

Hepatic encephalopathy: Best practice and management

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Outline

- Definition and Pathophysiology
- Overview of management and classification
- Covert/Minimal HE
- Inpatient therapy
- Prevention of recurrence
- Special situations
- Future management strategies

Definition of Hepatic Encephalopathy (HE)

- ▶ Hepatic encephalopathy is brain dysfunction caused by liver insufficiency and/or porto-systemic shunting
- ▶ It manifests as a wide spectrum of neurological/psychiatric abnormalities ranging from subclinical alterations to coma

Why should we care?

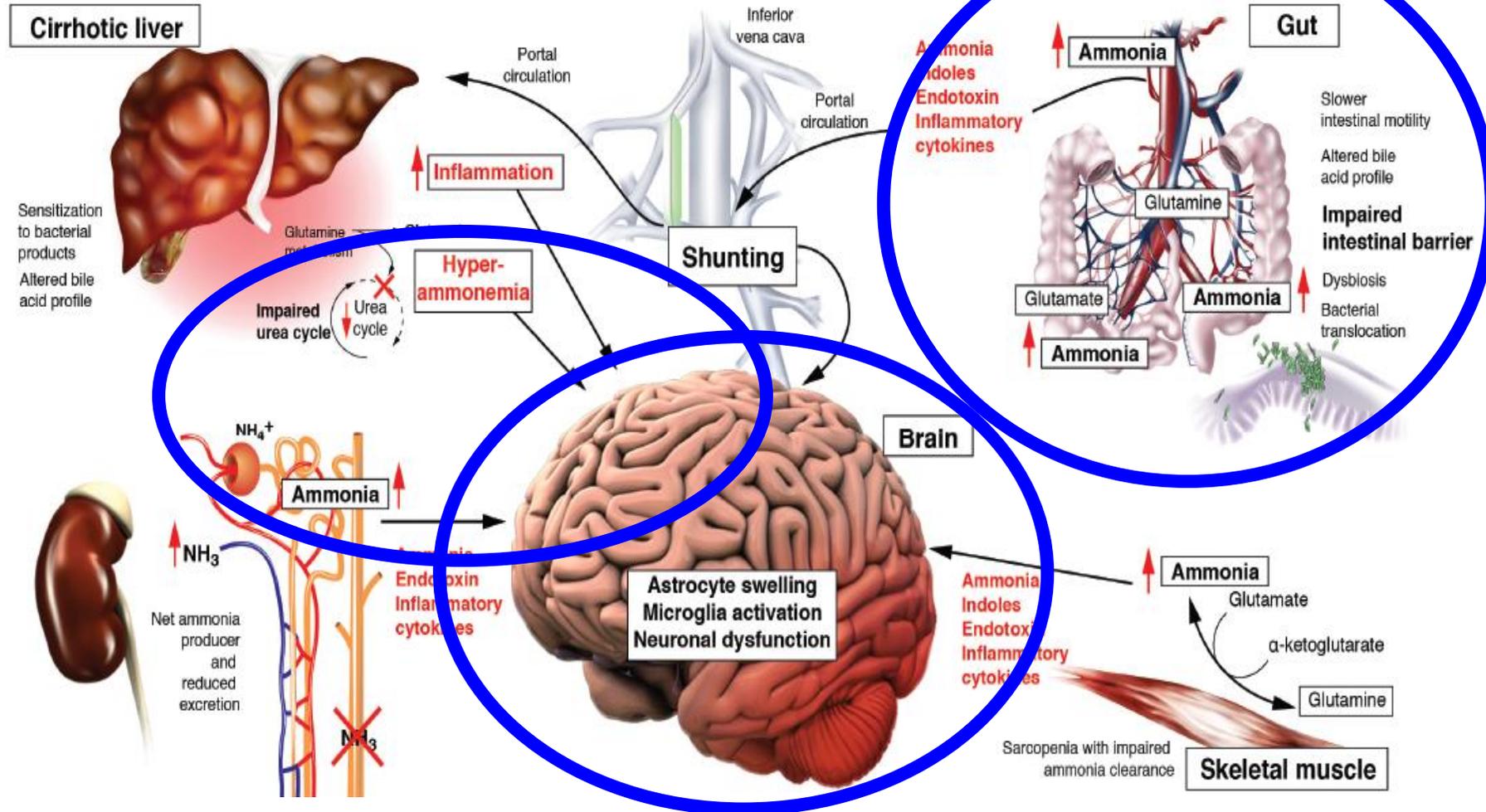
**Comatose people with HE wake up after
bowel movements!!**

**The best human model for the gut-brain
axis in action!!!**

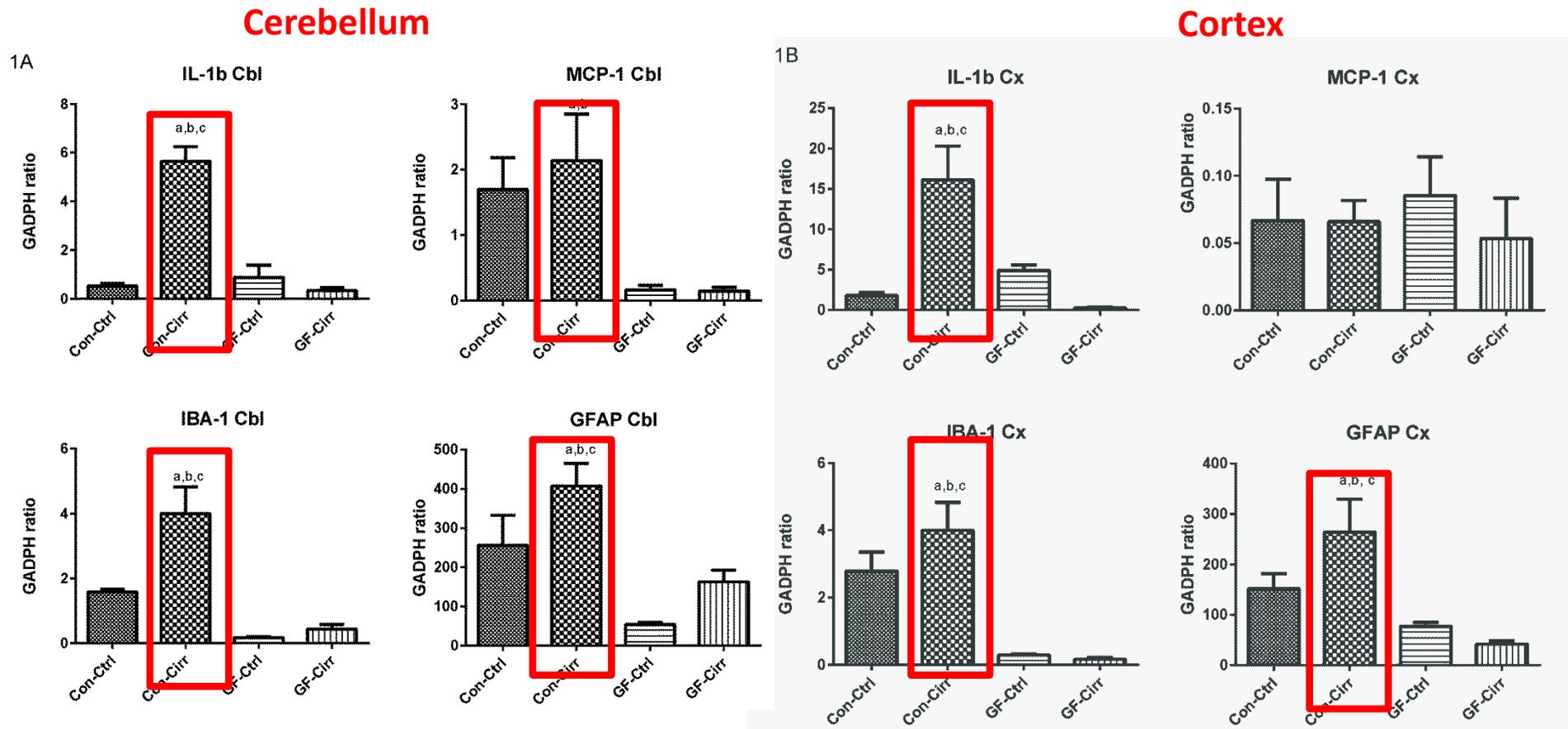
The question is how and why?

Bustamante et al J Hepatol 2009, Cordoba et al J Hepatol 2014, Bajaj et al CGH 2015,
Bajaj et al Hepatol 2016, Rakoski et al Hepatol 2012, Volk et al Am J Gastro 2014, Bajaj et al
Am J Gastro 2011, Ampuero et al Gastro 2014, Sanyal et al NEJM 2021

Pathophysiology of HE: not just the liver and the brain!



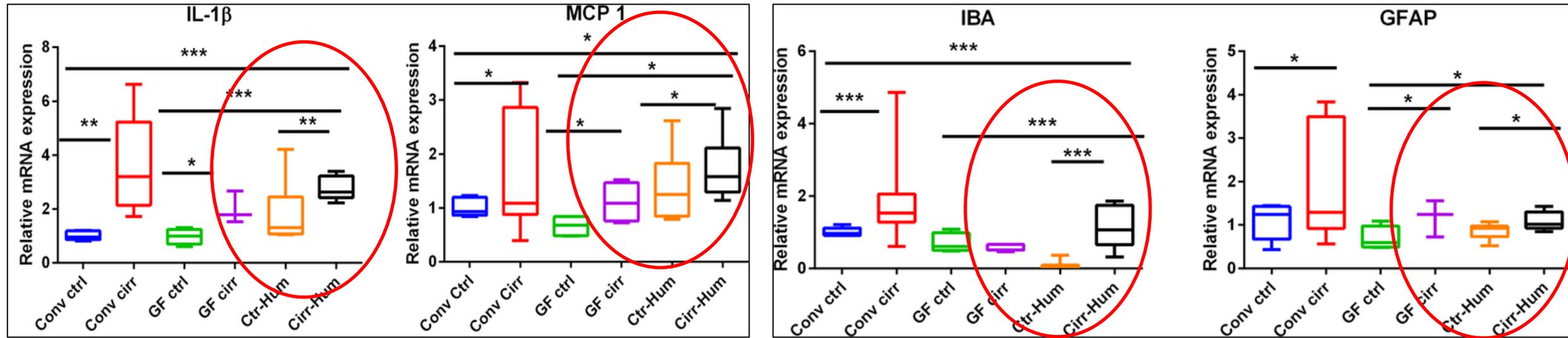
Gut microbiota are necessary for brain inflammation (microglial and glial) in cirrhotic mice



4 mouse groups: GF, GF made cirrhotic using CCL4 gavage,
Conventional control and Conventional mice made cirrhotic using
CCL4 gavage

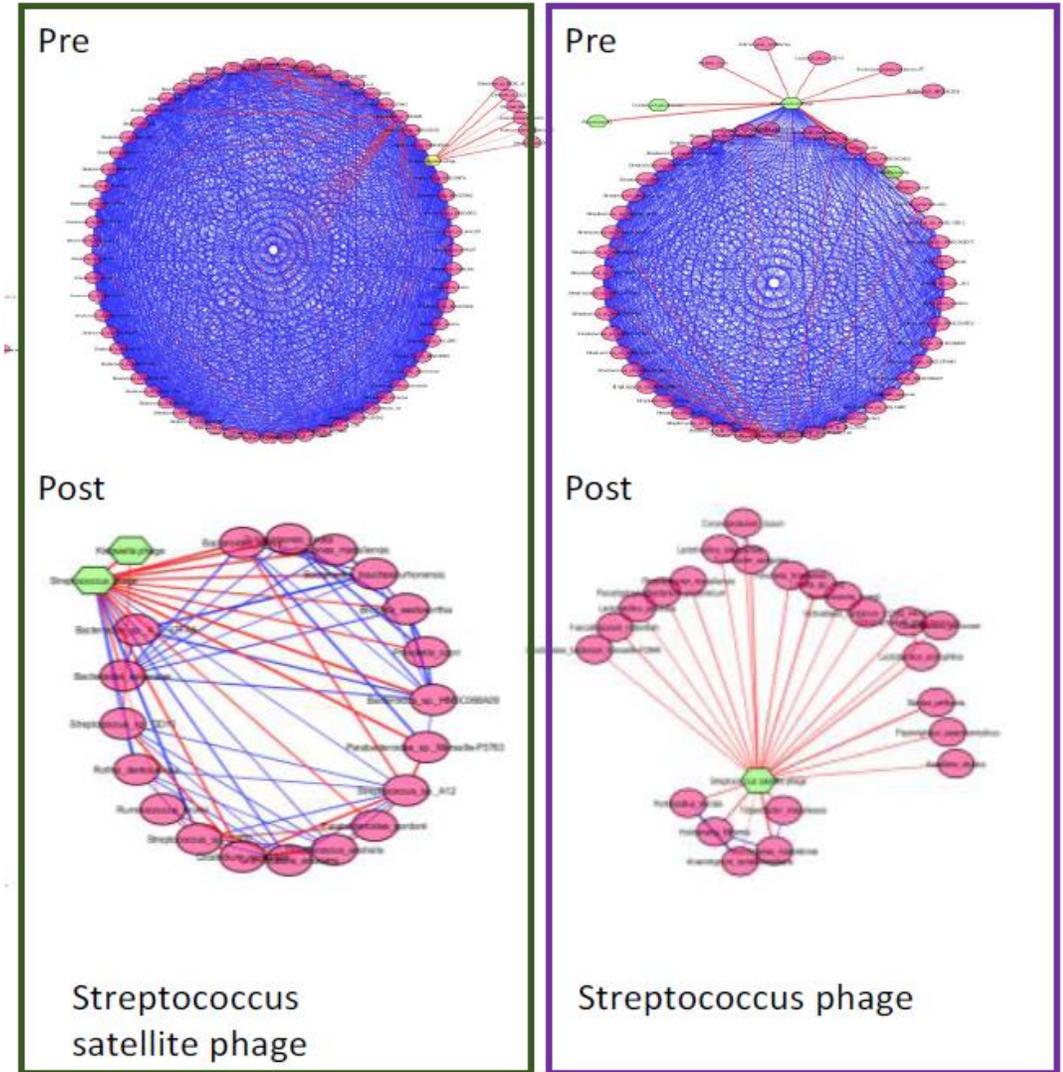
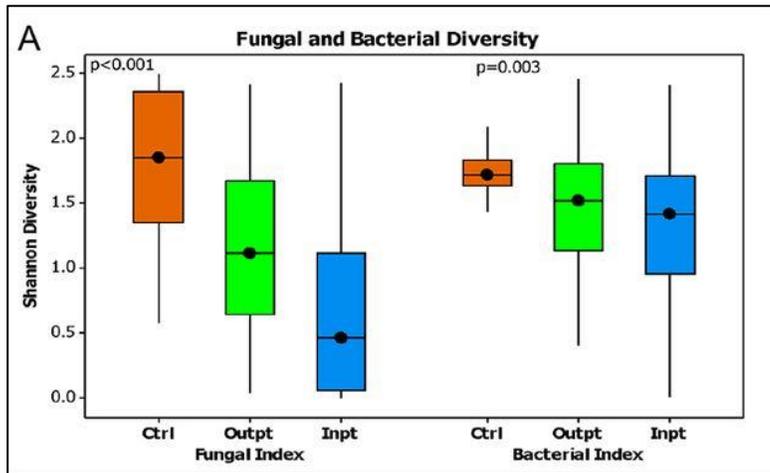
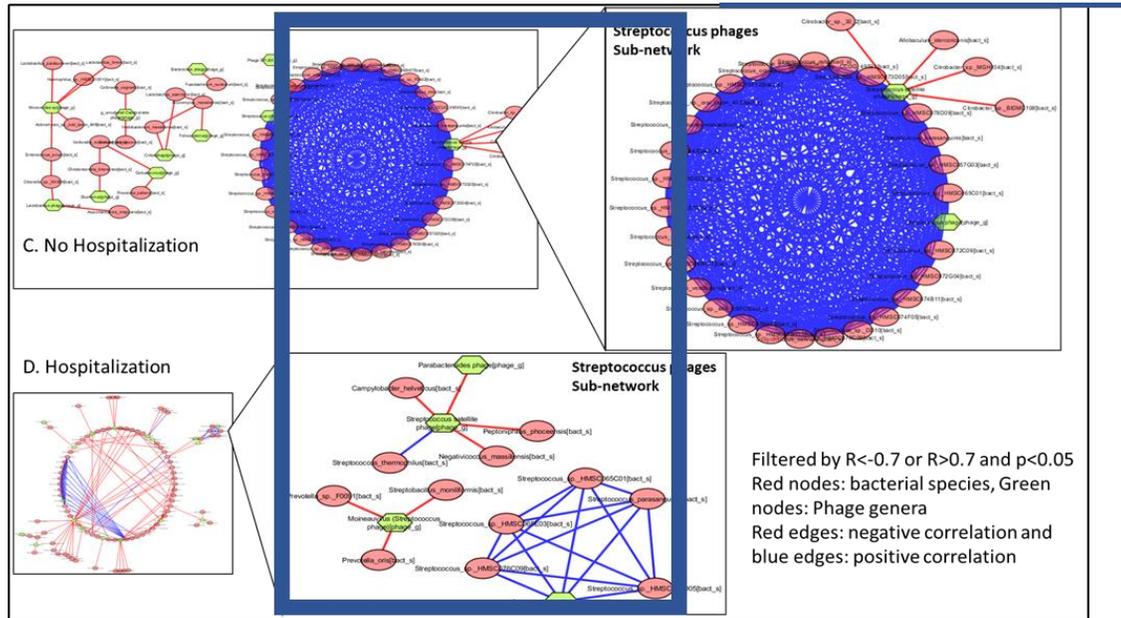
The brain is sensitive to the type of microbiota

