Hepatic Encephalopathy: An Update on Diagnosis and Management

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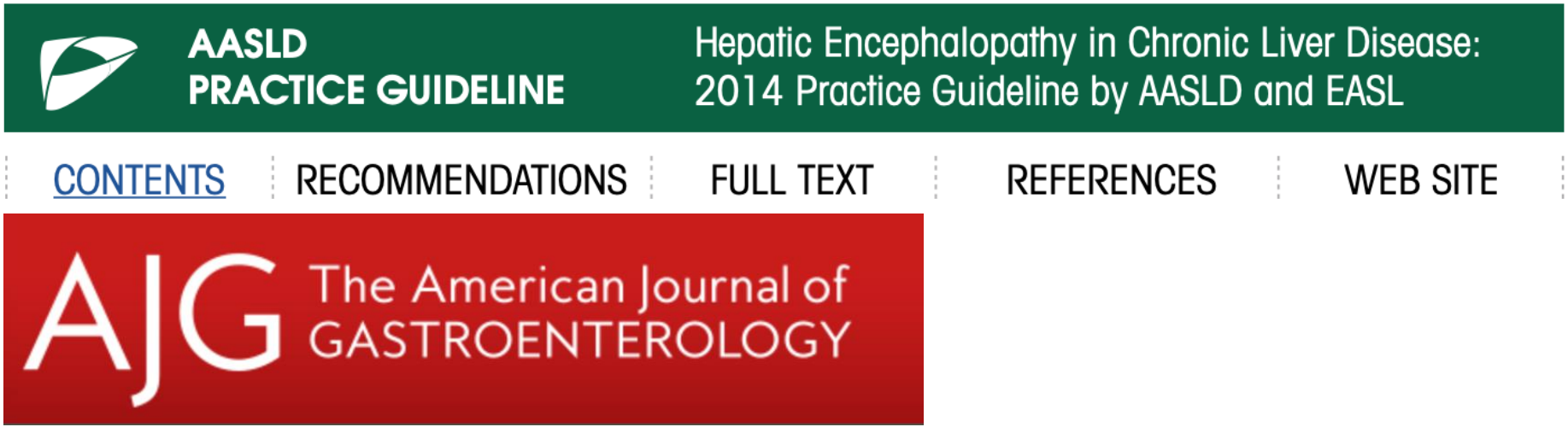
Disclosures

- Advisory: AbbVie, Gilead, Arbutus, Salix, Intercept
- Research: AbbVie, Gilead

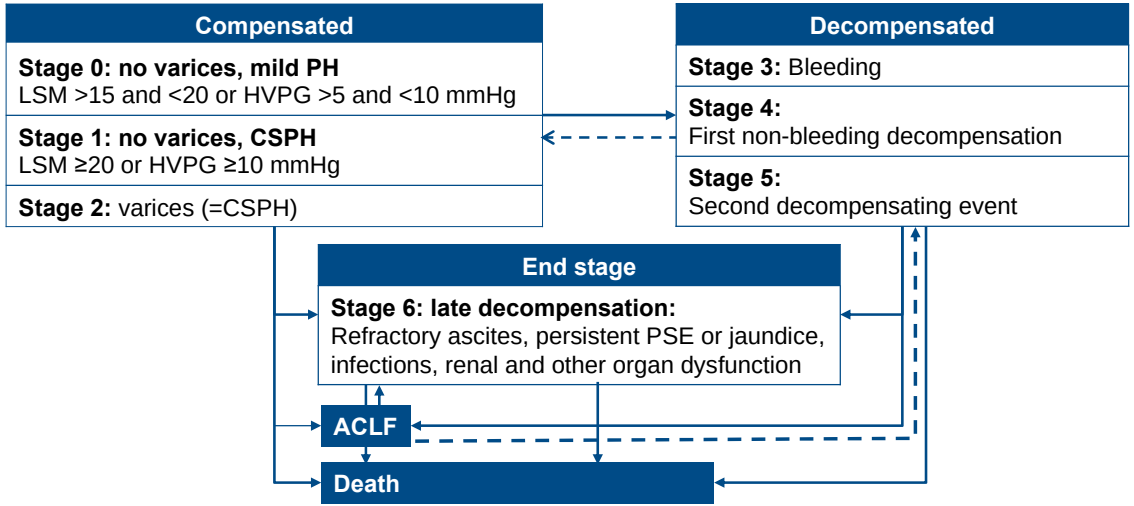
Guidelines – FREE!



Acharya, Chathur1; Bajaj, Jasmohan S.1 Current Management of Hepatic Encephalopathy, American Journal of Gastroenterology: November 2018 - Volume 113 - Issue 11 - p 1600-1612. doi: 10.1038/s41395-018-0179-4;
https://www.aasld.org/sites/default/files/2019-06/141022_AASLD_Guideline_Encephalopathy_4UFd_2015.pdf.

Multi-Stage Model for the Clinical Course of Cirrhosis

- Transition from compensated cirrhosis to DC occurs at a rate of ~5-7% per year
- DC is a systemic disease, with multi-organ/system dysfunction



D'Amico G, et al. *J Helpatol.* 2018;68:563-76; EASL CPG decompensated cirrhosis. *J Hepatol*. 2018;doi: 10.1016/j.jhep.2018.03.024.

