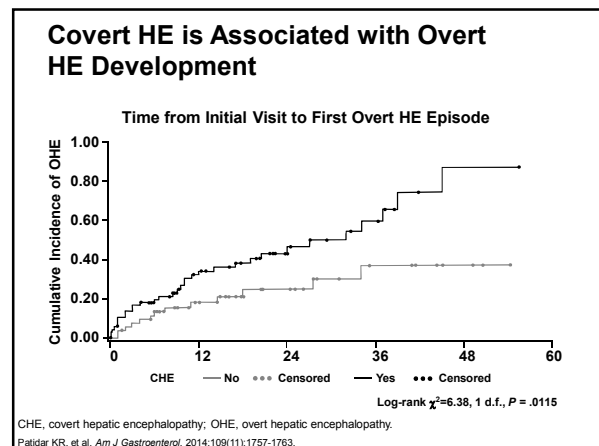
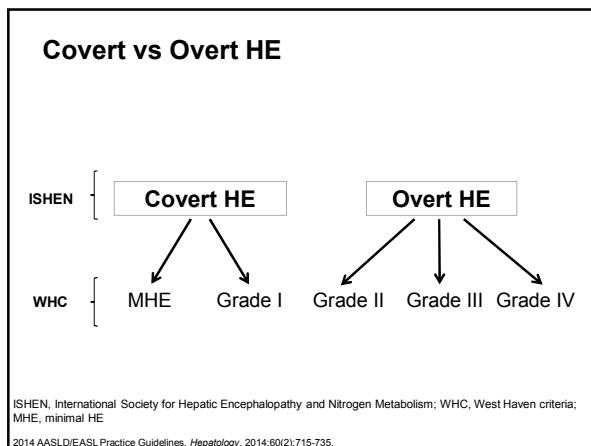
WHC	DESCRIPTION	SUGGESTED OPERATIVE CRITERIA
Unimpaired	• No encephalopathy, no HE history	• Normal test results
Minimal	• Alterations in psychomotor speed/executive functions or on neurophysiological measures • No clinical evidence of mental change	• Abnormal results on established psychometric or neurophysiological 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. 21

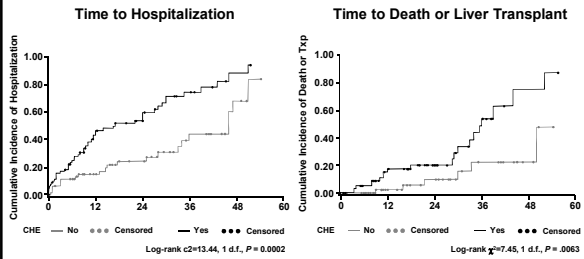
West Haven Criteria (Grades II, III, and IV HE)

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 the month, day of the 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. 22



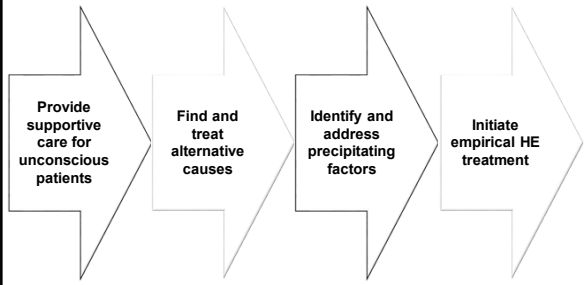
Covert HE Is Associated with Decreased Survival and Increased Risk for Hospitalization and Deaths



Txp, transplant.
Patidar KR, et al. *Am J Gastroenterol.* 2014;109(11):1757-1763.

Management of Overt HE

A Four-pronged Approach to the Management of Overt HE



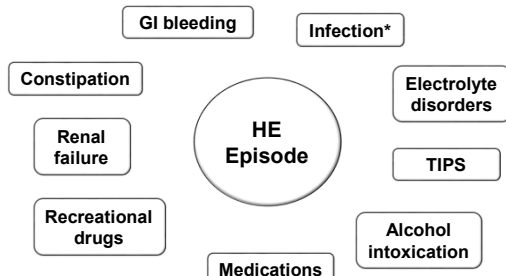
2014 AASLD/EASL Practice Guidelines. *Hepatology.* 2014;60(2):715-735.