HE pathogenesis is related to microbes with inflammatory potential



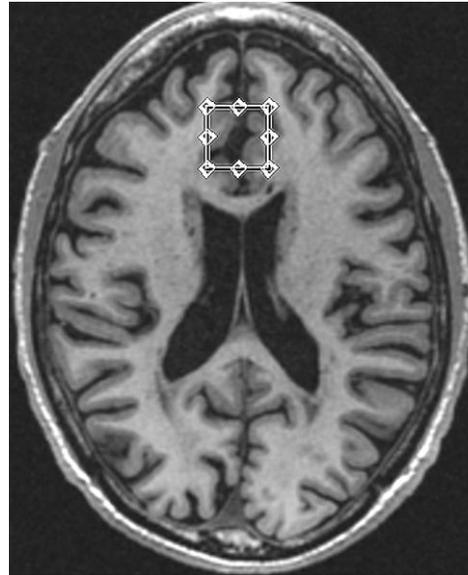
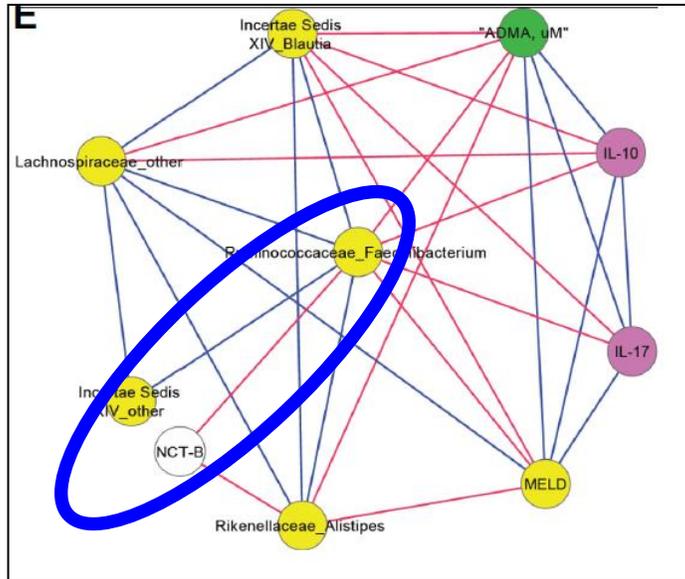
No impact of Germ-Free Supernatants

Non-Bacterial Kingdoms and HE



Hepatic Encephalopathy and Hospitalizations in Outpatients

Microbial changes related to brain dysfunction in **Hepatic encephalopathy (HE)**

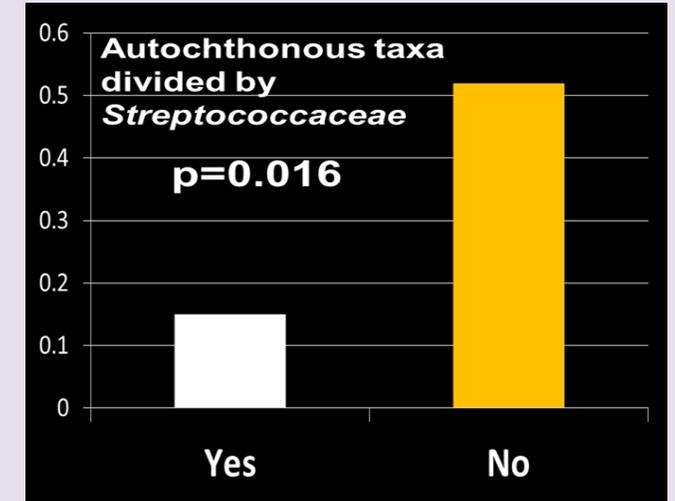


SCFA-producing bacteria= ↓ ammonia-related changes

Oral bacteria= ↑ Inflammation-related changes

Hospitalizations in Outpatients

Saliva

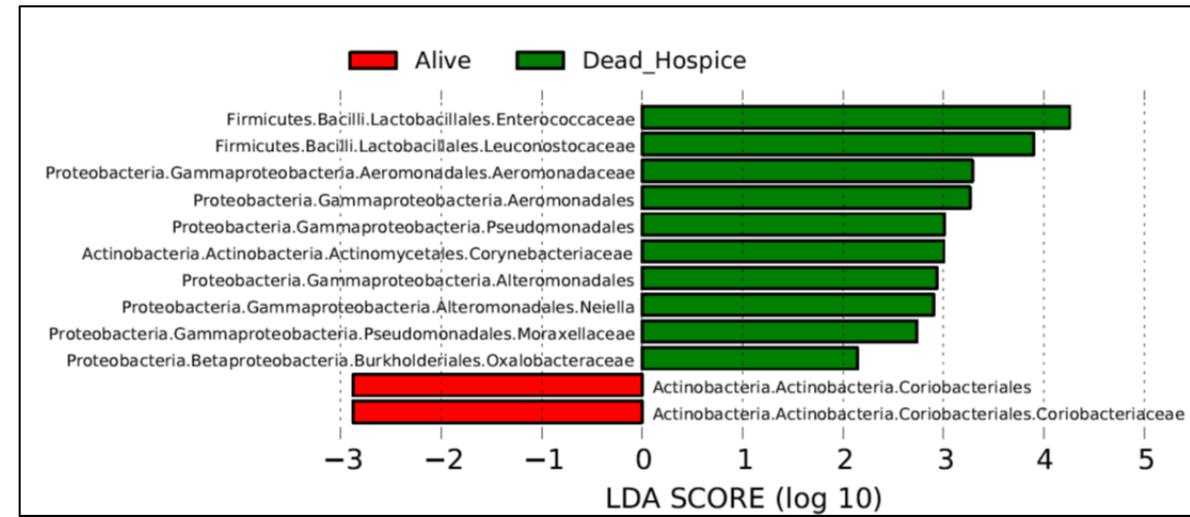
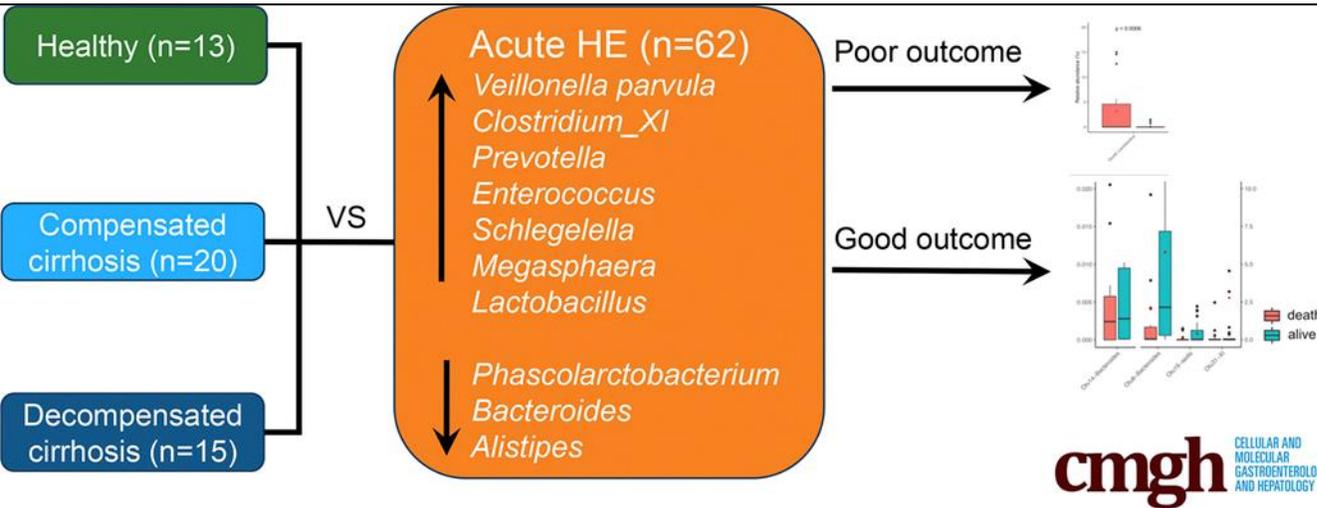


Stool: 278 patients, 37% hospitalized within 90 days

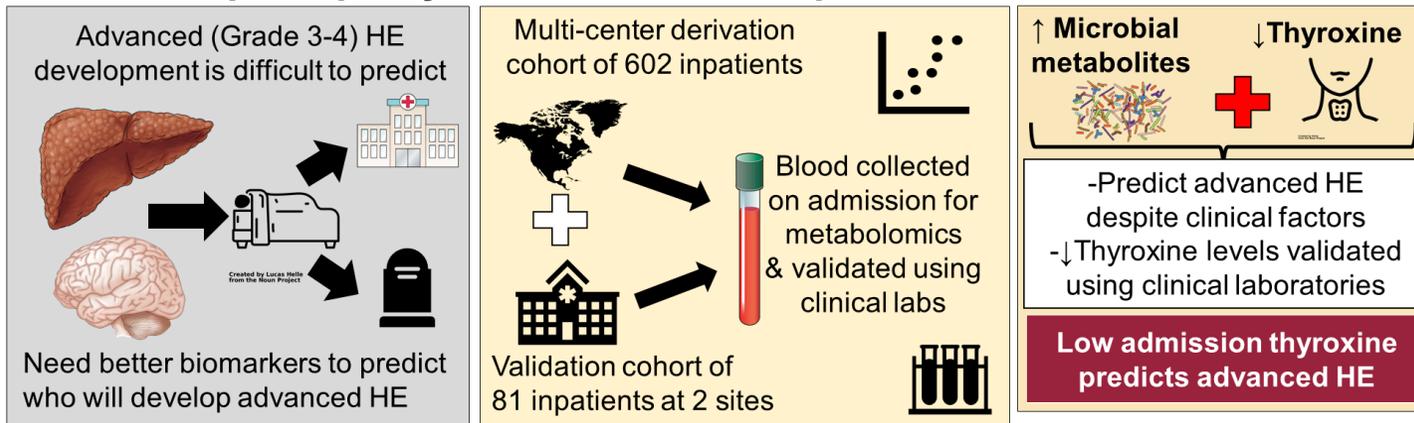
Predictors of hospitalization

- MELD score, PPI, HE PLUS
- **Clostridiales Cluster XIV and**
- **Bacteroidaceae**

Microbiota and HE-related outcomes in Inpatients



Admission Serum Metabolites and Thyroxine Predict Advanced Hepatic Encephalopathy in a Multi-center Inpatient Cirrhosis Cohort



Bajaj JS et al NACSELD 2022

Microbial composition and metabolites can predict

- Death
- ACLF
- ICU transfer
- Who develops grade 3-4 HE
- Recovery and recurrence of HE

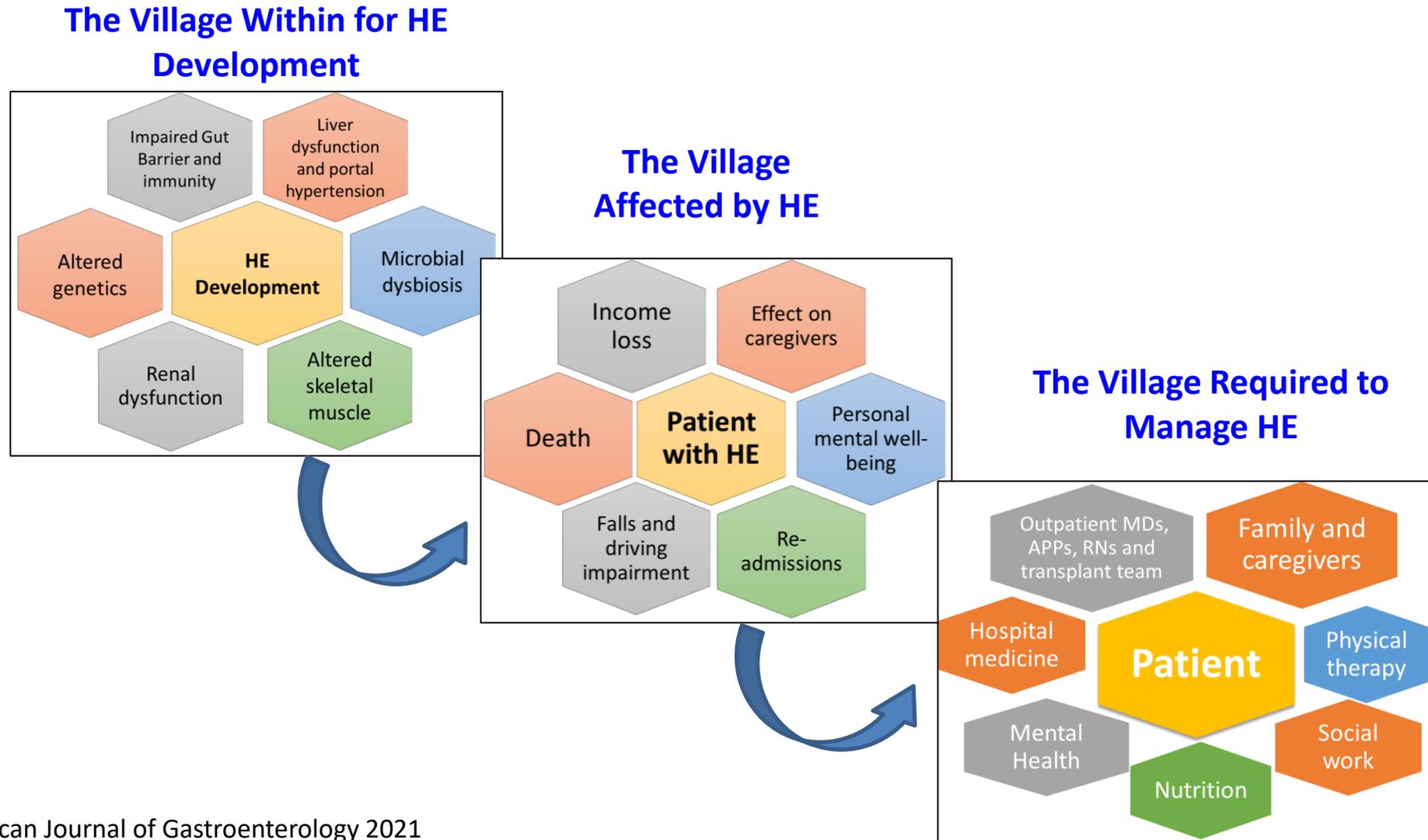
Lin et al CMGH 2019, Chen et al J Gastro Hep 2015, Bajaj et al J Hepatol 2014, Bajaj et al Clin Gastro Hep 2018, Bajaj et al CGH 2022