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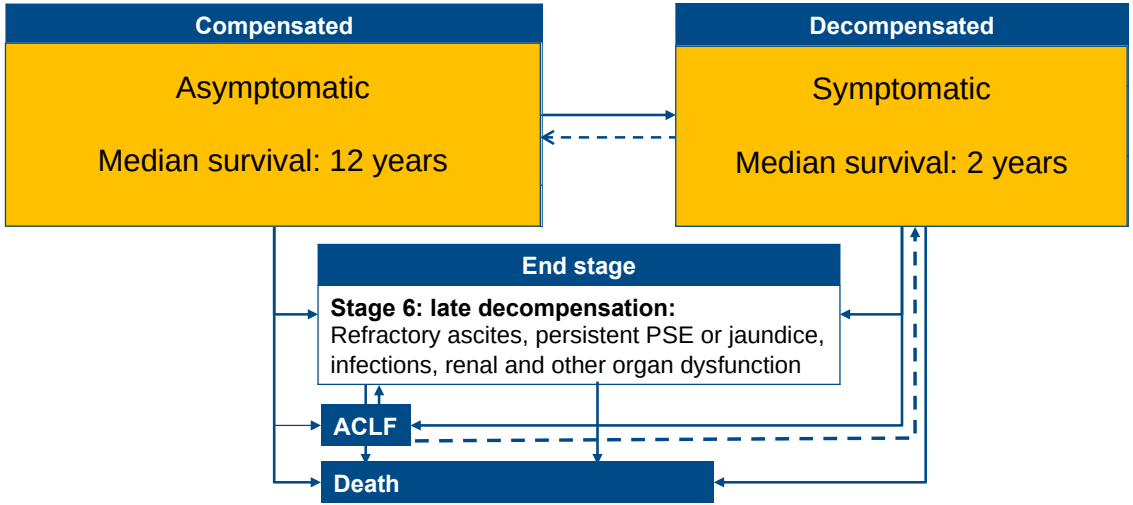
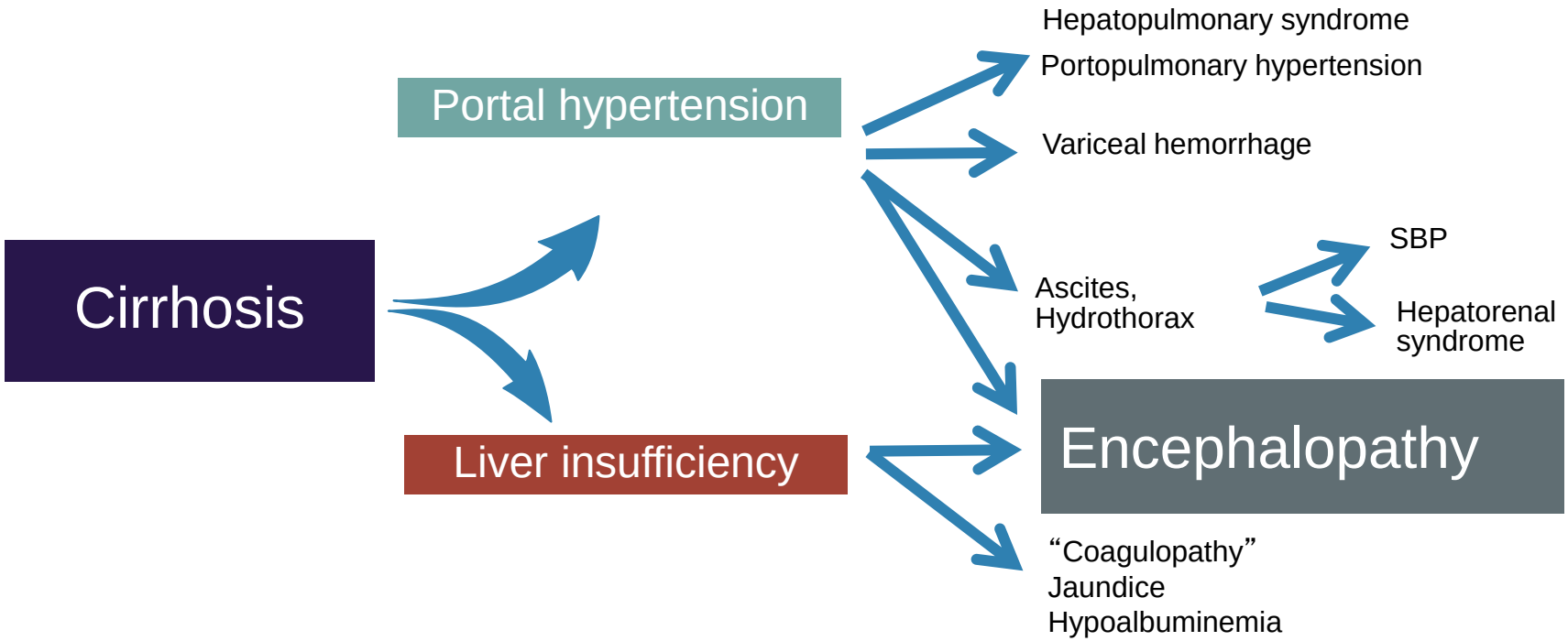
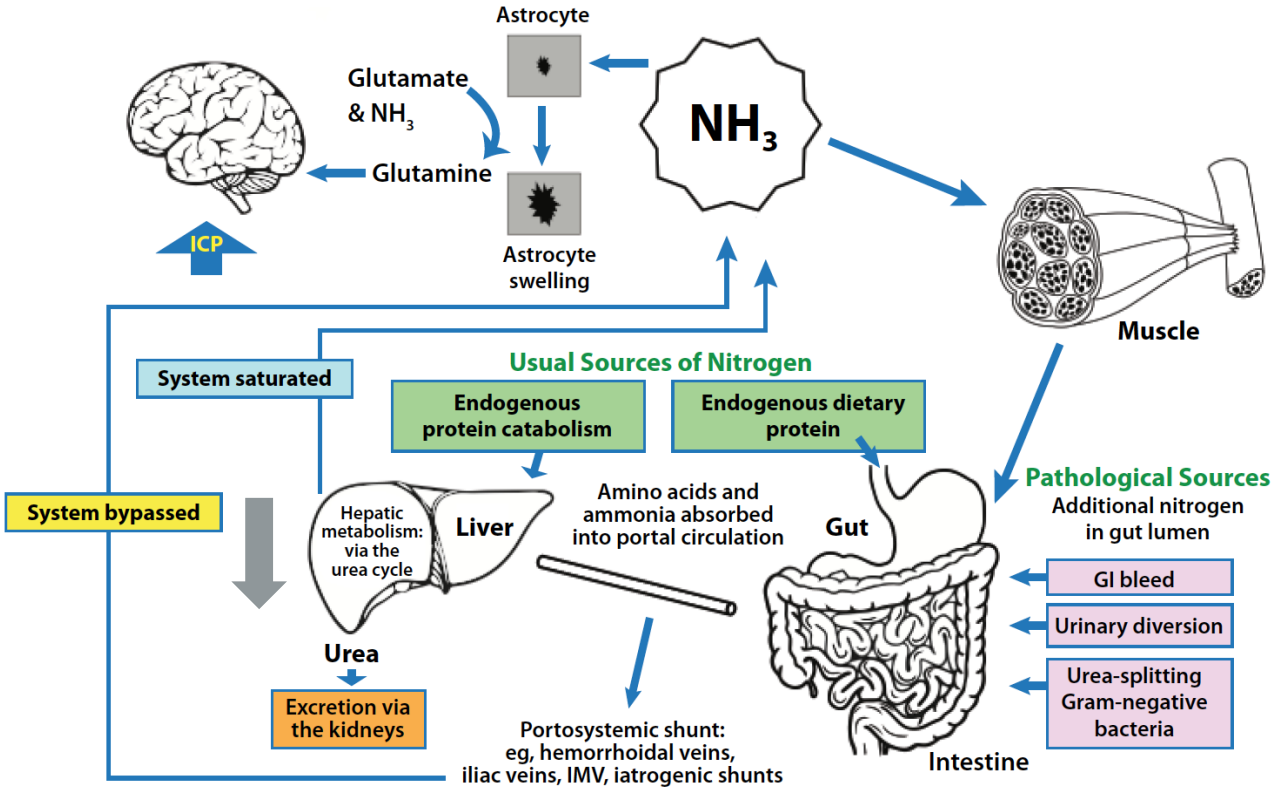


D'Amico G, et al. *J Helpatol.* 2018;68:563-76; EASL CPG decompensated cirrhosis. *J Hepatol*. 2018;doi: 10.1016/j.jhep.2018.03.024.