Differential Diagnosis of HE

Overt HE or Acute Confusional State	
<ul style="list-style-type: none"> Alcohol Drugs Neuroinfections Electrolyte disorders Diabetes 	<ul style="list-style-type: none"> Nonconvulsive epilepsy Psychiatric disorders Intracranial bleeding and stroke Severe medical stress
Other Presentations	
<ul style="list-style-type: none"> Dementia Brain lesions Obstructive sleep apnea 	

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

Precipitating Factors for Overt HE



*Recent unpublished case series confirm the dominant role of infections.
GI, gastrointestinal; TIPS, transjugular intrahepatic portosystemic shunt

2014 AASLD/EASL Practice Guidelines. *Hepatology.* 2014;60(2):715-735.
Liu A, et al. *World J Hepatol.* 2015;7(29):2871-2879.

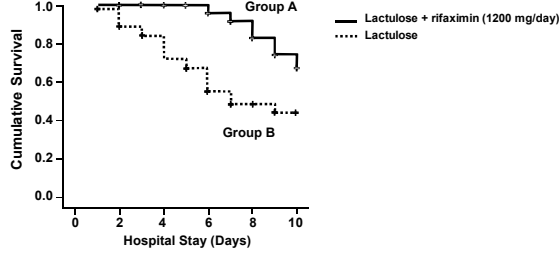
Available Treatments for HE

Pharmacologic
<ul style="list-style-type: none"> Nonabsorbable disaccharides Rifaximin (RIX)* Zinc L-ornithine-L-aspartate† BCAAs
Nonpharmacologic
<ul style="list-style-type: none"> Percutaneous embolization of large PSSs MARS‡

*Indicated for prophylaxis; †Not available in the US; ‡Primarily for research purposes.
BCAAs, branched chain amino acids; PSS, portosystemic shunt; MARS, molecular adsorbent recirculating system

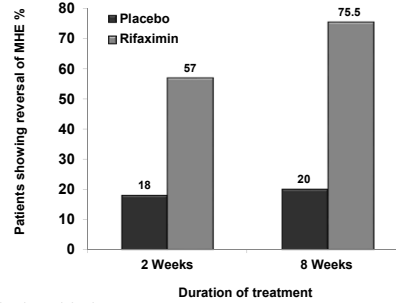
Leise MD, et al. *Mayo Clin Proc.* 2014;89(2):241-253.
Flamm SL. *Ther Adv Gastroenterol.* 2011;4(3):199-206; Lynn AM, et al. *Liver Transpl.* 2016. [epub ahead of print]

RIX Added on to Lactulose in the Treatment of Overt HE



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

Impact of RIX Treatment on Covert HE



MHE, minimal hepatic encephalopathy

Sidhu SS, et al. *Am J Gastroenterol* 2011.

Adverse Effects of Lactulose

- Aspiration
- Dehydration
- Hyponatremia
- 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.

Adverse Effects of RIX

- Peripheral edema
- Nausea
- Dizziness
- Fatigue
- Ascites
- Diarrhea
- Headache

Note: Although these AEs were reported in ≥5% patients, incidences did not differ significantly between the PBO and RIX groups ($P > .05$ for all comparisons).

PBO, placebo.

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

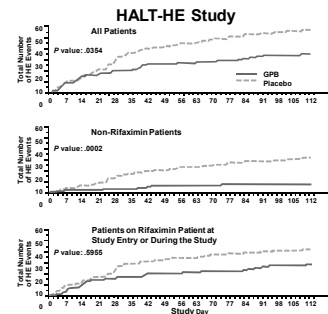
Emerging Ammonia-lowering Agents

Agent	Mechanism of action/by product
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
AST-120	• Binding of neuroactive substances (including ammonia) in the GI tract

PAGN, Phenylacetylglutamine.

Rahimi RS, et al. *Clin Liver Dis*. 2015;19(3):539-549.