Clinical Classification of HE

Overall Classification of HE: Four Axes

Type	Grade		Time Course	Presence of precipitating factor
A (<u>A</u> cute Liver Failure)	Minimal	Covert	Episodic (no further HE for ≥ 6 months)	Precipitated (specific factor found)
	1			
B (porto-systemic <u>B</u> ypass or shunt without cirrhosis)	2	Overt	Recurrent (further episode within 6 mths)	Spontaneous (no precipitating factor found)
	3			
C (<u>C</u> irrhosis)	4			

Multi-disciplinary Approach: The Three Villages of Hepatic Encephalopathy



- **Covert HE**
- **Inpatient Management**
- **Preventing Recurrence**

Diagnosing patients earlier

Covert HE

Covert HE is important to our patients

Outcomes in cirrhotic patients	Affected?
Progression to overt HE	
Health-related Quality of life	
Driving impairment and accidents	
Overall Survival	
Socio-economic status	
Can be tested for	

Covert/Minimal HE is present in almost 40% of patients

Prevalence of MHE in patients with cirrhosis

Aim



To determine the prevalence of minimal hepatic encephalopathy (MHE) in different subgroups in a large, multinational cohort using the Psychometric Hepatic Encephalopathy Score (PHES)

Study cohort

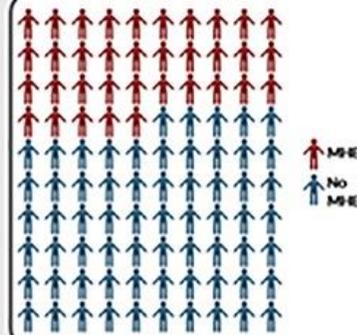


1,868 patients with cirrhosis

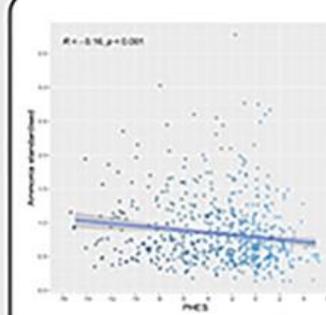


10 centers (Europe, US)

Results

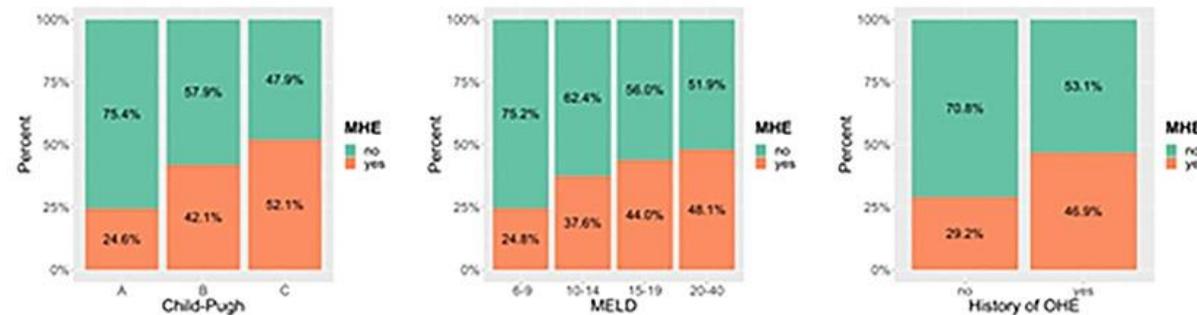


Overall MHE prevalence: 35%



Standardized ammonia levels correlated significantly, albeit weakly with PHES

MHE prevalence varied considerably when stratified by disease stage



Covert HE testing time & resource requirements

Real world testing <15%



Time and Resources

Real-World Settings

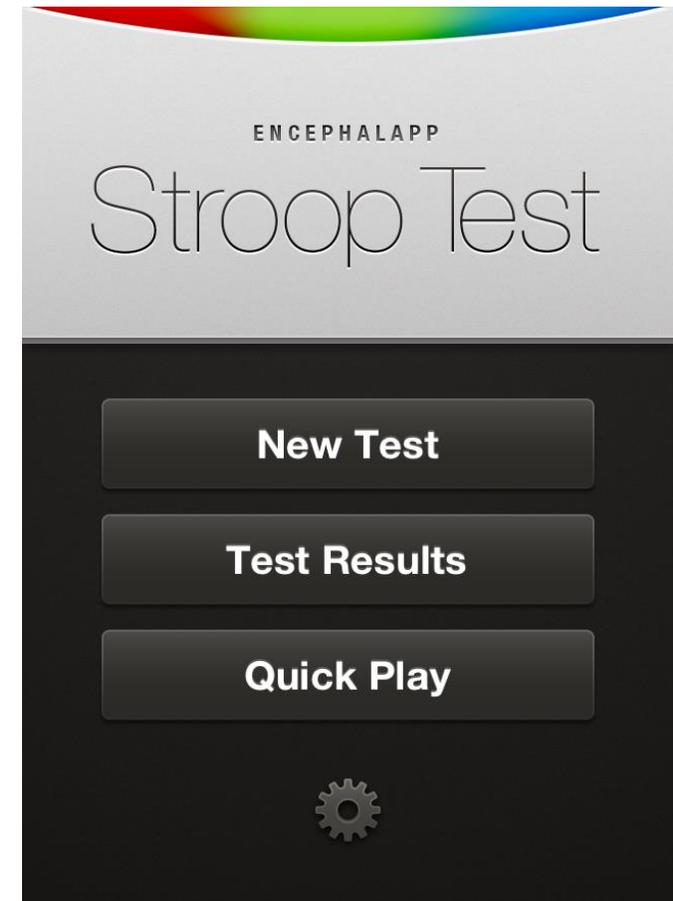
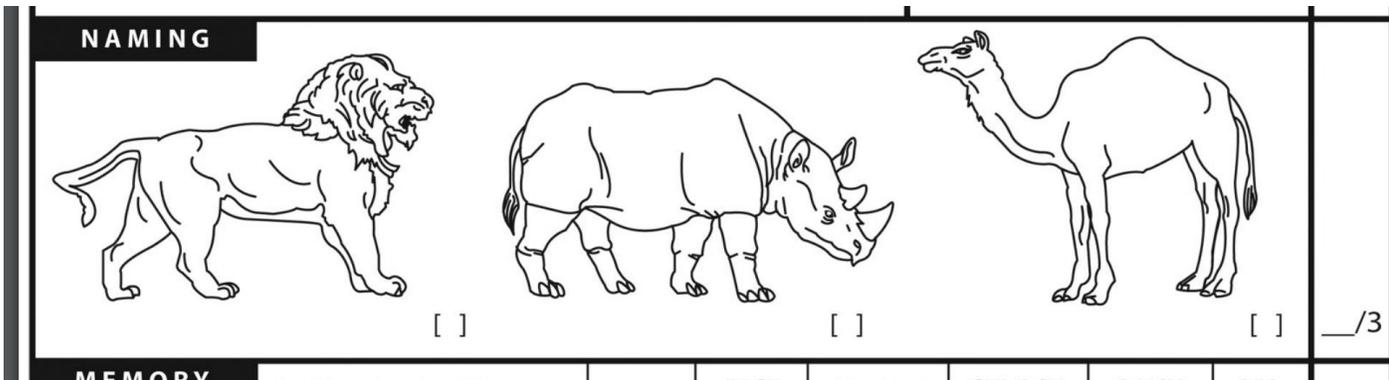
HRQOL, Animal Naming and EncephalApp Stroop can be used to diagnose covert/minimal HE

I do not maintain balance

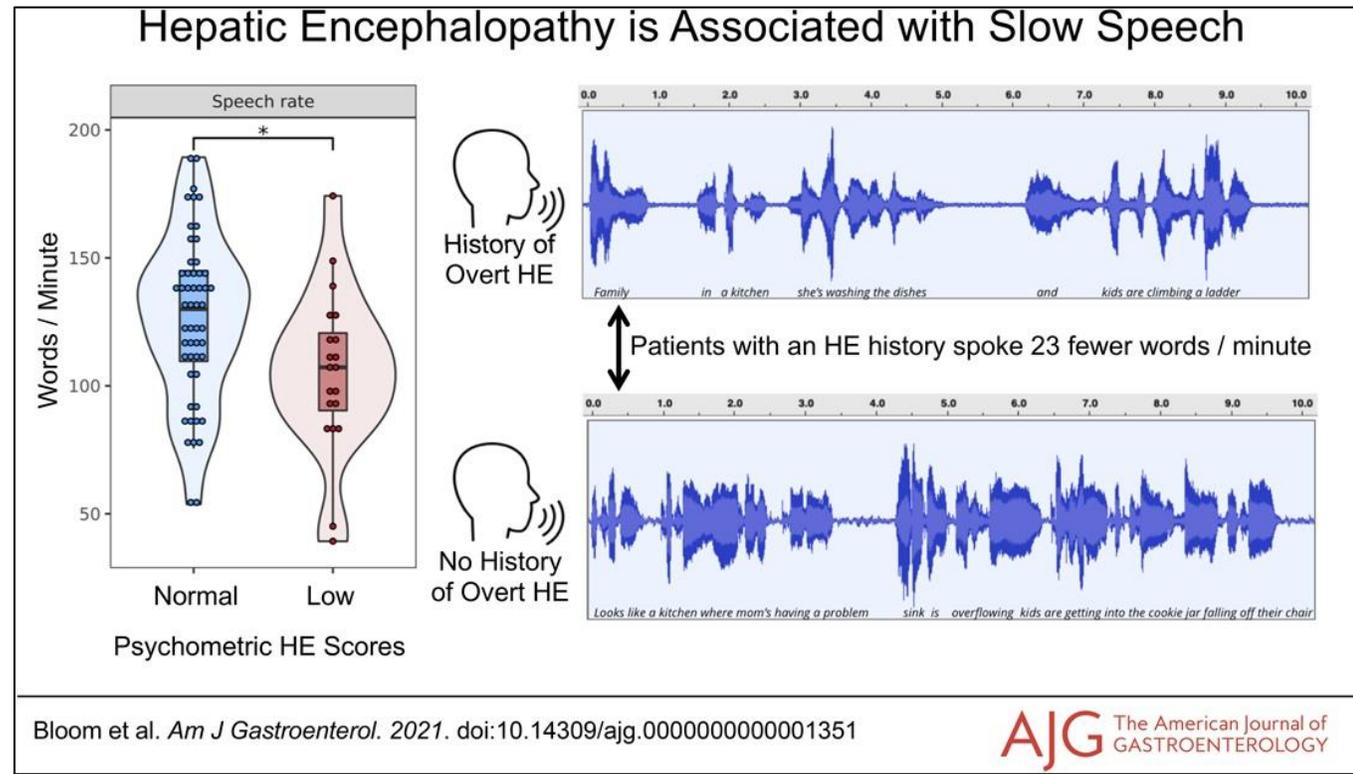
I act irritable or impatient with myself