Complications of Cirrhosis



Impact Prognosis


Astrocyte
Glutamate & NH_3
Glutamine
ICP
Astrocyte swelling
NH_3
Muscle
System saturated
Usual Sources of Nitrogen
Endogenous protein catabolism
Endogenous dietary protein
System bypassed
Hepatic metabolism: via the urea cycle
Liver
Amino acids and ammonia absorbed into portal circulation
Gut
Pathological Sources
Additional nitrogen in gut lumen
GI bleed
Urinary diversion
Urea-splitting Gram-negative bacteria
Urea
Excretion via the kidneys
Portosystemic shunt: eg, hemorrhoidal veins, iliac veins, IMV, iatrogenic shunts
Intestine

Primary Prophylaxis

- Nutritional management of patients with cirrhosis
  - No evidence that restricting dietary protein will prevent episodes of OHE
- Sarcopenia is associated with HE
  - Improve nutritional status and muscle mass with a high-protein diet and a before-bed-time high-protein snack

Conditions That Increase Ammonia Production or Decrease its Elimination

Table 1. Conditions That Either Increase Ammonia Production or Decrease its Elimination

Conditions That Increase Ammonia Production
• Multiple myeloma
• Chemotherapy
• Bone marrow transplant: idiopathic hyperammonemia
• Urea-producing bacteria: *Proteus mirabilis, Escherichia coli, Klebsiella* species, *Providencia rettgeri, Helicobacter pylori*
• Increased protein metabolism: seizures, exercise, starvation, total parenteral nutrition, gastrointestinal bleeding

Adapted from Laish I, Ben Ari Z. *Liver Int.* 2011;31(9):1259-1270.[21]

Conditions That Decrease Ammonia Elimination
• Organic acidurias
• Urea-cycle disorders
• Dibasic aminoaciduria
• Impaired fatty acid oxidation
• Pyruvate metabolism errors
• Congenital portosystemic shunts
• Medications: valproic acid, glycine, ribavirin, carbamazepine, 5-fluorouracil, cyclophosphamide, salicylates
• Portosystemic shunts (eg, vascular malformations in Osler-Weber-Rendu disease)

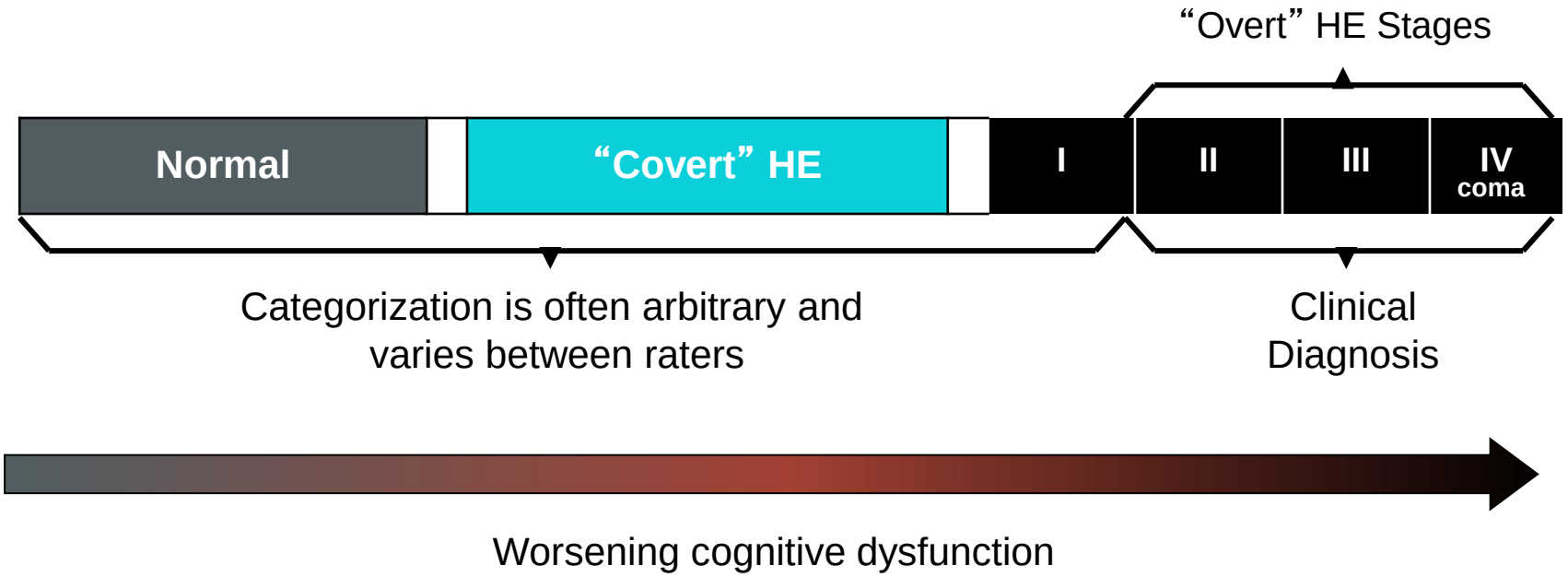
Adapted from Laish I, Ben Ari Z. *Liver Int.* 2011;31(9):1259-1270.[21]

consequences, and enable preventive strategies. The purpose of this article

Diagnosis

1. **Recognize patients at risk- the diagnosis is <u>clinical</u>**
2. **Exclude alternative etiologies**
   - Biochemical studies and imaging to EXCLUDE
   - Consider cerebral imaging
3. **Gauge response to therapy**
   - Grade encephalopathy

Characterization of HE Stages



Bajaj JS, et al. *Hepatology*. 2009;50:2014-2021.

Clinical Classification of HE

<table>
<tr><th>Type</th><th colspan="2">Grade</th><th>Time Course</th><th>Spontaeous or Precipitated</th></tr>
<tr><td rowspan="2">A</td><td>MHE</td><td rowspan="2">Covert</td><td>Episodic</td><td rowspan="2">Spontaeous</td></tr>
<tr><td rowspan="2">B</td><td>1</td><td rowspan="2">Recurrent</td></tr>
<tr><td>2</td><td rowspan="3">Overt</td><td rowspan="3">Precipitated (specify)</td></tr>
<tr><td>3</td><td rowspan="2">C</td><td rowspan="2">Persistent</td></tr>
<tr><td>4</td></tr>
</table>

- Hepatic encephalopathy should be classified according to the type of underlying disease, severity of manifestations, time course, and precipitating factors (GRADE III, A, 1).

Neurologic Manifestations

Common
Confusion → coma
Asterixis
Loss of fine motor skills
hyperreflexia
Less Common
Babinski sign
Slow, monotonous speech
Extrapyramidal-type movement
Clonus
Decerebrate posturing
Decorticate posturing
Hyperventilation
Seizures

Conditions That Mimic or Precipitate OHE

Conditions that can mimic OHE
Delirium
CVA/Hemorrhage
Uremia

Precipitating Factors of OHE
Gastrointestinal bleeding
Infection: UTI, SBP, bacteremia
Medications: alcohol, narcotics, benzodiazepines, sedatives
Electrolyte abnormalities: Sodium, glucose
Renal Failure
Dehydration or Constipation
Dietary
Medication Nonadherence

Review the Med List!

- Management of HE should begin with non-pharmacological strategies before an official diagnosis.
  - Eliminate or reduce opioids, sedatives, sleep aids, psychoactive medications, and anticholinergic medications prescribed for unclear reasons.
  - Discontinuation should be done in consultation with the prescribing provider to prevent rebound phenomena that could alter mentation.