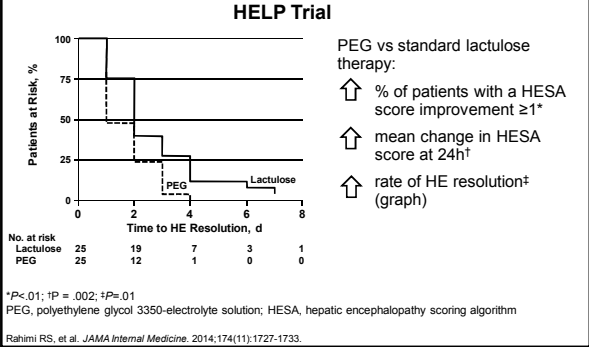
Effect of Glycerol Phenylbutyrate Treatment in Patients with HE



GPB, glycerol phenylbutyrate.

Rockey, DC et al. *Hepatology*. 2014;59(3):1073-1083.

PEG Treatment in Patients with Cirrhosis Hospitalized for HE

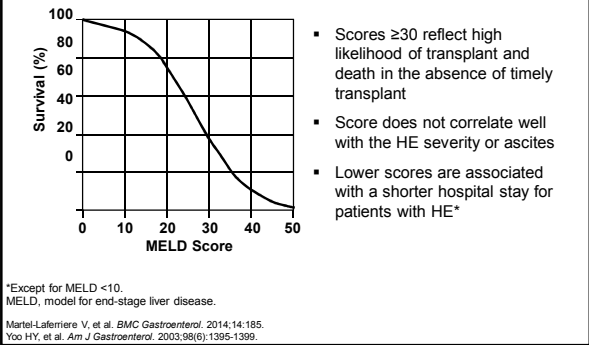


Liver Transplantation

- 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.

Significance of MELD Scoring



Child-Pugh Scoring

Measure	+1 Points	+2 Points	+3 Points
Bilirubin	<2 mg/dL	2–3 mg/dL	>3 mg/dL
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.85 g/dL
INR	<1.7	1.7–2.2	>2.2
Ascites	None	Medically controlled	Poorly controlled
Encephalopathy	None	Medically controlled	Poorly controlled

INR, international normalized ratio

Available at: <http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality/>

Secondary Prophylaxis of HE



Case Study #2: Patient Background

- 45-year-old female presents with complaints of worsening HE symptoms over the past 2 weeks
 - Increased fatigue
 - Somnolence
 - Diminished concentration and ability to communicate at work
- Medical History:
 - Chronic hepatitis C (genotype 1)
 - Previously treated for 2 OHE episodes
 - Prescribed lactulose prophylaxis on both occasions
 - Only sporadically adherent reportedly due to poor tolerance



Case Study #2: Physical Examination and Laboratory Testing

- Physical examination:
 - Lethargic
 - Asterixis
 - Ascites (confirmed by ultrasound)



Case Study #2: Discussion

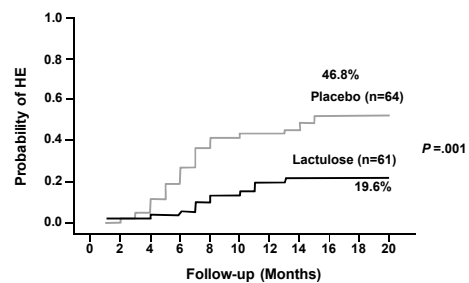
- What modification to the patient's therapeutic regimen, if any, would you recommend?
- How long should this patient be maintained on prophylactic treatment? What factors should be taken into consideration?

Summary of AASLD/EASL Guideline Recommendations for HE Prophylaxis

1. Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1)
2. Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1)
3. Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1)

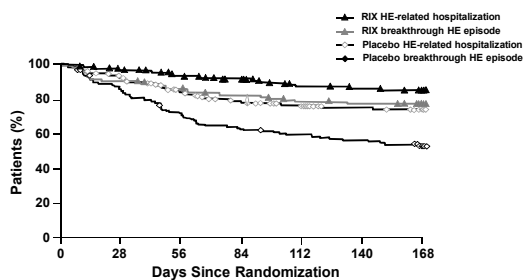
2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