I am not doing any of my usual physical recreation or activities

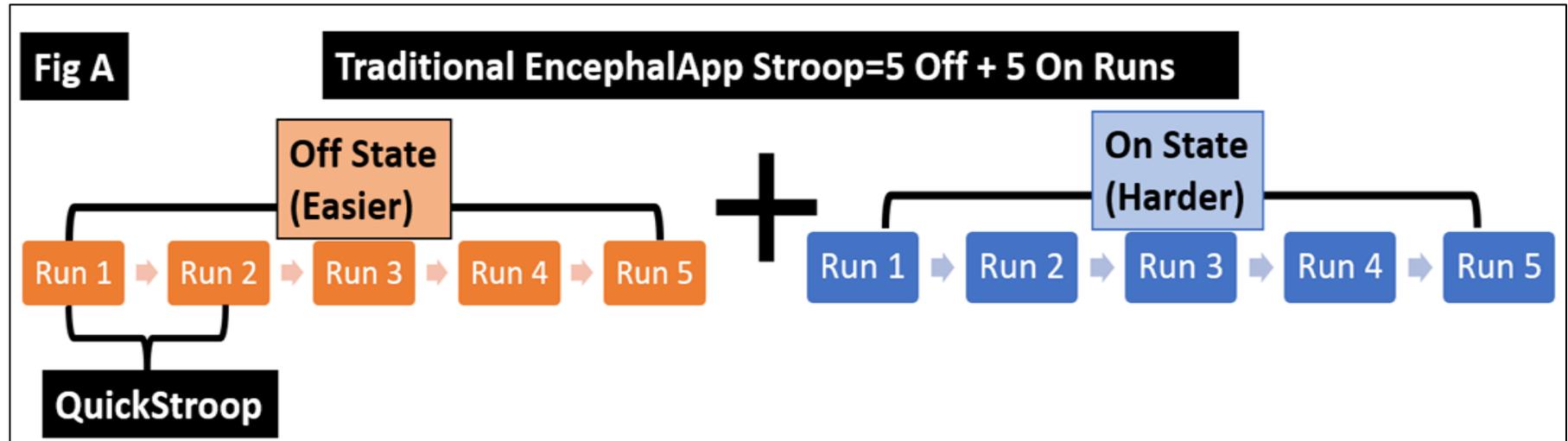
I am eating much less than usual



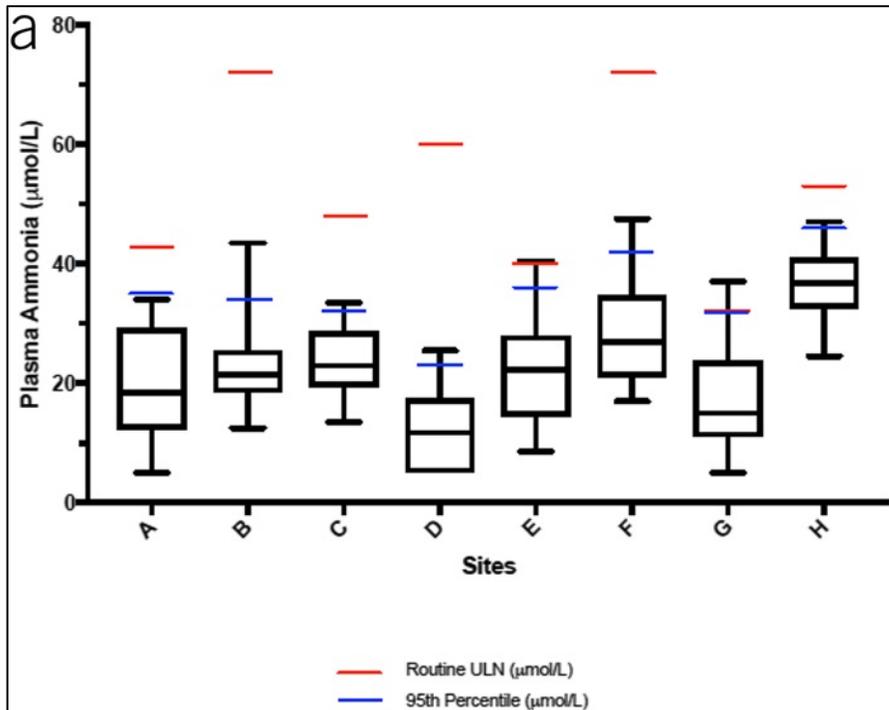
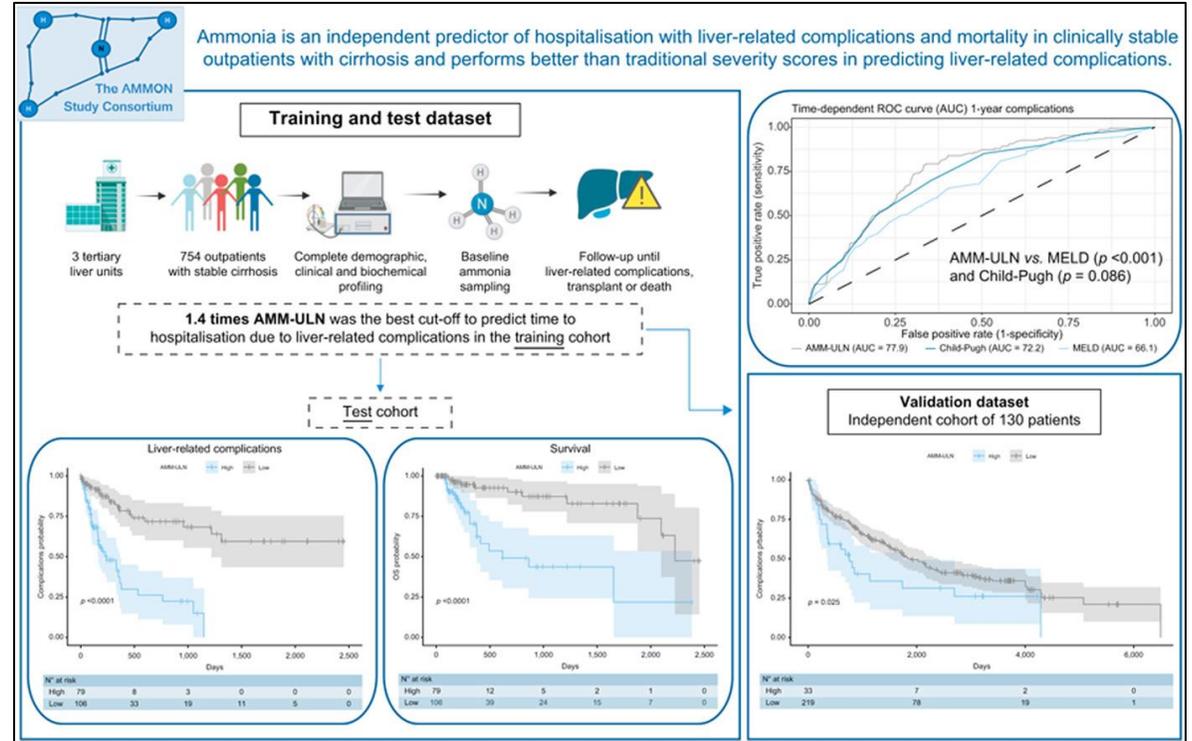
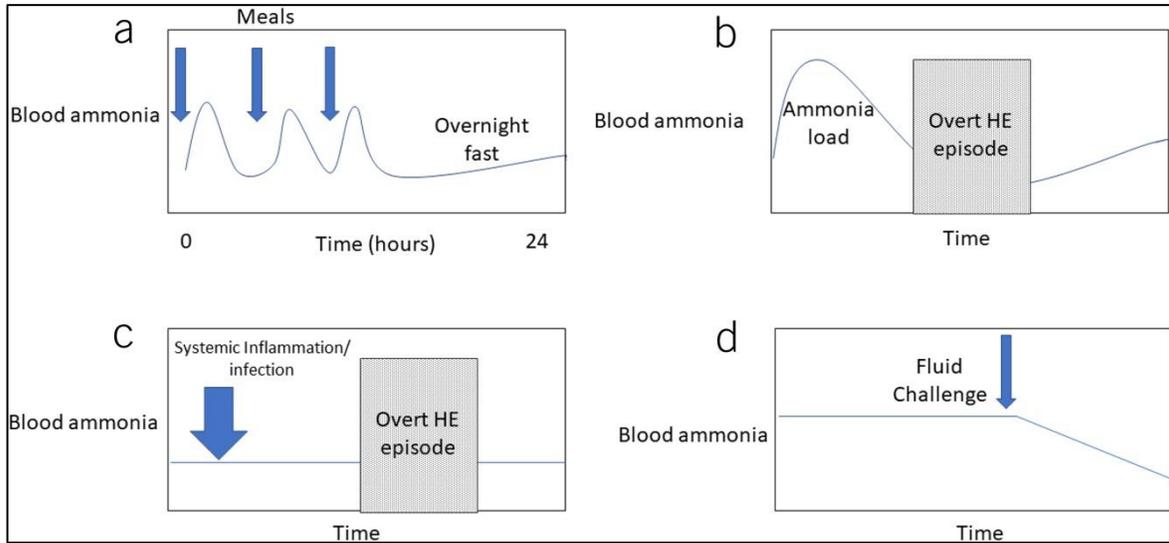
Slow Speech



QuickStroop

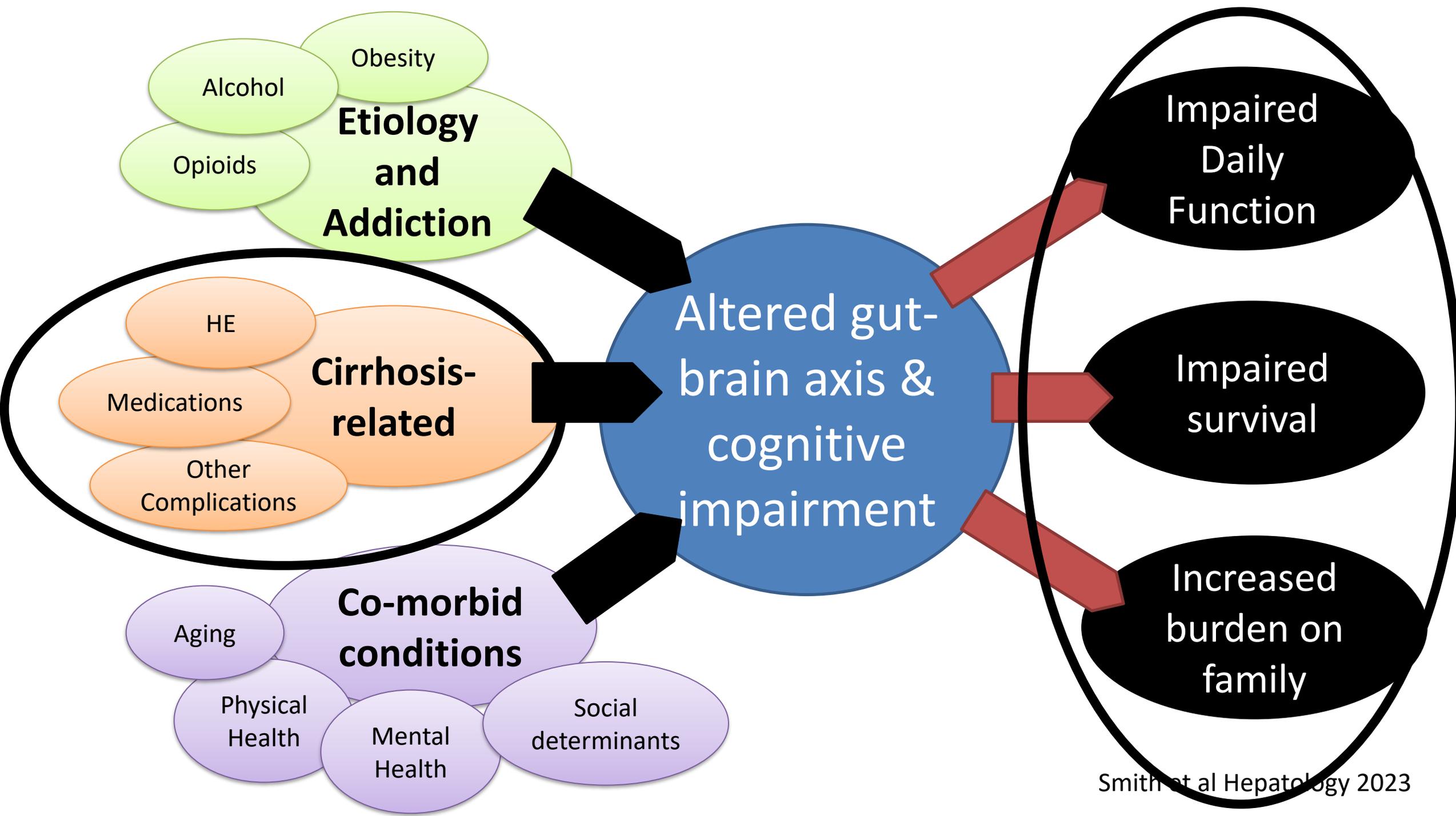


Ammonia levels?



- Exclusionary for HE if normal; not diagnostic if high
- Could be prognostic
- Vary with dehydration, meals, and methods of drawing blood
- Upper limit of normal varies between laboratories

AASLD/EASL 2014 HE Guidelines, EASL HE CPG 2021, Bajaj JS et al Am J Gastro 2019, ISHEN Consensus Am J Gastro 2020, Tranah et al J Hepatol 2021

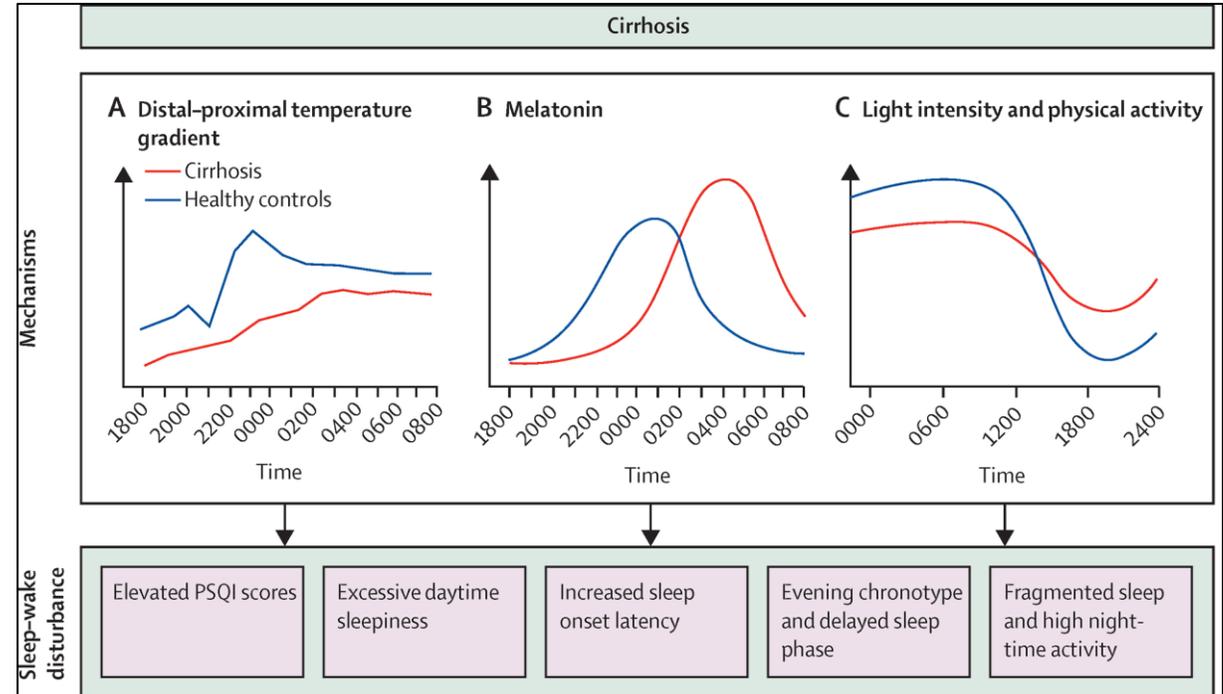
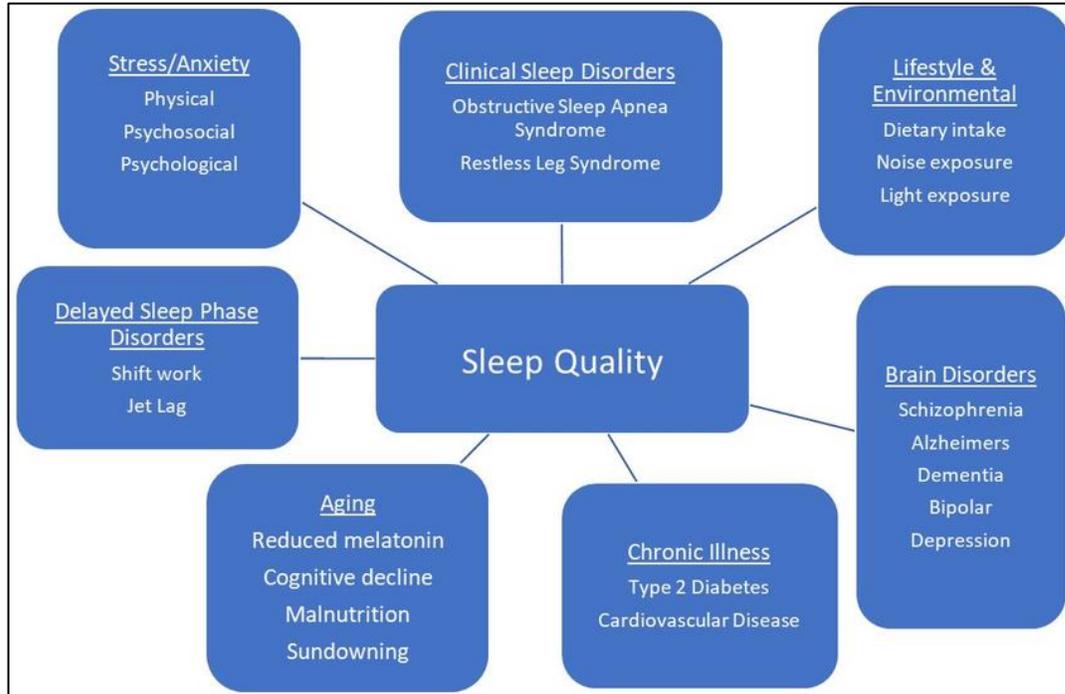


Are all cognitive complaints in cirrhosis HE?

<50% of patients with cognitive complaints seen in the specialized clinic had Covert or Minimal HE

- **Dementia/MCI**
- **Obstructive sleep apnea**
- **Alcohol-related**

What about sleep as an indicator for HE? Not a slam dunk!