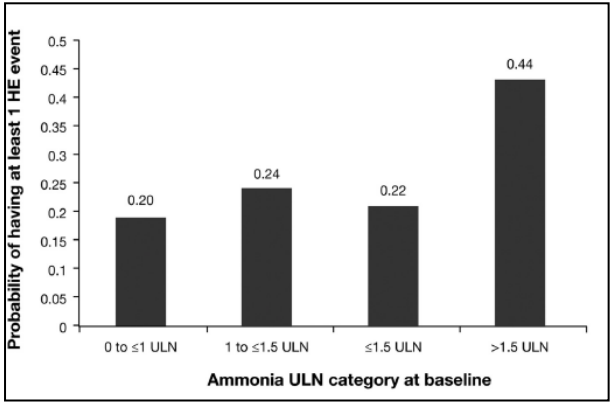
Role of Ammonia Testing in HE

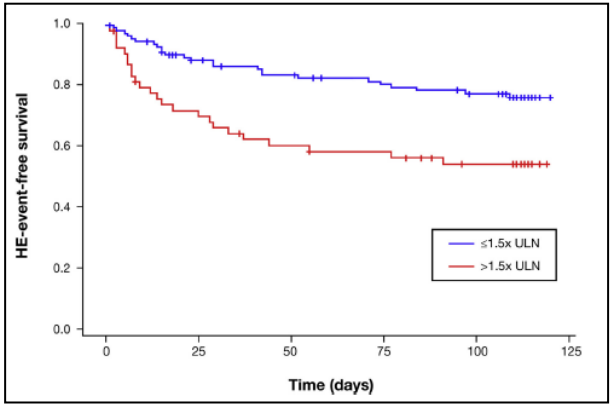
- Insufficient for diagnosis
  - Normal in 10% with OHE
  - Elevated in 70% without clinical OHE
- “Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)”
- → Order when confusion regarding etiology of confusion

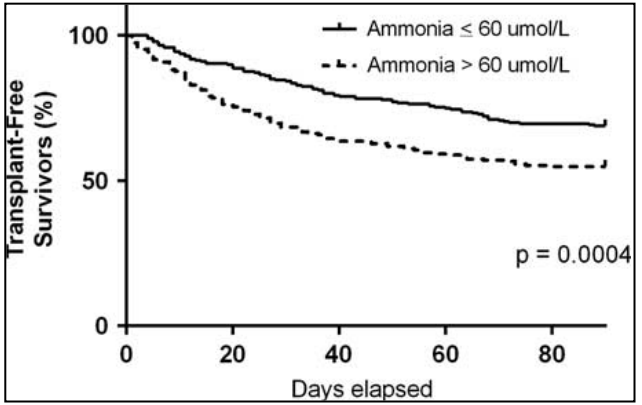
Vilstrup H et al. *Hepatology*. 2014;60:715-35.

Hyperammonemia Is Associated With Clinical Events

Fasting Blood Ammonia Predicts Risk and Frequency of Hepatic Encephalopathy Episodes in Patients With Cirrhosis



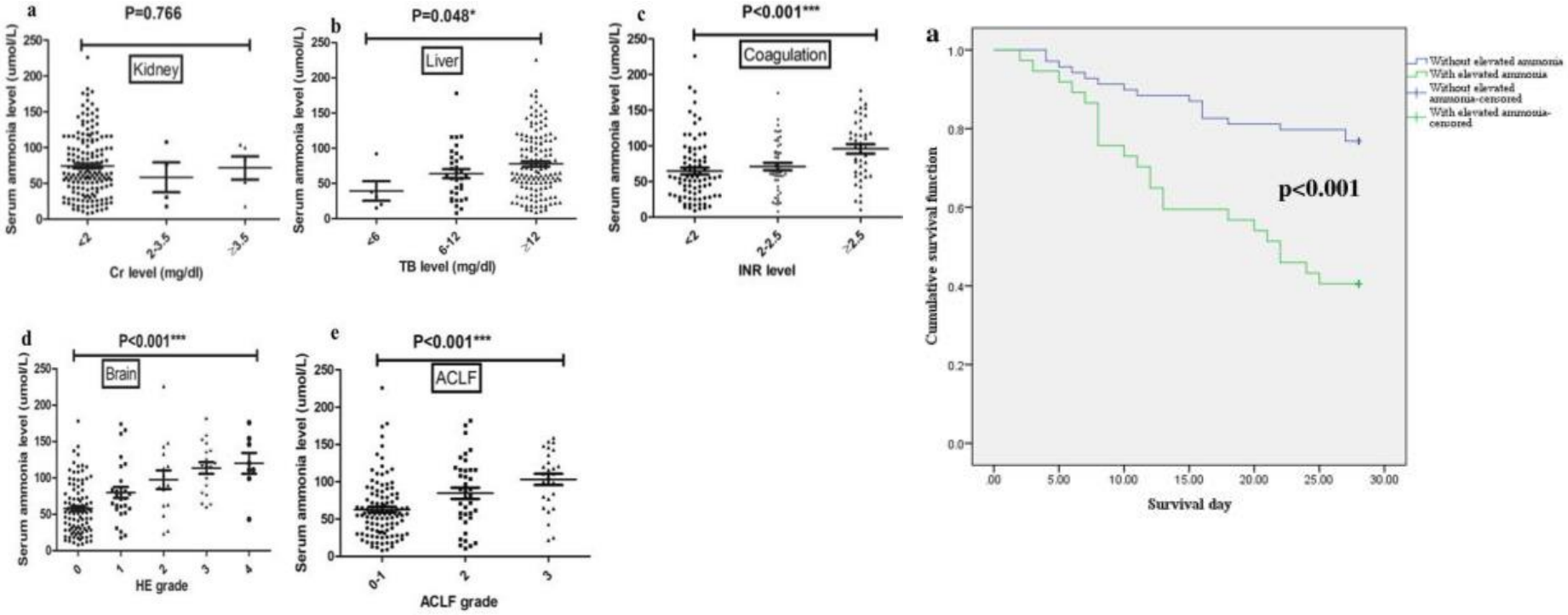




Admission Serum Ammonia Associated With 90 day Transplant-free Survival in Hospitalized Patients With Acutely Decompensated Cirrhosis

Patwardhan. *J Clin Gastroenterol*. 2016; Vierling. *Clin Gastroenterol. Hepatol*. 2016.

Serum Ammonia Is a Strong Prognostic Factor for Patients With Acute-on-Chronic Liver Failure



Hu. *Sci Rep*. 2020; 10: 16970.

Specific Approach to Overt HE Treatment

Four-pronged approach to management of HE (GRADE II-2, A, 1)

1. Initiation of care for patients with altered consciousness
2. Alternative causes of AMS should be sought and treated
3. Identification of precipitating factors and their correction
4. Commencement of empirical HE treatment

Vilstrup H et al. *Hepatology*. 2014;60:715-35.

Management of Overt HE (OHE)

First-Line Therapy

- Lactulose is the first choice for treatment of episodic OHE (GRADE II-1, B, 1)
- Rifaximin: consider if lactulose isn't effective

Second-Line Therapy: alternative or additional agents

- Oral BCAAs (GRADE I, B, 2).
- IV LOLA (GRADE I, B, 2).
- Neomycin (GRADE II-1, B, 2)
- Metronidazole (GRADE II-3, B, 2)

AASLD Practice Guideline, 2014.