Lactulose Prevents HE Recurrence in Patients with Cirrhosis



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

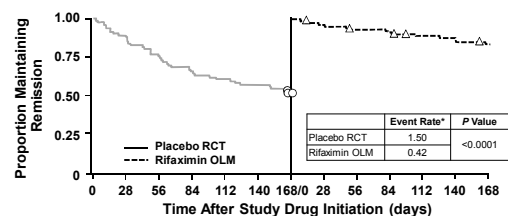
RIX vs Placebo: Time to First Breakthrough HE Episode and HE-related Hospitalization



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

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

Time to First Breakthrough HE Event During Treatment with RIX or Placebo



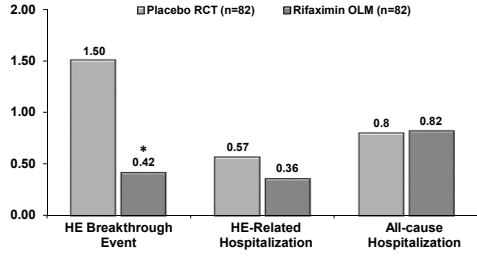
Patients at risk
Placebo RCT: 82, 72, 62, 54, 50, 47, 33
Rifaximin OLM: 82, 78, 75, 73, 69, 66, 63

*Event rate was calculated for 168 days of the RCT and the first 168 days in the OLM study.

OLM, open-label maintenance; RCT, randomized placebo-controlled trial.

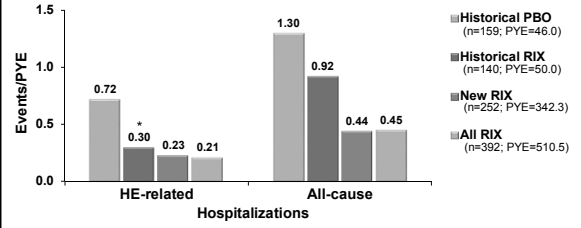
Bajaj JS, et al. *Alimentary Pharmacology & Therapeutics*. 2015;41(1):39-45.

Treatment with RIX Decreases the Rate of HE Breakthrough Episodes



*P < .0001 vs placebo.
Bajaj JS, et al. *Aliment Pharmacol & Ther.* 2015;41(1):39-45.

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 placebo.
PYE, person-years of exposure; bid, twice a day.
Mullen KD, et al. *Clin Gastroenterol Hepatol.* 2014;12(8):1390-1397.e1392.

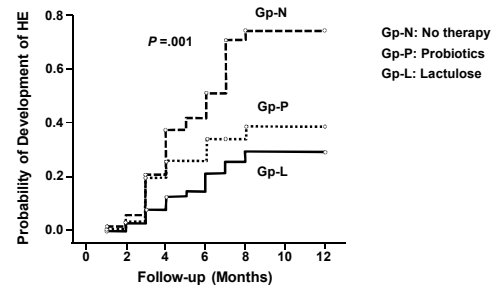
RIX Treatment Improves HRQOL in Cirrhotic Patients with HE

Domain	P Value
Fatigue	.0087
Abdominal symptoms	.0090
Systemic symptoms	.0160
Activity	.0022
Emotional function	.0065
Worry	.0436
Overall	.0093

LS Mean Difference and 95% CI

LS, least squares; CI, confidence interval.
Sanyal A, et al. *Aliment Pharmacol Ther.* 2011;34(8):853-861.

Comparison of Lactulose and Probiotics Vs Placebo for the Prevention of HE Recurrence



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



Case Study #2: Management

- Medications prescribed:
 - Rifaximin 550 mg bid
- Patient education:
 - Critical importance of medication adherence
 - Recognition of symptom onset
 - Precipitating factors
 - Nutritional guidance
 - Family/caregiver involvement

Nutritional Considerations for HE Management

ISHEN/AASLD/EASL 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.

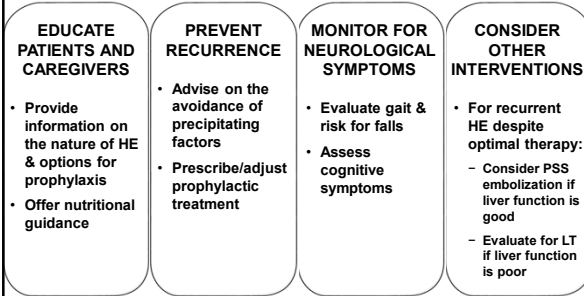
2013 ISHEN Consensus Statement. *Hepatology*. 2013;58(1):325-336.
2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.