Sleep alterations alone are inadequate to diagnose HE and HE-treatment does not resolve sleep problems

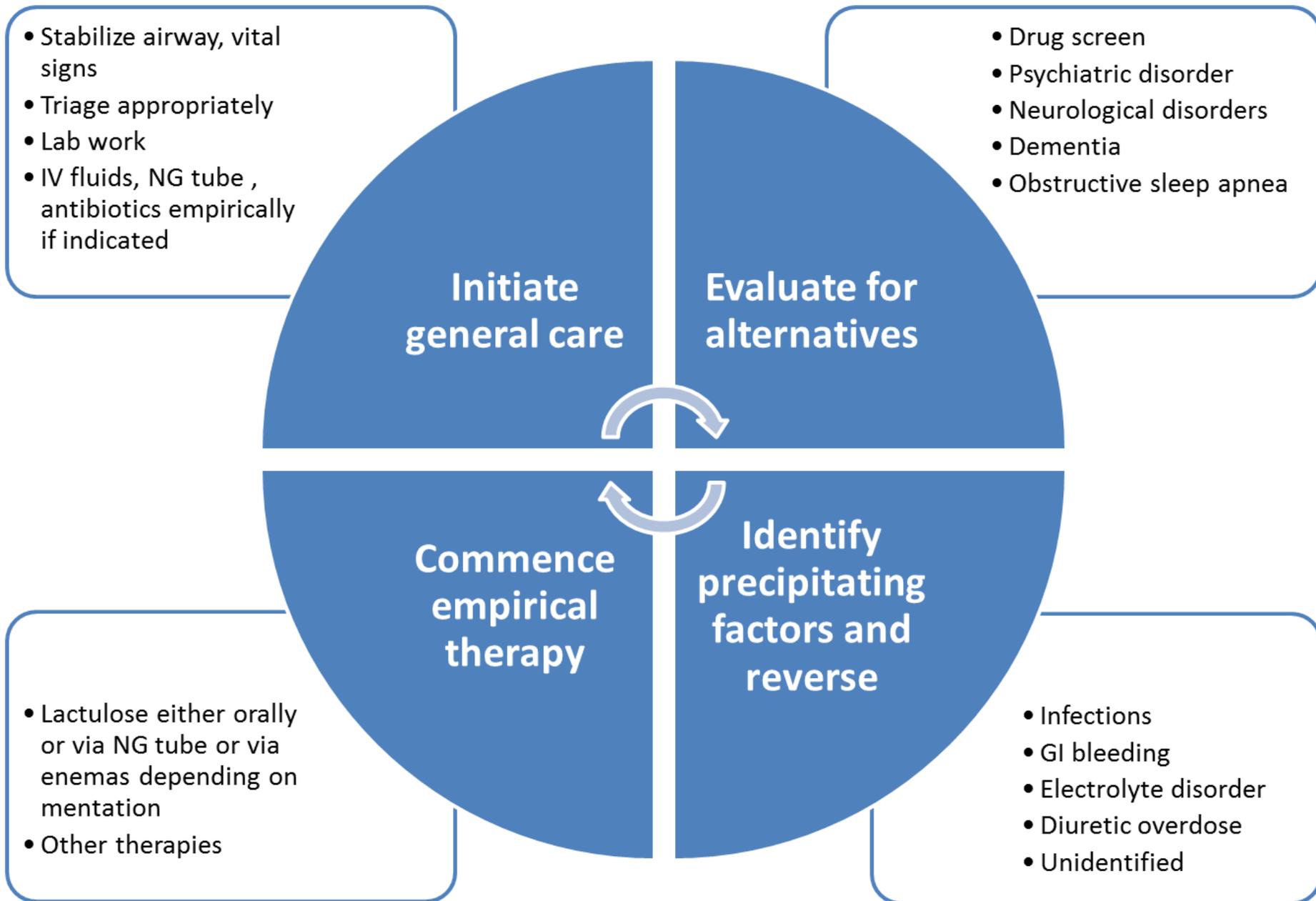
Also consider:

- **Obstructive sleep apnea**
- **Alcohol-related or medication-related issues**

HE therapies overview

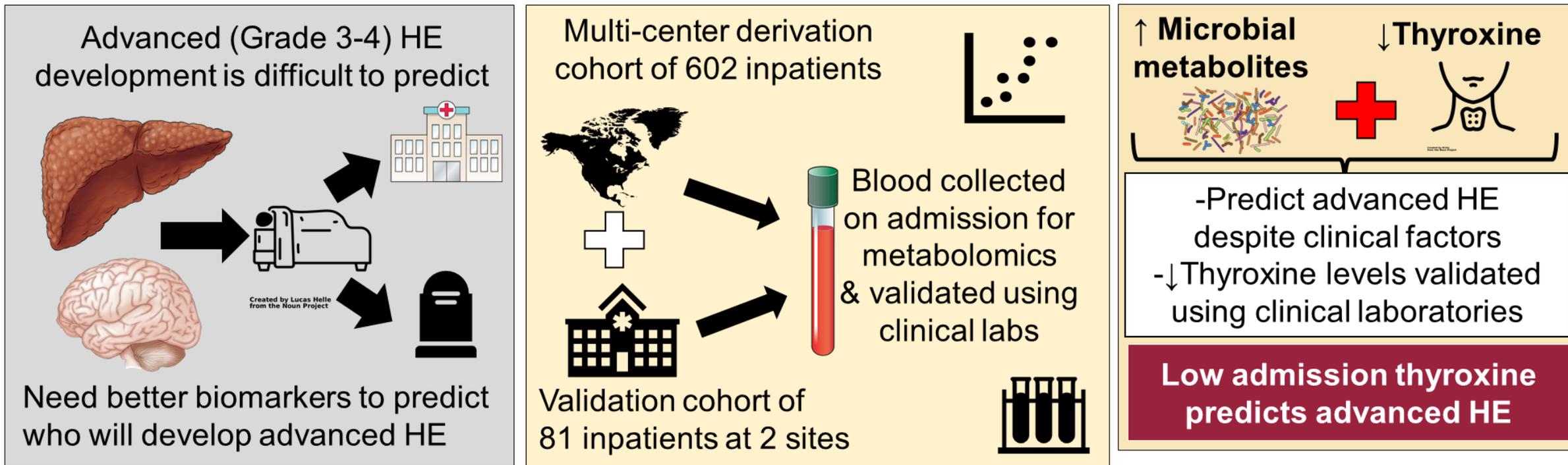
Focus on the gut-brain axis

Optimization of Inpatient Therapy



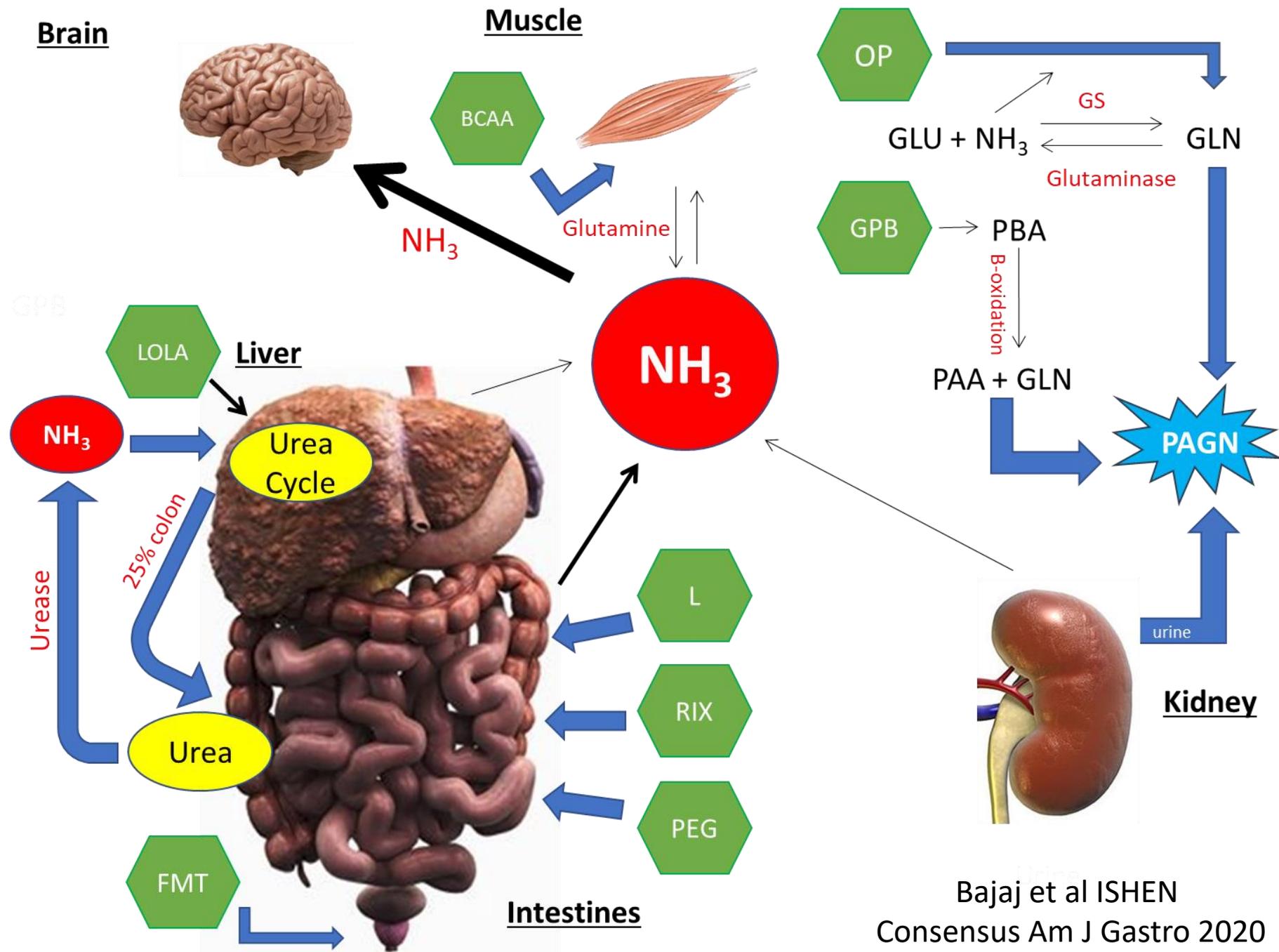
Who will develop advanced HE?

Admission Serum Metabolites and Thyroxine Predict Advanced Hepatic Encephalopathy in a Multi-center Inpatient Cirrhosis Cohort



Bajaj JS et al NACSELD 2022

Bajaj JS et al NACSELD Clin Gastro Hep 2022



Bajaj et al ISHEN
 Consensus Am J Gastro 2020

Drugs for Acute HE episodes

Agent	Mechanism of Action/Comments	Potential AEs and challenges
Nonabsorbable disaccharides	Potential shifting of microbes from urease- to non-urease-producing bacteria; exerts a cathartic effect	<ul style="list-style-type: none"> • Aspiration pneumonia • Dehydration • Hyponatremia • Severe perianal skin irritation
Rifaximin	Reduces NH ₃ by eliminating NH ₃ -producing colon bacteria; indicated for reducing risk of OHE recurrence in adults	<ul style="list-style-type: none"> • None major compared to placebo • Cost considerations
Zinc	Enhances urea formation from NH ₃ and amino acids	<ul style="list-style-type: none"> • None but not efficacious alone
PEG 3350-electrolyte solution	Purgative; causes water to be retained in the colon, produces a watery stool	<ul style="list-style-type: none"> • Needs more study

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; Elwir S, et al. J Clin Transl Hepatol. 2017;5(2):142-151., Bajaj et al Am J Gastro 2020

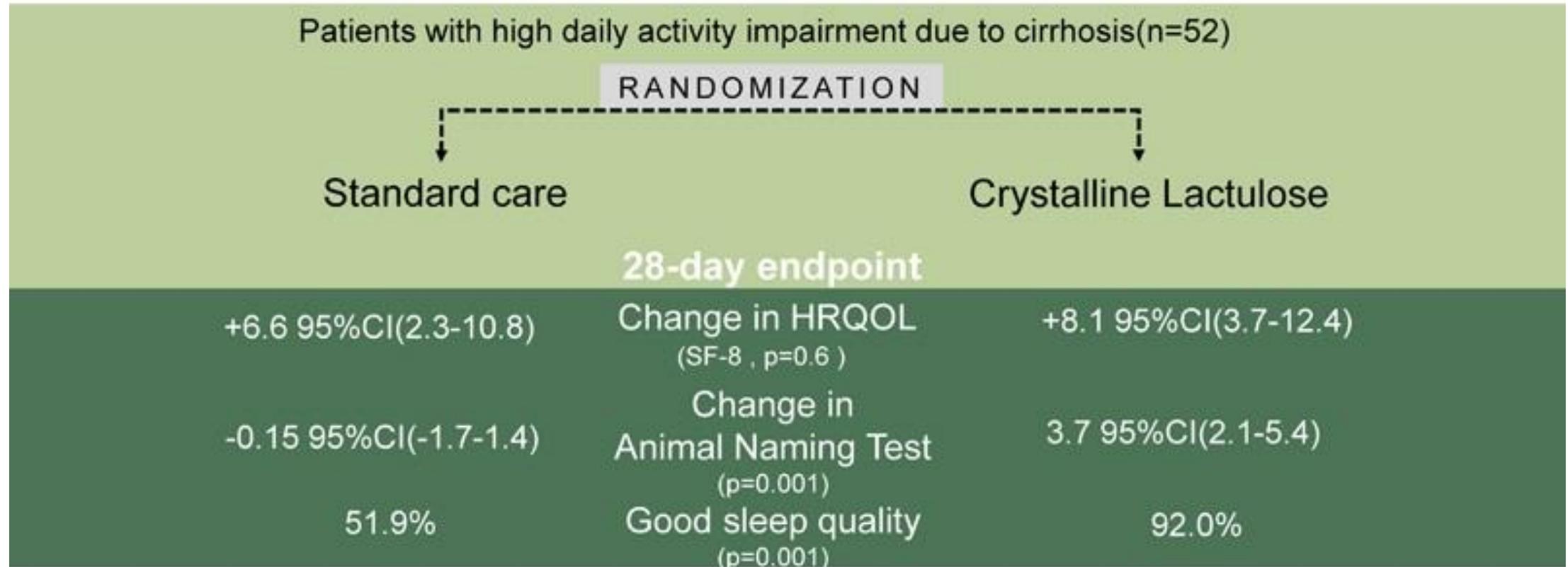
Prevention of HE Recurrence

- 1. Medication-related approaches**
- 2. Other approaches**

Checklist at discharge

Topics	
Does the patient know the change in their prognosis and daily function and tested for covert HE?	
Does the patient and family know signs of recurrence and ways to get in touch?	
Do they have a scheduled appointment for follow-up?	
Do they have medications to prevent HE recurrence with instructions in hand?	
Have potential recurring precipitating factors been investigated?	
Are they candidates for transplant?	