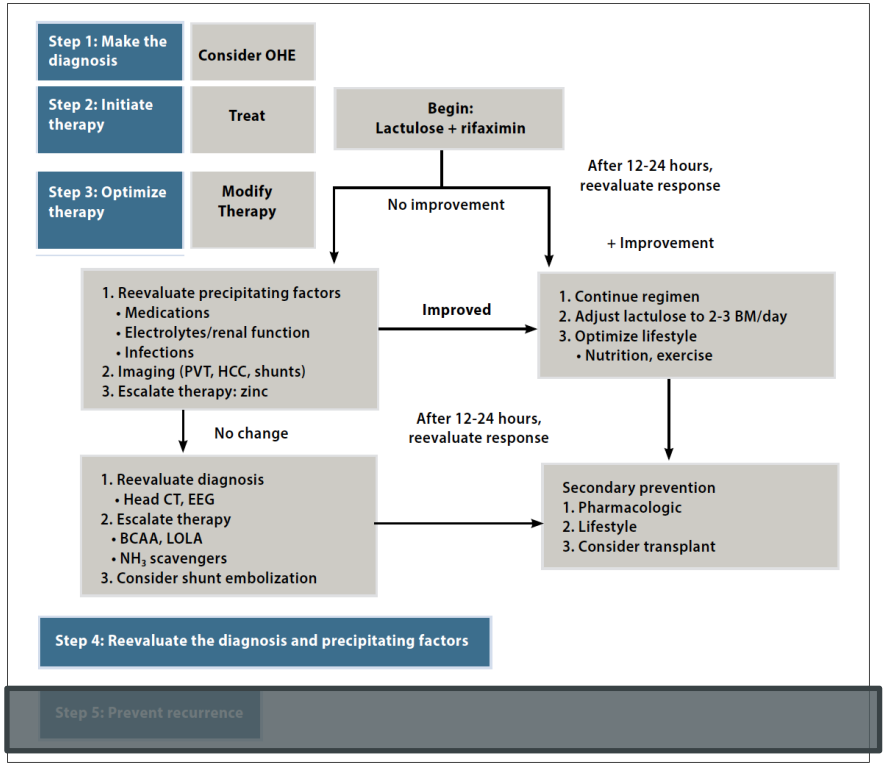
Management of Hepatic Encephalopathy

Drug	Dose	Undesirable effects
First-line therapy for acute episodic OHE in the United States		
Lactulose	20 g/30 ml—30 g/45 ml 3–4 per day titrated for 2–3 bowel movements a day orally. If unable to administer orally, use a similar dose via NG or 300 ml of enemas 3–4 per day till clinical improvement is noted.	Diarrhea, flatulence, and bloating. Unpleasant taste
Second-line therapy for acute episodic OHE in the United States (intolerant to lactulose)		
Rifaximin	400–550 mg PO twice daily indefinitely	No major side effects
Third-line (not approved by FDA) therapy for acute episodic OHE		
PEG	4 l of PO or via NG tube × 1 single dose (in lieu of lactulose)	None clinically in short-term use

List of current pharmacological options for management of OHE.

Current Management of Hepatic Encephalopathy Acharya, Chathur; Bajaj, Jasmohan S. *Official journal of the American College of Gastroenterology*. ACG113(11):1600-1612, November 2018.doi: 10.1038/s41395-018-0179-4.

Lactulose:
20-30g QID- titrate to 2/3 BM
Enema: 300 mL (200g) in 1L



Reau. *Gastroenterology & Hepatology.* Volume 12, Issue 12, Supplement 5 December 2016.

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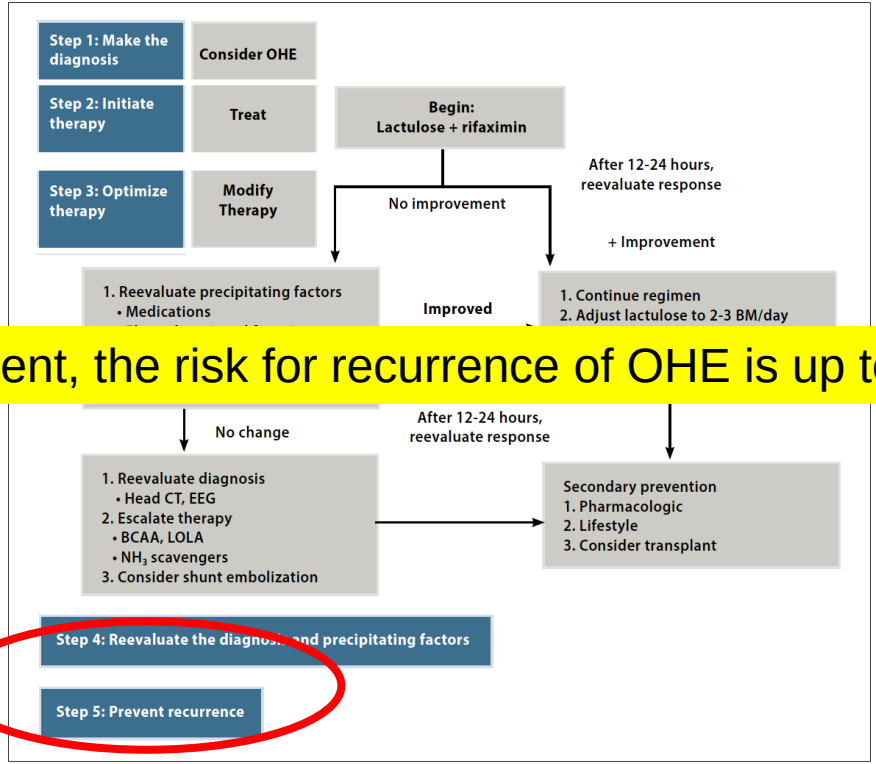


Despite optimal treatment, the risk for recurrence of OHE is up to 40% within a month

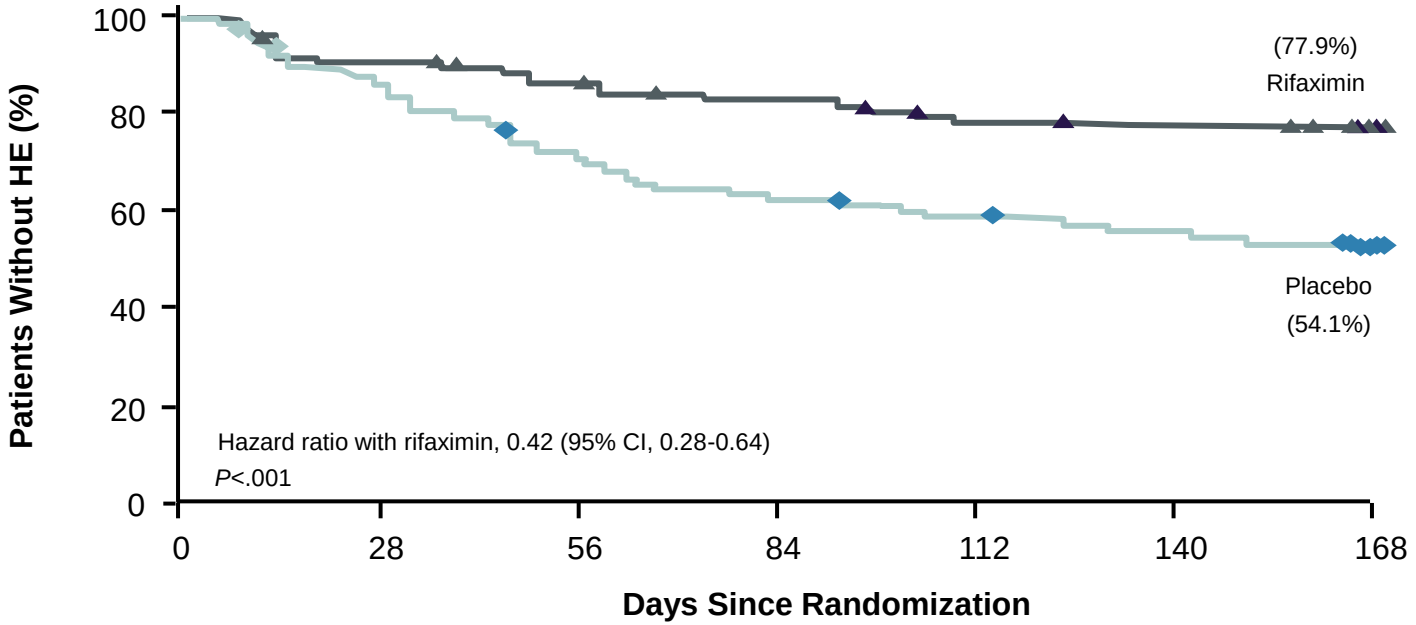
Reau. *Gastroenterology & Hepatology.* Volume 12, Issue 12, Supplement 5 December 2016.