ISHEN Recommendations: Fiber and Micronutrient Provision

	Recommendations
Prebiotics	<ul style="list-style-type: none"> • 25 g to 45 g of fiber daily
Micronutrients	<ul style="list-style-type: none"> • 2-week multivitamin course for decompensated cirrhosis or 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.

Action Plan for Long-term HE Management



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

Summary

- HE is a major neurological complication of liver disease that imposes a significant health and economic burden on patients, families, and caregivers
- Management goals include active treatment of acute episodes, prevention of recurrence, and evaluation for surgical intervention
- Several available agents have shown good efficacy when administered as acute treatment or secondary prophylactic therapy
- Appropriate therapy, patient education, and guidance can prevent unnecessary recurrence and hospitalization, and improve overall patient outcomes

Thank You!

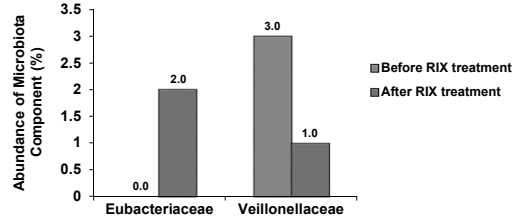
Backup Slides

Common Clinical Manifestations of HE by WHC Class

WHC 1		WHC 2		WHC 3		WHC 4	
Symptom	%	Symptom	%	Symptom	%	Symptom	%
Lethargy	46	Confusion	72	Confusion	89	Coma	100
Confusion	44	Asterixis	59	Disorientation to Time	74	Change in mental state	100
Difficulty in concentration	44	Lethargy	54	Disorientation to time, place, person	74	Lethargy	75
Forgetfulness	44	Change in mental status	48	Change in mental status	68	Somnolence	75
Asterixis	38	Disorientation to time, place,	46	Disorientation to place	53	Confusion	75
Changes in mental status	31	Changes in sleep pattern	37	Disorientation to person	42	Disorientation to time	50

WHC, West Haven Criteria.
Landis CS, et al. *Dig Dis Sci*. 2016.

Microbiota Changes Associated with RIX Therapy

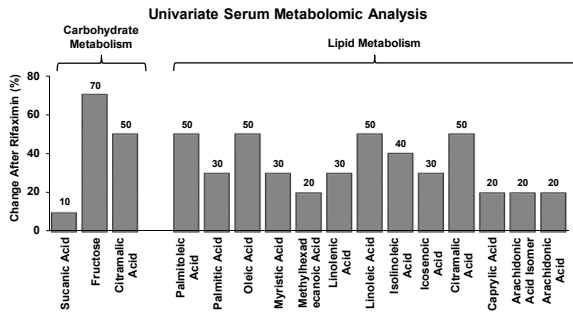


A significant decrease in *Veillonellaceae* and increase in *Eubacteriaceae* abundance were observed after RIX therapy.*

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

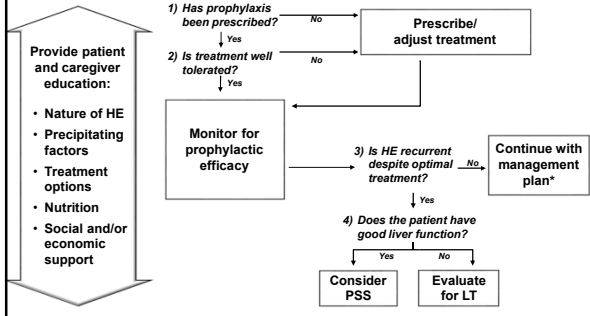
Bajaj JS, et al. *PLoS One*. 2013;8(4):e60042.

Fatty Acids and Intermediates of Carbohydrate Metabolism Are Increased Following RIX Therapy



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

Algorithm for Disease Management Following an Episode of HE



*Under circumstances where the precipitating factors have been well controlled (ie, infections and variceal bleeding) or liver function or nutritional status improved, prophylactic therapy may be discontinued.
2014 AASLD/EASL Practice Guidelines. *Hepatology*. 2014;60(2):715-735.