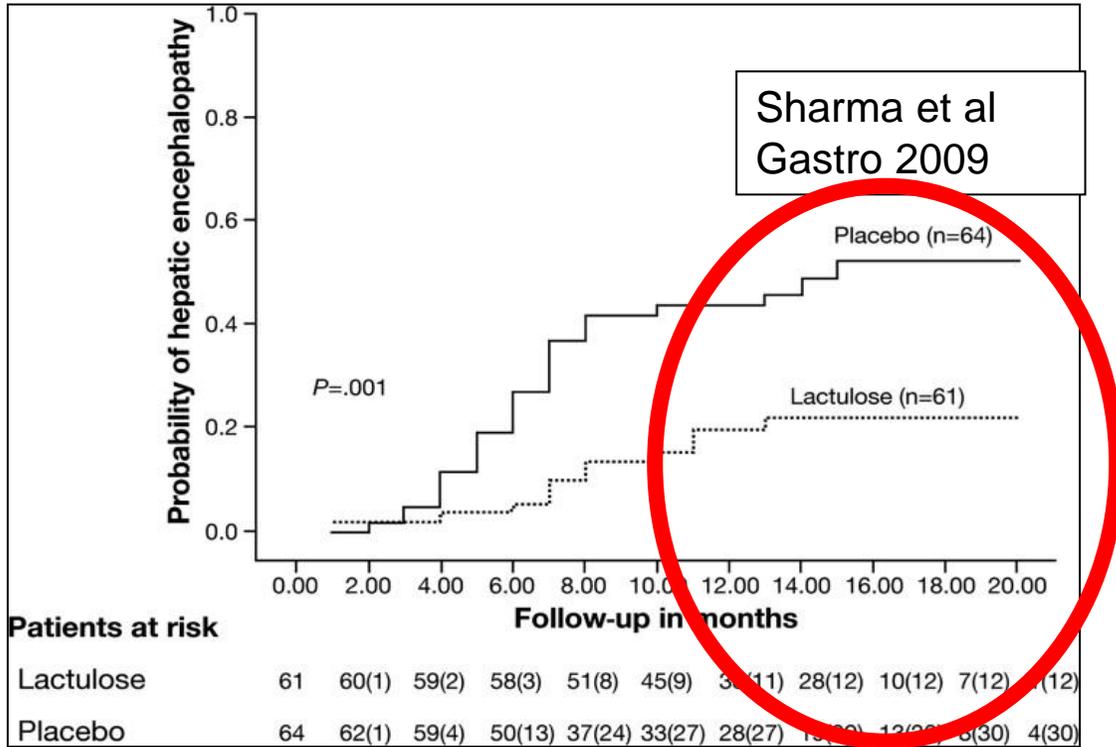
The MiKristal RCT: Lactulose therapy for patients with cirrhosis, portal hypertension, and poor patient reported outcomes



Tapper, et al. *Hepatology*.

HEPATOLOGY

Prevention of Overt HE recurrence: Lactulose



- Minimal change in microbiome structure or function
- Poorly tolerated and Western countries have poor acceptance
- Lactulose non-adherence is the #1 reason for HE-related readmissions

Sharma et al Gastro 2009, Wang et al JDD 2019, Rathi et al JCEH 2018, Bajaj et al NACSELD APT 2019

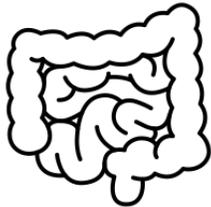


Quality not just Quantity of Stools: Bristol Stool Scale for HE

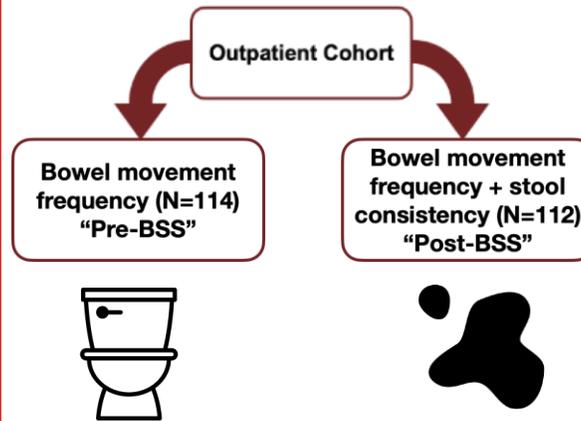
Bowel movement frequency is often used to titrate lactulose



Bristol stool scale (BSS) is a quick and low-cost method to assess stool consistency



Two outpatient cirrhosis groups analyzed prior to and after BSS incorporation



In Post-BSS group versus pre-BSS cohort



Lower 6-month total admission (4% vs 36%, p<0.001)



Lower Hepatic Encephalopathy-related admission (1% vs 12%, p=0.002)



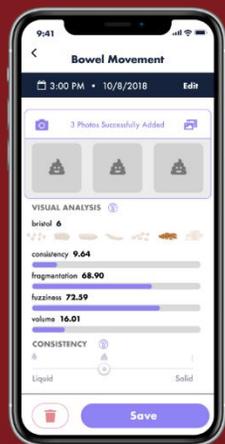
Greater stability of HE Medication Regimens (37% vs 20%, p=0.04)

Improves stability of HE Rx and prevents recurrence

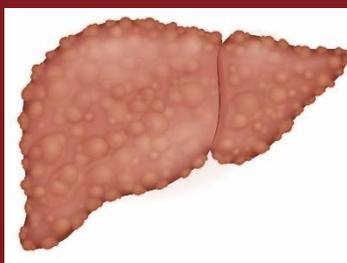
If BSS ≥ 5 = don't increase lactulose dose or initiate it

Dieta App to Manage Hepatic Encephalopathy in Cirrhosis

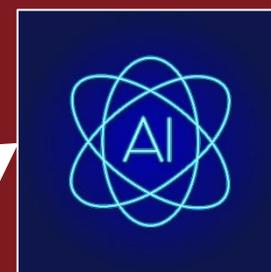
Using Bristol Stool Scale (BSS) rather than simple Bowel movement Numbers can reduce lactulose dose fluctuation but could be difficult to gauge in patients with Hepatic Encephalopathy



AI-based Dieta App calculates BSS using stool pictures & transmits back to users securely



Patients with Cirrhosis & Controls with Cross-sectional & Longitudinal Analysis with and without AI communication

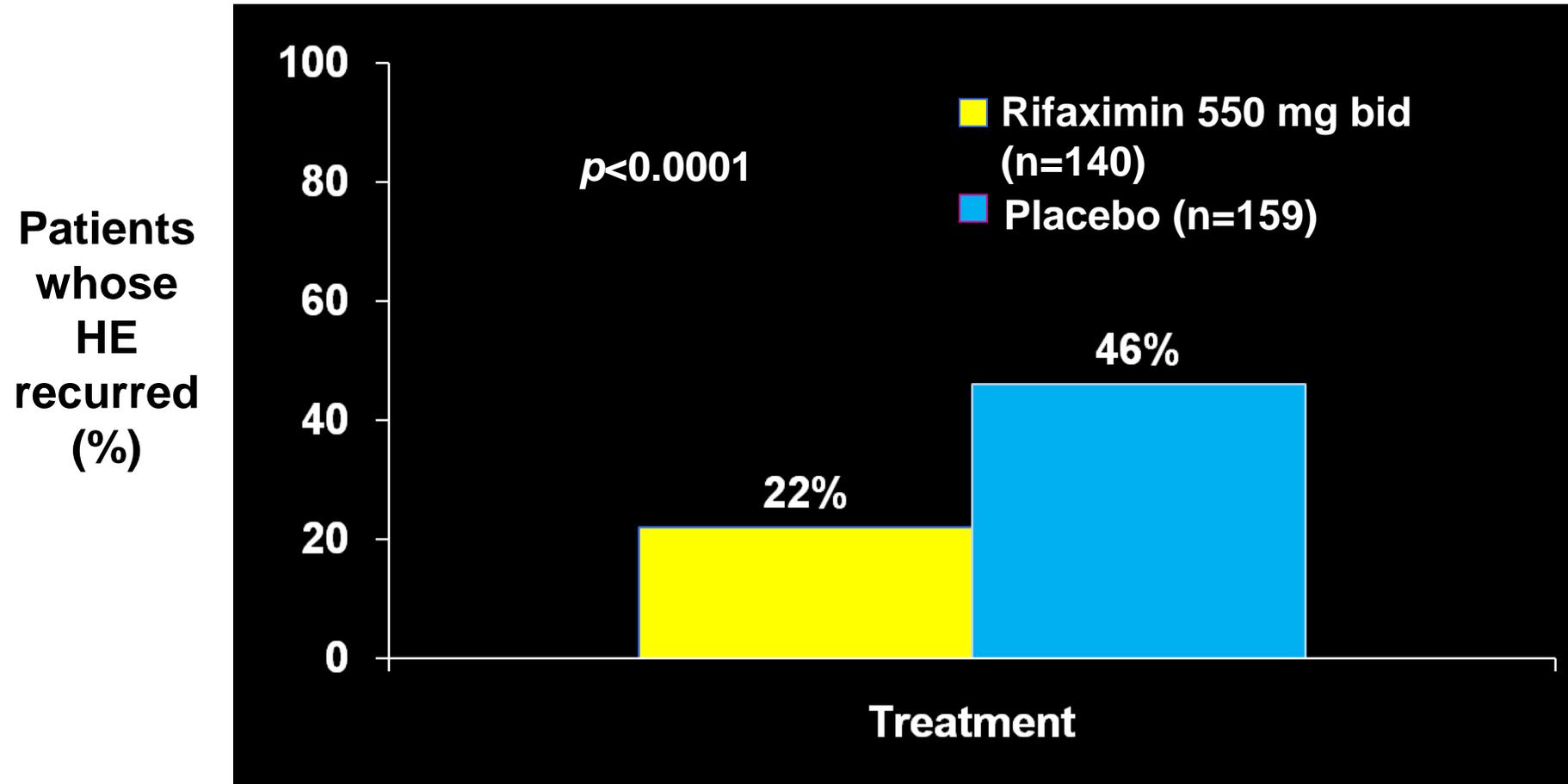


Outcomes

- Comfort with App and taking stool pictures
- Lactulose dose adjustment when AI generated BSS was communicated or not
- Correlation of self and AI-generated BSS

- Most subjects were comfortable with the App and taking  pictures
- AI and Self-generated BSS correlations increased over time
- Self-titration of lactulose was \uparrow when AI communication was switched on

Prevention of Overt HE recurrence: Lactulose + Rifaximin

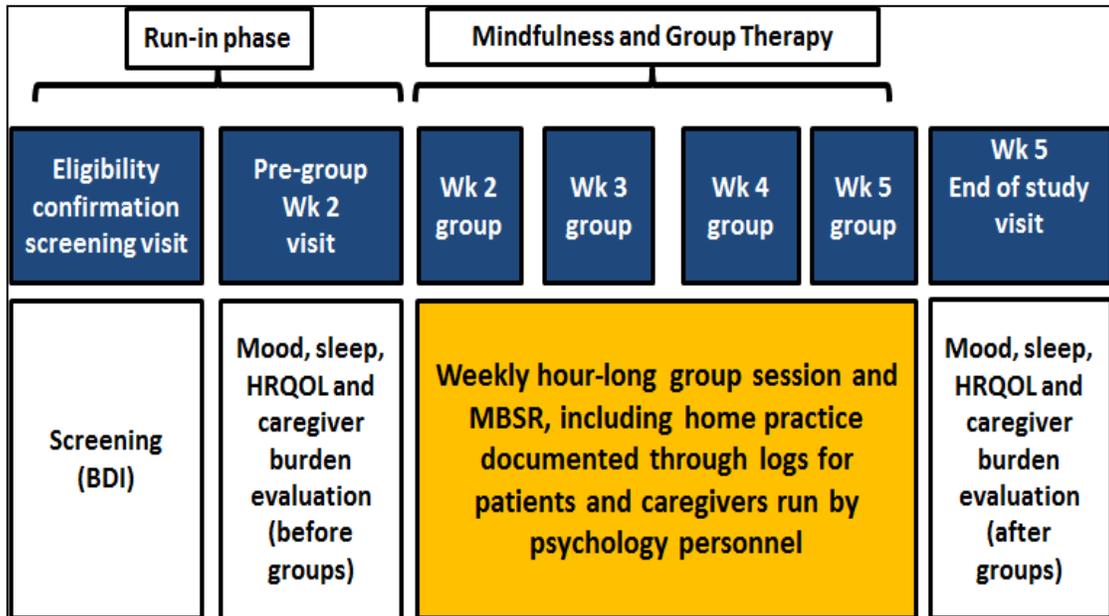
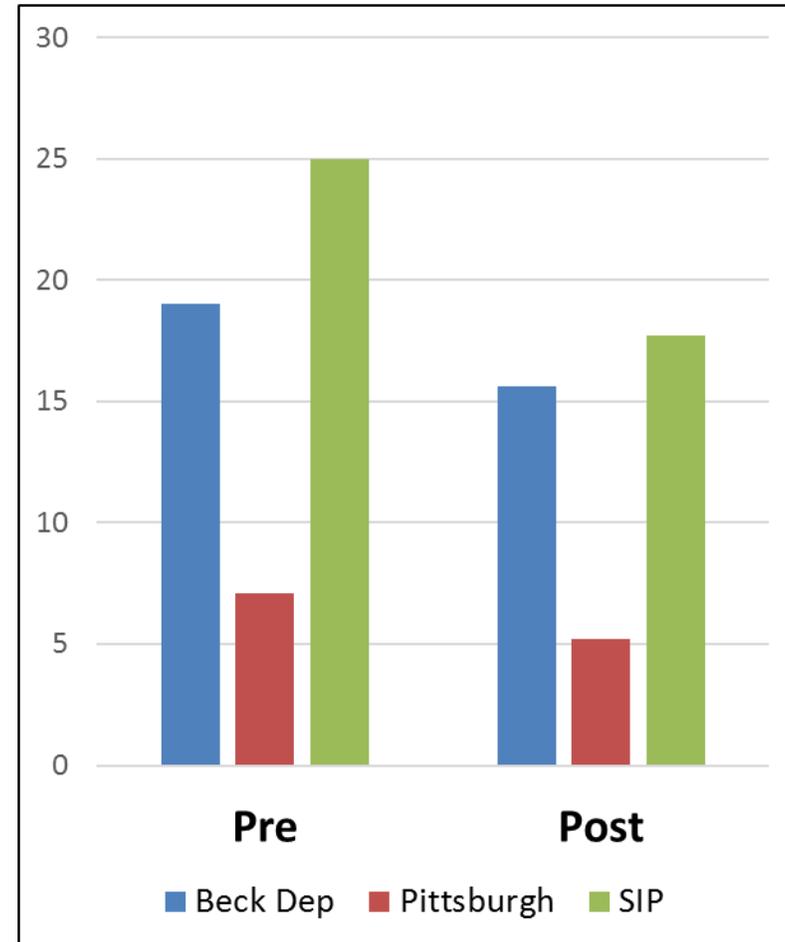
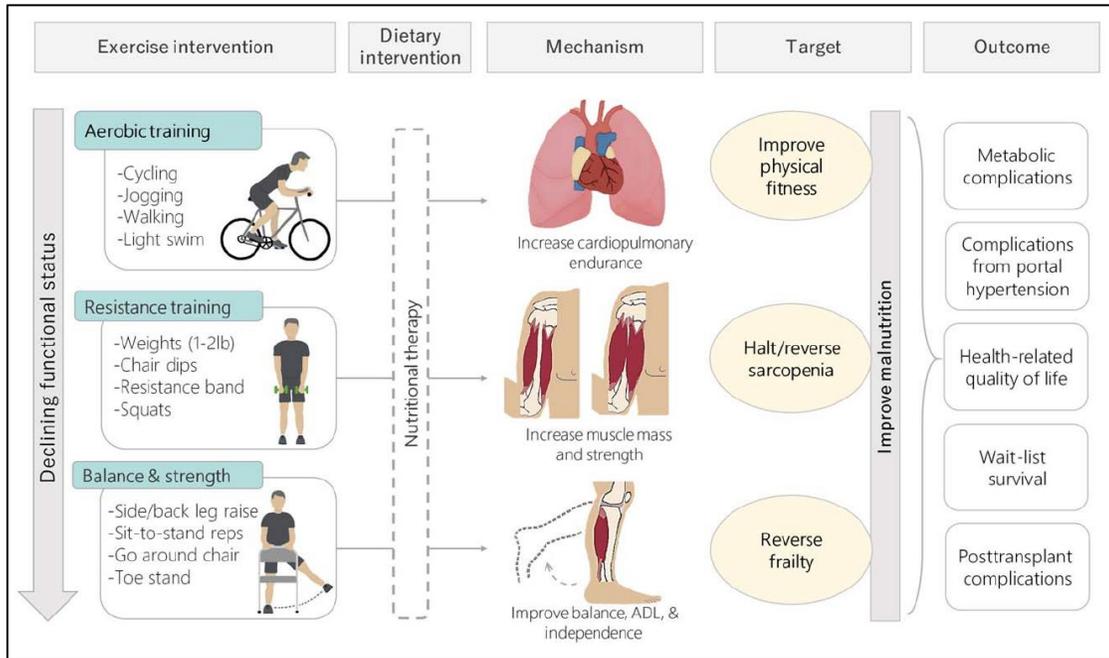