Secondary Prevention of Overt HE (OHE)

- Lactulose after the initial episode (GRADE II-1, A, 1)
- Rifaximin as an add-on to lactulose after the second episode (GRADE I, A, 1)
- If the precipitating factors have been well controlled (i.e., infections and VB) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2)

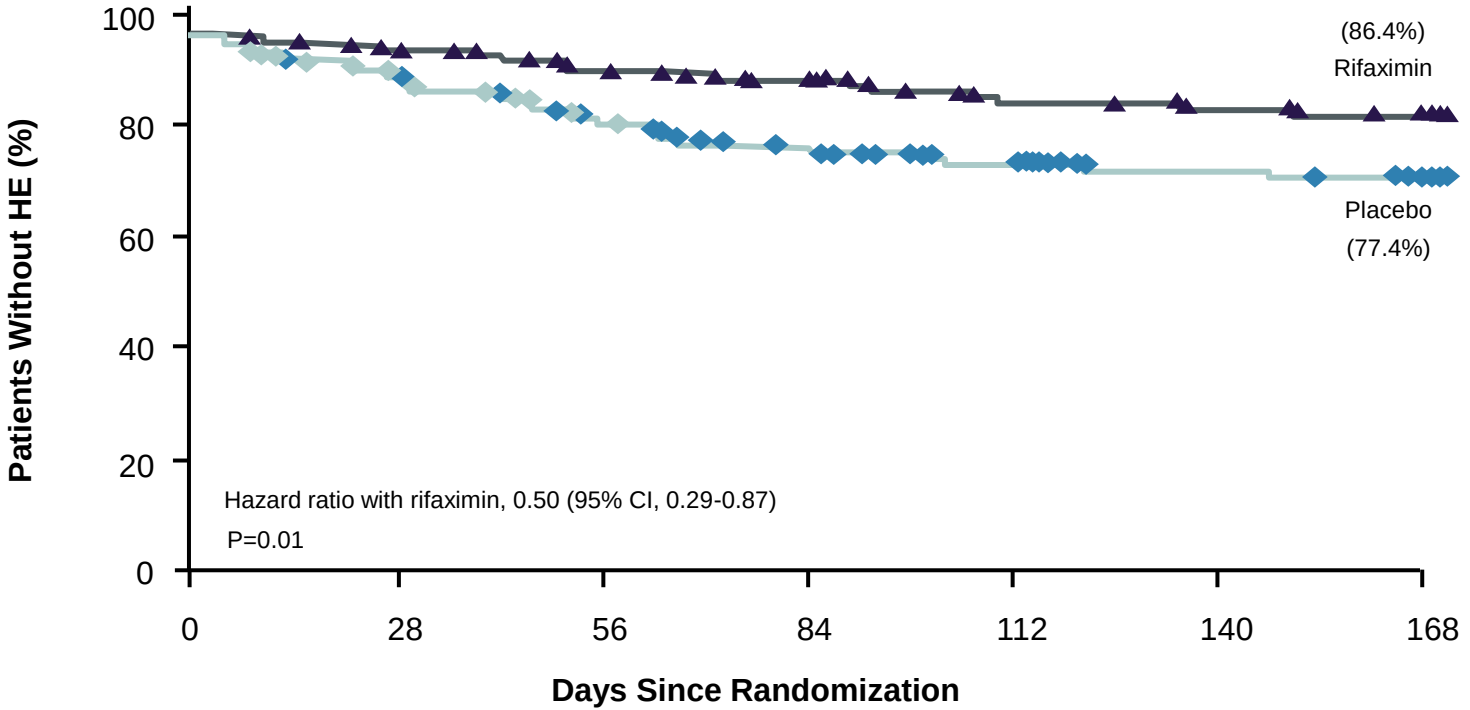
AASLD Practice Guideline. 2014.

Rifaximin Treatment in OHE: Time to First Breakthrough Episode (Primary End Point)



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

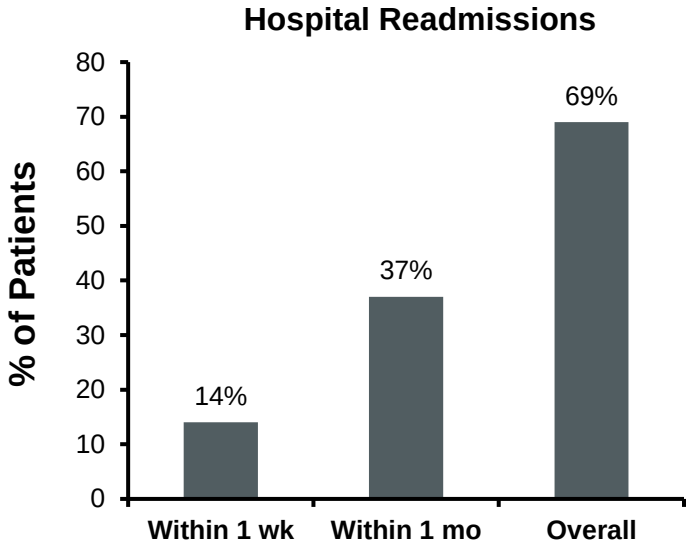
Rifaximin Treatment in OHE: Time to First HE-Related Hospitalization (Secondary Endpoint)



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

Hospital Readmissions Common With Cirrhosis

- Single center retrospective study
  - N=402 with a median follow-up 203 days
- Cirrhosis with ascites, SBP, renal failure, hepatic encephalopathy, or variceal hemorrhage
- Median time to readmission was 67 days
- Median number of readmissions was 2
  - Range 0-40
  - Overall rate was 3 hospitalizations/person-year