*Patients who had ≥ 2 episodes of HE within 6 months prior to screening and who were in remission at trial start

Challenges:

1. Needs bile to solubilize for optimal bio-availability
2. Expensive in certain countries, which can be a barrier
3. Not available in some countries, which is also a barrier

Work the body and mind



In patients with cirrhosis and depression, Mindfulness decreased depression, Sleep impairment, improved QOL and Caregiver burden

Co-morbid conditions and drugs affect cognitive test results and HE risk differently

Affecting HE risk

PPIs ↑

Opioids ↑

Statins ↓

Beta-blockers ↑

Other neuro-active drugs
(benzodiazepines,
gabapentin) ↑

Affecting cognitive tests

Age **Impairs**

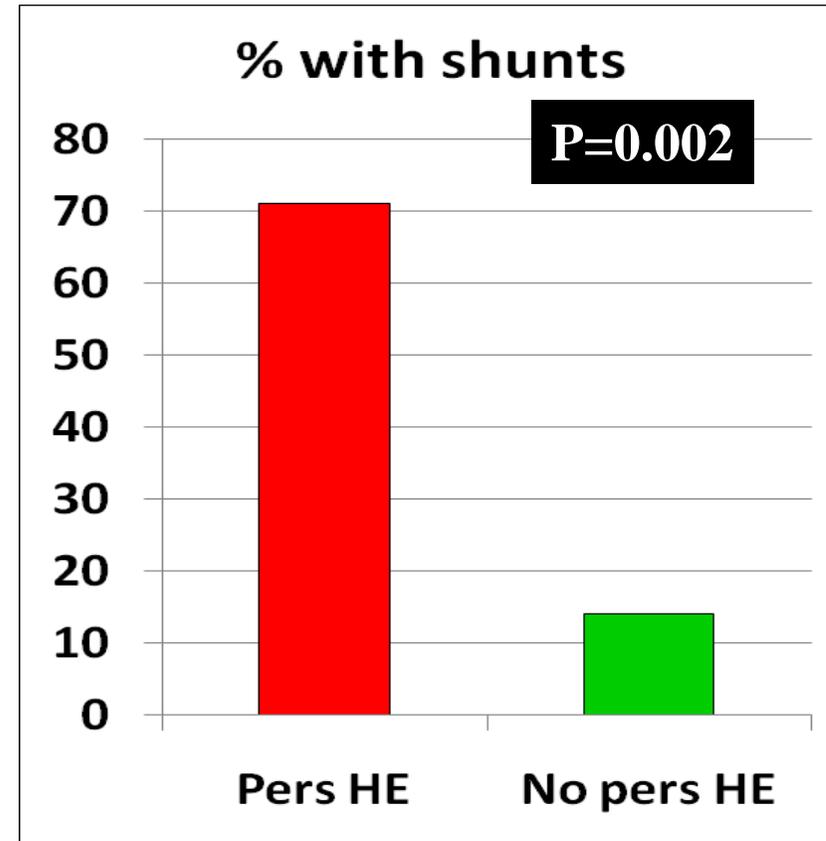
Opioids **Impairs**

Antidepressants **Improves**

Diabetes ~

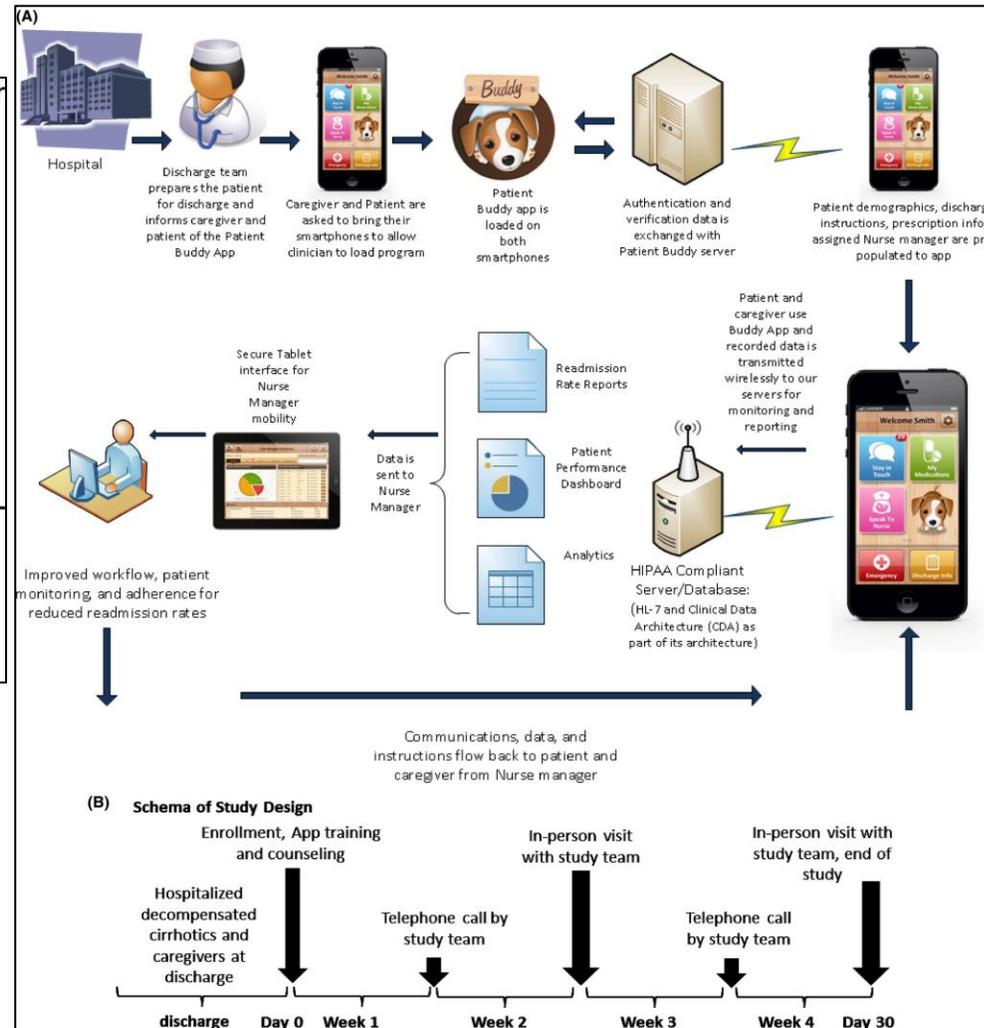
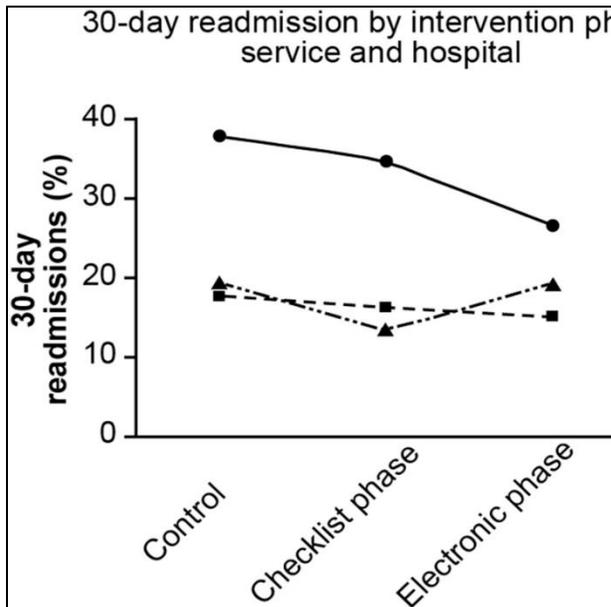
Renal Impairment ~

Persistent HE may be associated with shunts



Embolization of these shunts can improve the course of HE
Especially with low MELD <11 and a single shunt

Enforce Checklists and Keep in Touch with Patients To prevent Readmissions



CirrhoCare®

Novel digital-health system to diagnose and treat early new decompensation events in advanced cirrhosis

Daily patient data input and communication to hepatologist

- Measurements of hemodynamics, weight, water percentage, and cognitive testing
- Self-reported well-being and intake of food, fluid and alcohol
- Voice messages
- Text messages

Direct two-way communication to patient

- Phone calls
- Text messages
- Community intervention, e.g. advice on fluid intake, adjustment of diuretic and laxative doses

A pilot study of CirrhoCare® - remote home management in patients with decompensated cirrhosis

- 20 patients with advanced cirrhosis
- Home management for a mean of 10 weeks
- 20 contemporaneous cirrhosis control patients receiving standard-of-care management

CirrhoCare® prompts early diagnosis of new decompensating events and their specialist intervention in the community

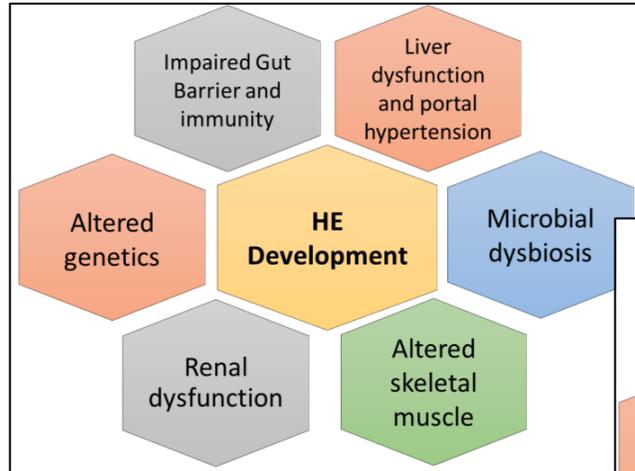
- High patient engagement
- Fewer and shorter readmissions than controls
- Markedly reduced unplanned paracentesis
- Improvement in disease severity scores

In addition to optimizing medications, further recurrence needs a multi- disciplinary approach

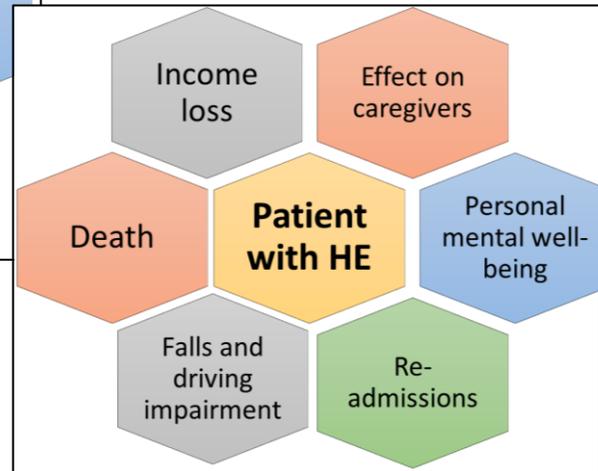
- A. Interventional Radiology (embolize SPSS)
- B. Nutrition (inpatient and outpatient consultation)
- C. Physical and occupational therapy (exercise, driving)
- D. Mental health (psychotherapy, mindfulness, mood disorders and substance abuse assessment)
- E. Oral health (attention towards gum disease and inflammatory foci in the mouth; clean teeth!)
- F. System changes (Checklists, Apps and other modes of communication)
- G. Driving safety