Driven by HE and volume overload

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

Prevention of Hepatic Encephalopathy

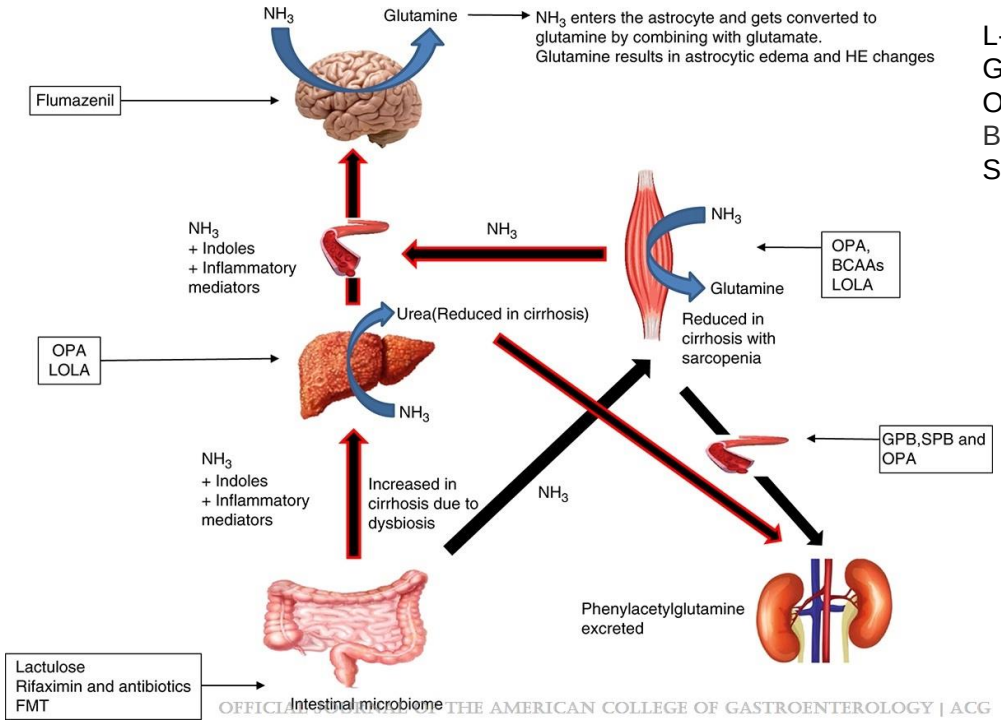
First-line therapy for prevention of recurrent OHE in the United States		
Lactulose	20 g/30 ml—30 g/45 ml 3–4 per day titrated for 2–3 bowel movements a day orally for low grades or use 300 ml of 3–4 per day enemas till clinical improvement is noted.	Diarrhea, flatulence, and bloating. Unpleasant taste
Rifaximin	400–550 mg PO twice daily in conjunction with lactulose or as monotherapy for lactulose-intolerant patients.	No major side effects
Experimental (not approved by FDA) therapy for secondary prophylaxis of OHE		
Probiotics	Dose dependent on the type of mixture used	No major side effects
FMT	One small open-label randomized clinical trial	Bloating and diarrhea

PEG polyethylene glycol, *LOLA* L-Ornithine L-Aspartate, *BCAA* branched-chain amino acids, *GPB* glycerol phenylbutyrate, *FMT* fecal microbiota transplant

List of current pharmacological options for management of OHE.

Current Management of Hepatic Encephalopathy Acharya, Chathur; Bajaj, Jasmohan S. *Official journal of the American College of Gastroenterology*. ACG113(11):1600-1612, November 2018.doi: 10.1038/s41395-018-0179-4.

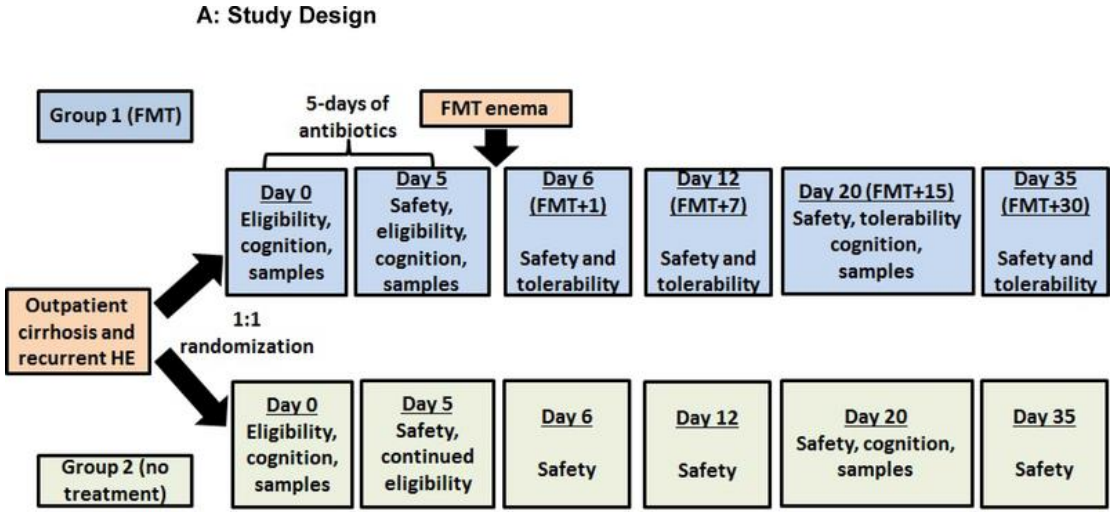
Areas of Action for Different Therapies in Cirrhosis and HE

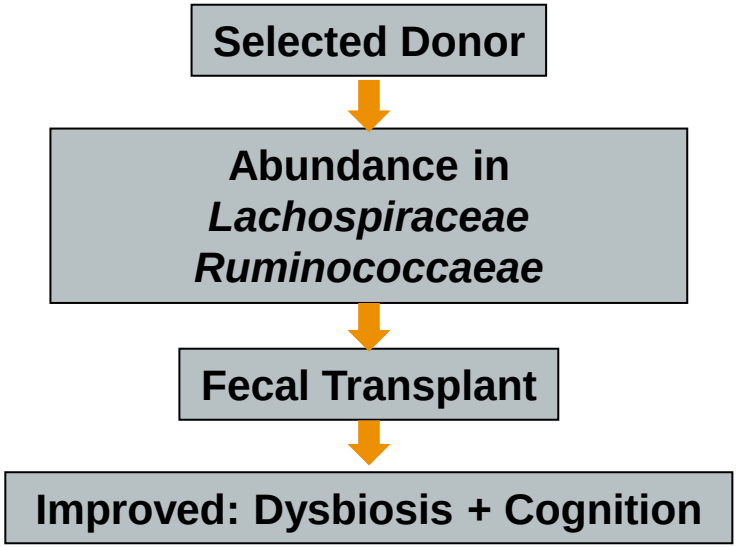


L-Ornithine L-Aspartate (LOLA)
Glycerol phenylbutyrate (GPB)
Ornithine phenylacetate (OPA)
Branched-chain amino acids (BCAAs)
Sodium Phenylacetate (SPB)

Acharya, Chathur; Bajaj, Jasmohan S. *ACG*. 113(11):1600-1612, November 2018. doi: 10.1038/s41395-018-0179-4.

FMT for HE





Bajaj et al. *Hepatology*. 2017.

HRQoL Affected by HE

- Disrupt sense of well-being:
  - Frequent falls
  - Impaired cognition
  - Depression
  - Poor sleep patterns
- Impact employment
- Limit personal autonomy
  - Especially driving capacity
- Significant care give burden

Driving and HE

- CHE and OHE - higher risk of traffic accidents
  - Most CHE patients are safe drivers
  - CHE does not predict the inability to drive a motor vehicle
- Medicolegal:
  - Not mandatory in the United States (in any state) to report a driving impairment related to a diagnosis of CHE to the DMV
  - Hx MVA: official evaluation by the state's department of motor vehicles. At the very least, these patients should avoid driving long distances, driving at night, and use GPS technology to prevent navigation errors
- Recent (<3 months) or current OHE does qualify as a reportable “lapses in consciousness” diagnosis that requires reporting, (some states mandatory)
- Counsel patients and caregivers about the risks and document

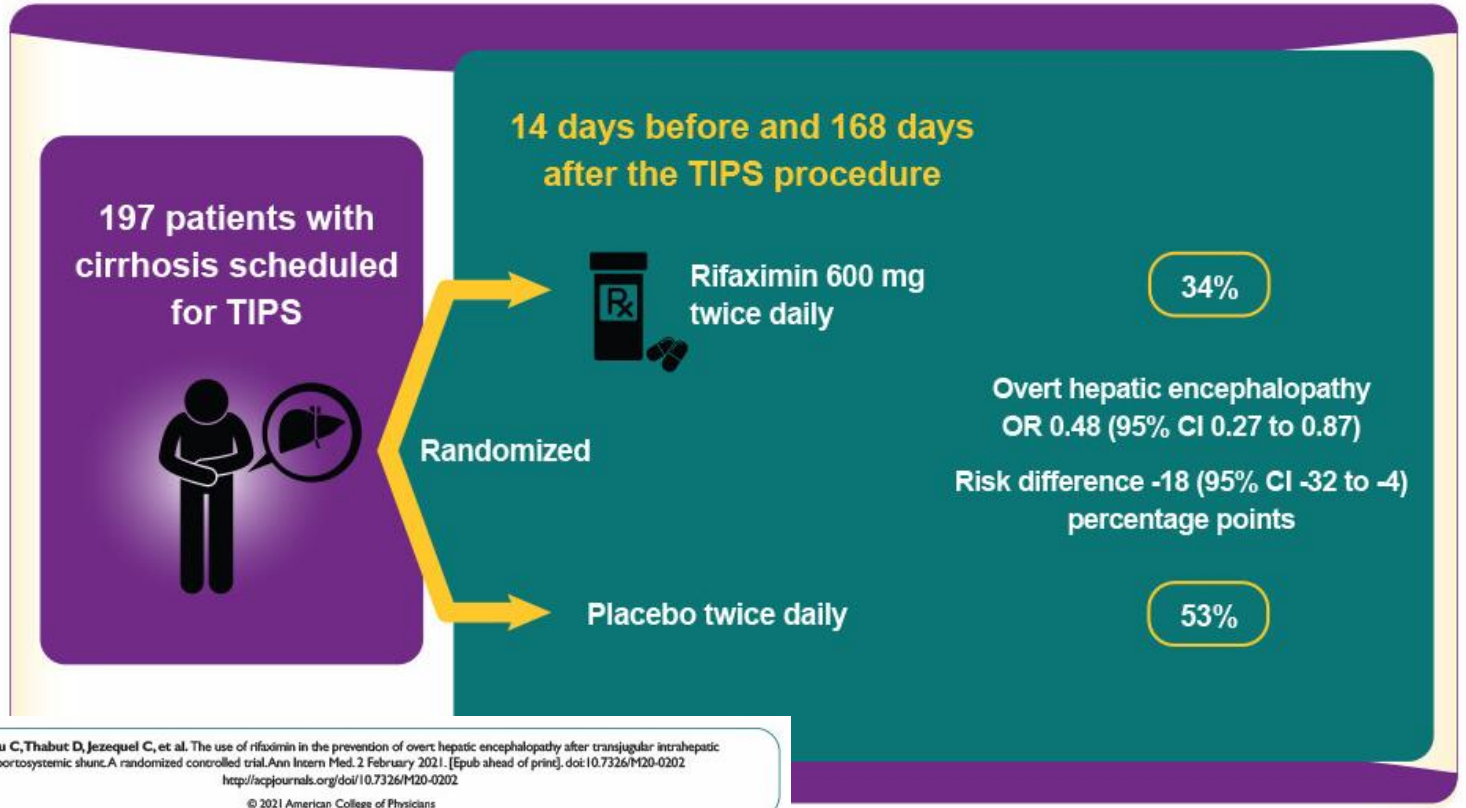
Acharya, Chathur; Bajaj, Jasmohan S. *ACG*. 113(11):1600-1612, November 2018. doi: 10.1038/s41395-018-0179-4.

TIPS and HE

- 30-55% develop HE
  - Risk factors
    - Older age (>65 years)
    - Previous HE
    - Child-Pugh score of ≥10
    - Possibly CHE
- ⇣ Portosystemic gradient ≤5 mmHg may increase refractory HE
- Prophylactic therapy does not decrease incidence of OHE
  - Prophylactic therapy (lactulose or rifaximin) is **not** recommended for prevention of post-TIPS HE (GRADE III, B, 1)

Practice Guideline.

Does Rifaximin Reduce Hepatic Encephalopathy After Transjugular Intrahepatic Portosystemic Shunt (TIPS) Compared With Placebo?



Annals of Internal Medicine

Bureau C, Thabut D, Jezequel C, et al. The use of rifaximin in the prevention of overt hepatic encephalopathy after transjugular intrahepatic portosystemic shunt: A randomized controlled trial. Ann Intern Med. 2 February 2021. [Epub ahead of print]. doi: 10.7326/M20-0202
http://acpjournals.org/doi/10.7326/M20-0202

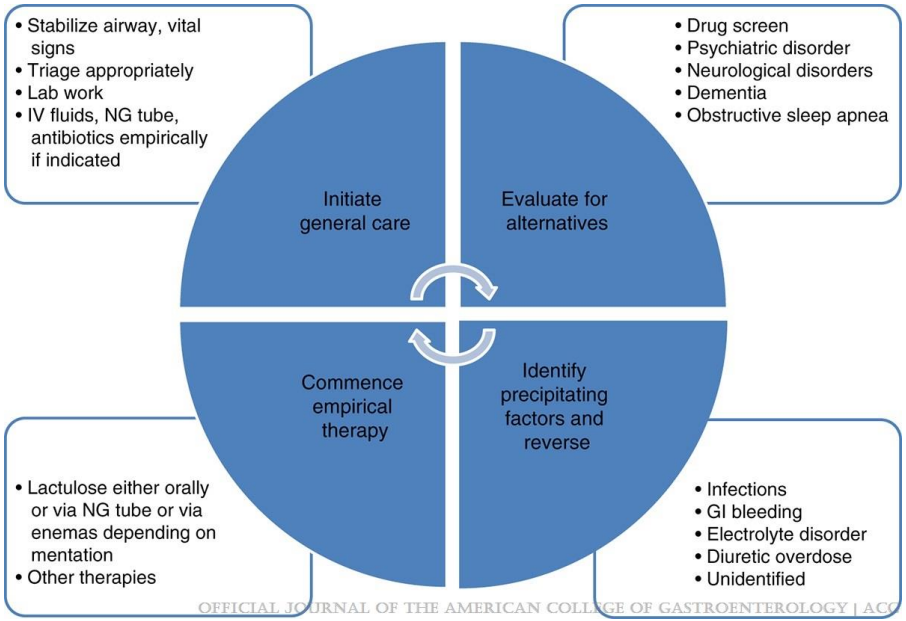
Covert HE (CHE)

- Deficits in attention, reaction time, working memory, visuoconstructive abilities and fine motor performance
  - 20% to 80% with cirrhosis
  - Subclinical-testing necessary for diagnosis
- Can predict OHE
  - >50% will develop OHE within 30 months
- Associate with poor HRQoL
  - Employability
  - Driving capacity
- Routine primary prophylaxis is not recommended
- CHE treatment on case-by-case basis

Reau. *Gastroenterology & Hepatology*. Volume 12, Issue 12, Supplement 5 December 2016.
Acharya, Chathur; Bajaj, Jasmohan S. *ACG*. 113(11):1600-1612, November 2018. doi: 10.1038/s41395-018-0179-4

Conclusion

- Hepatic encephalopathy is a key sign of end-stage liver disease
- Ammonia measurement should be used when diagnosis is questionable
- HE is readily treatable and active interventions can decrease hospital admission rates
- Lactulose and Rifaximin are first line in OHE management
- Continue therapy that controlled OHE for secondary prophylaxis



Q&A/Panel Discussion