The Three Villages of Hepatic Encephalopathy

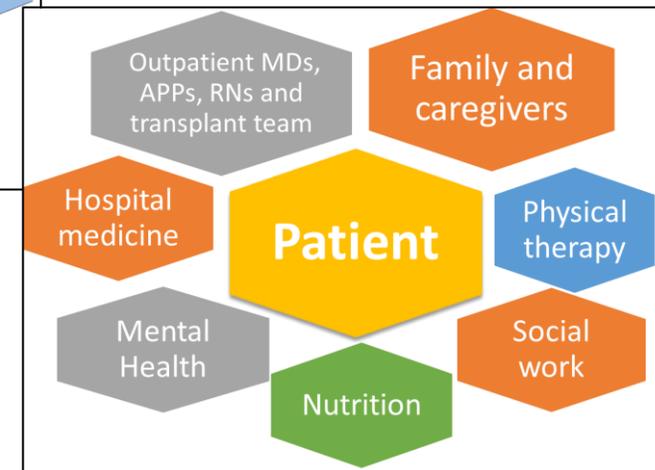
The Village Within for HE Development



The Village Affected by HE



The Village Required to Manage HE



Special Situations

- TIPS

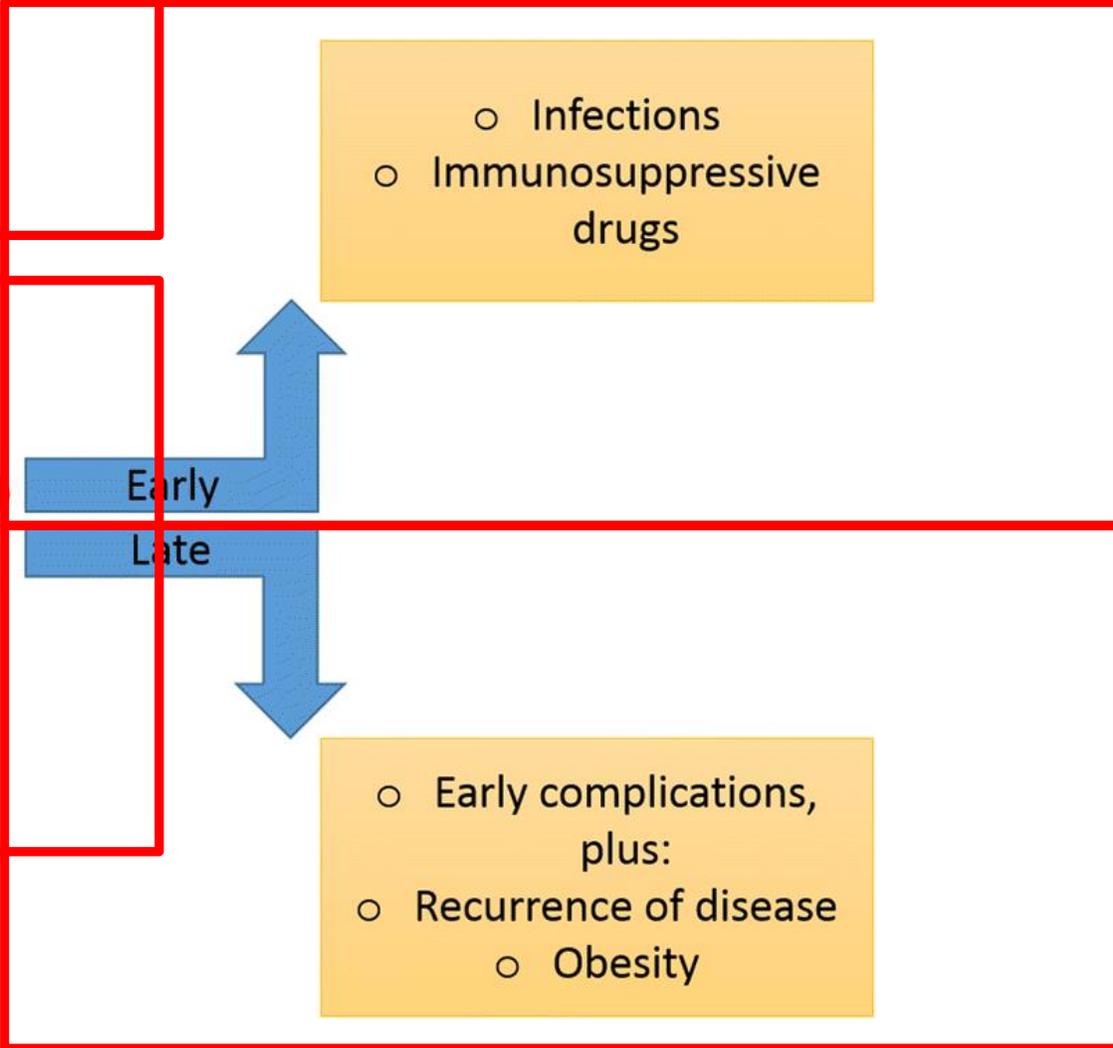
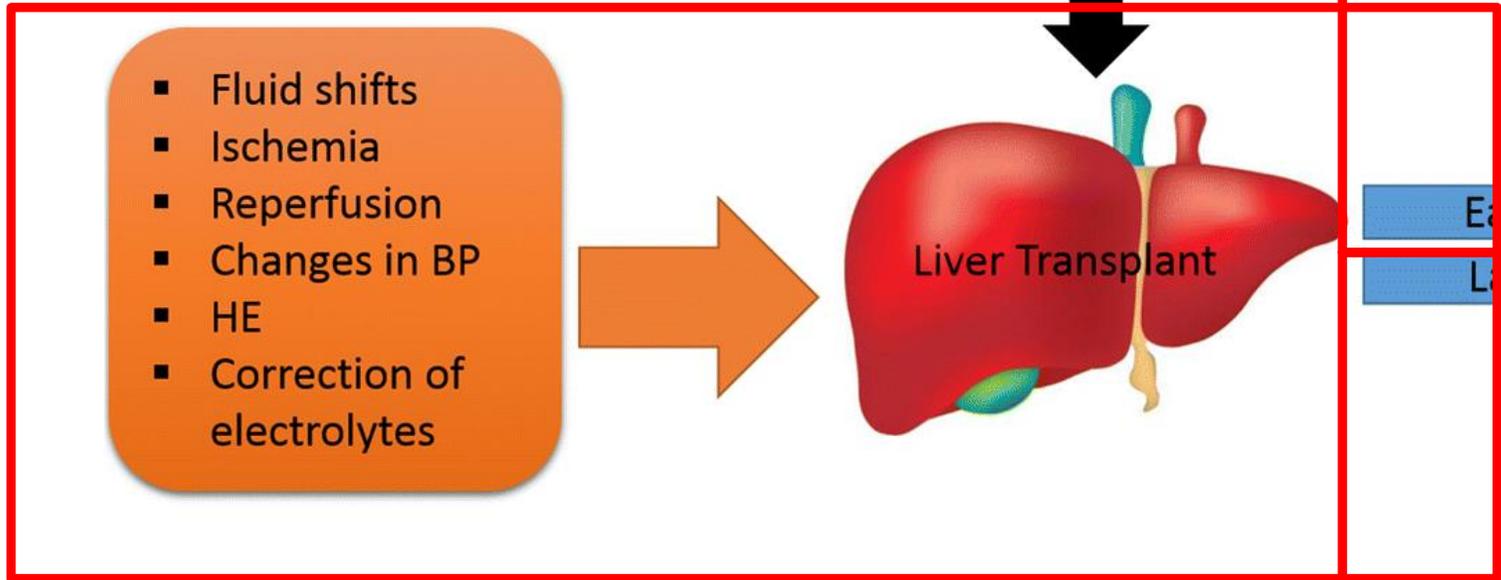
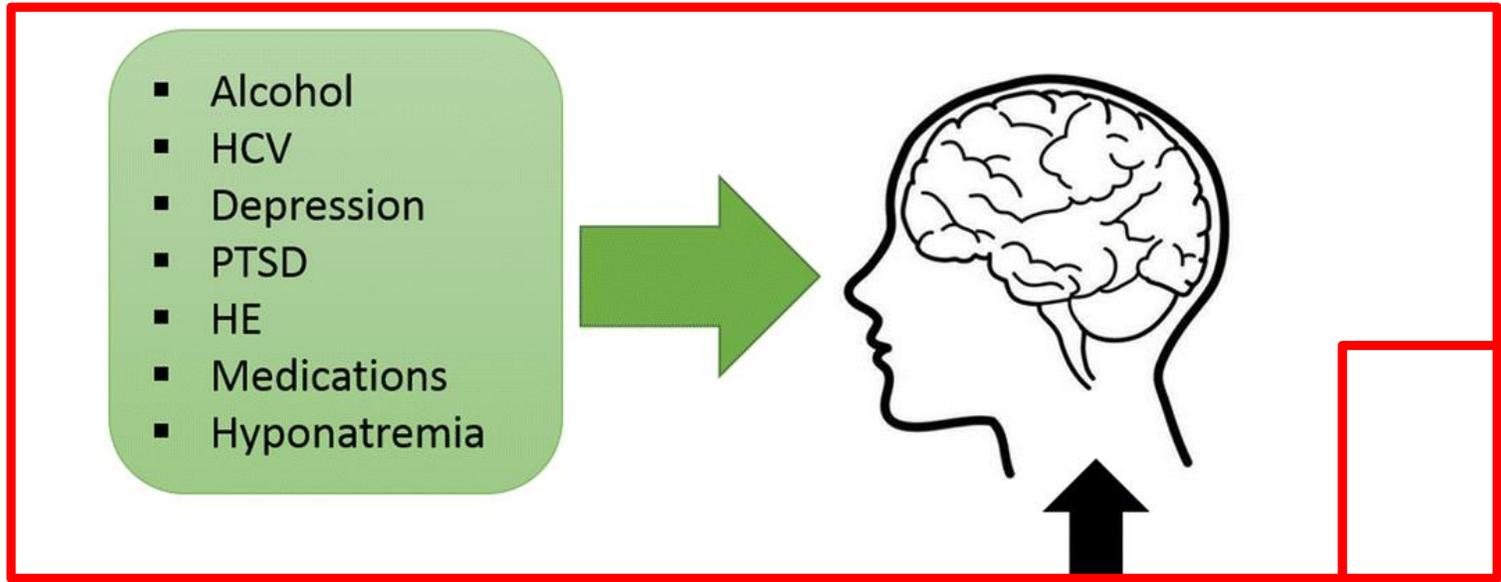
- Driving

- Post Liver Transplant

Liver transplant

Do things get better once the diseased liver is replaced by a healthy new liver?

It's complicated because
LT is not a perfect model



Substantial Burden of Neurological Complications Post-LT

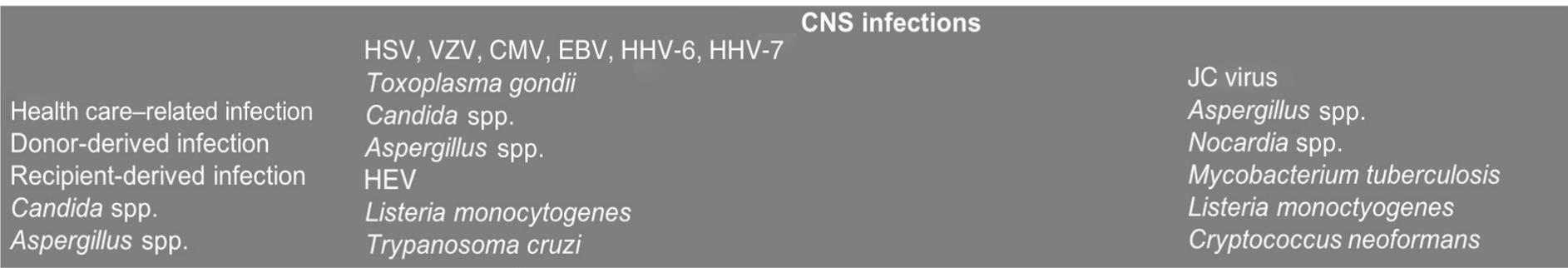
Early=15%

1 month

6 month

Later=30%

5-10%



2-7%

2-4%

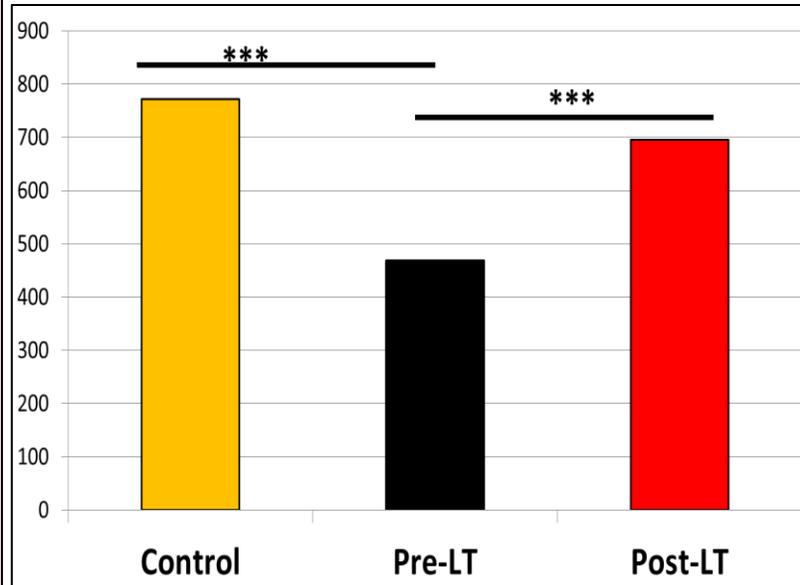
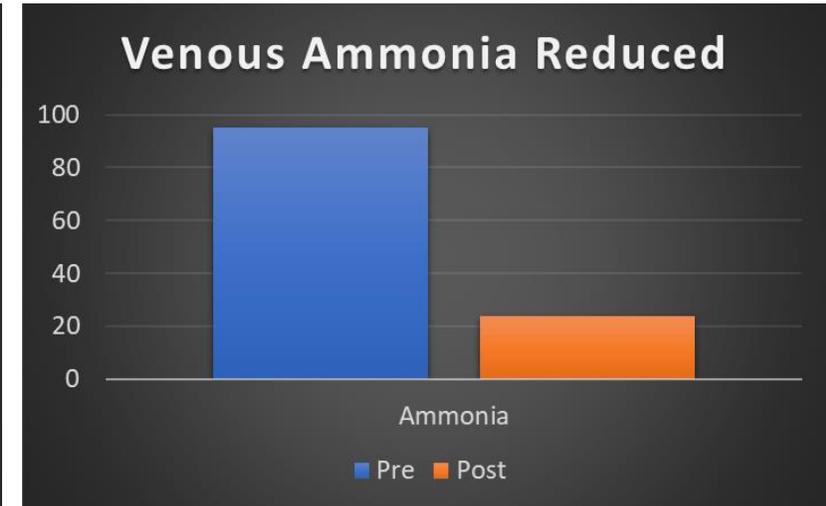
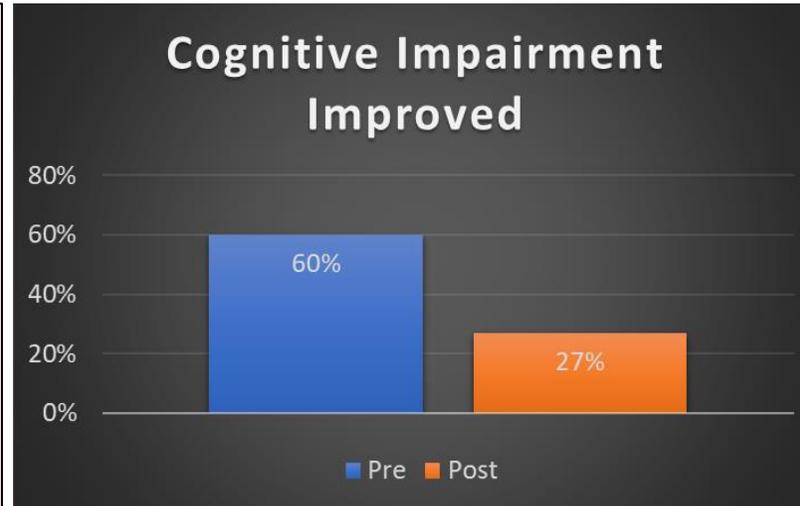
1-10%

1%

30%

Microbial diversity & function, and Cognition recovers post-LT

- ✓ **Cognitive function Improves** and is linked with **change in gram-negative bacteria**
- ✓ **Intercurrent events:** Microbiota are **disrupted** by infections, surgical issues and rejection
- ✓ **Stability after 6 mths:** Better diversity and **return of microbial function**



1. Total Fecal BAs ↑
2. Deconjugation =
3. Oxo-bile acid formation ↑
4. Iso-bile acid formation ↑
5. 7 alpha de-hydroxylation to form secondary BAs ↑

High Burden of HE after TIPS

- Overall, all comers =25-45%
- New or worsened?=13-36%
- Cause of 50% of readmissions post-TIPS
- Can result in multiple episodes
- Major reason for poor HRQOL post-TIPS
- However, should not stop one from putting one in for variceal bleeding

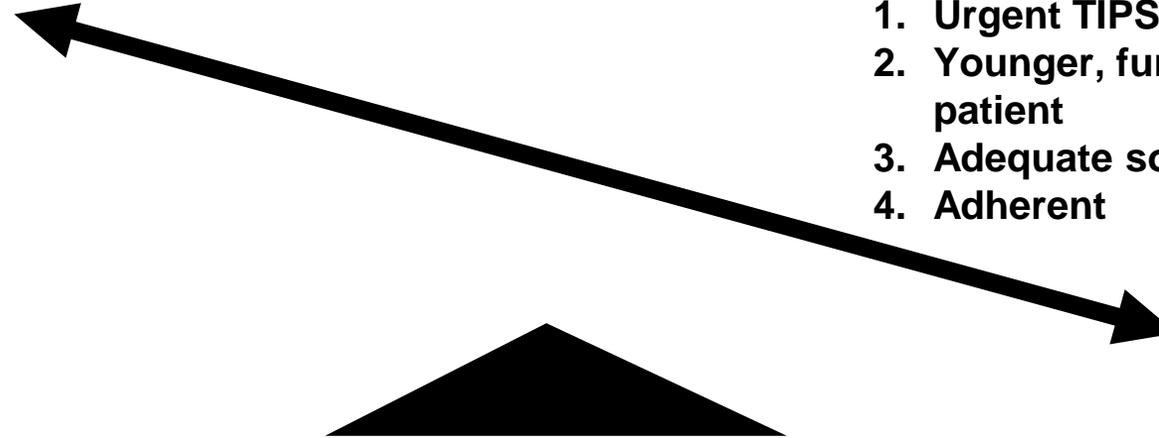
Predictors and Decision Points

RISK HIGH

- 1. Older patient without social support**
- 2. Prior Overt HE**
- 3. Current Cognitive Impairment**
- 4. Sarcopenia**
- 5. Advanced liver disease**
- 6. Elective TIPS with alternatives**

BENEFIT HIGH

- 1. Urgent TIPS**
- 2. Younger, functional patient**
- 3. Adequate social support**
- 4. Adherent**



Rifaximin ↓ HE after Elective TIPS Placement

Does rifaximin reduce hepatic encephalopathy after transjugular intrahepatic

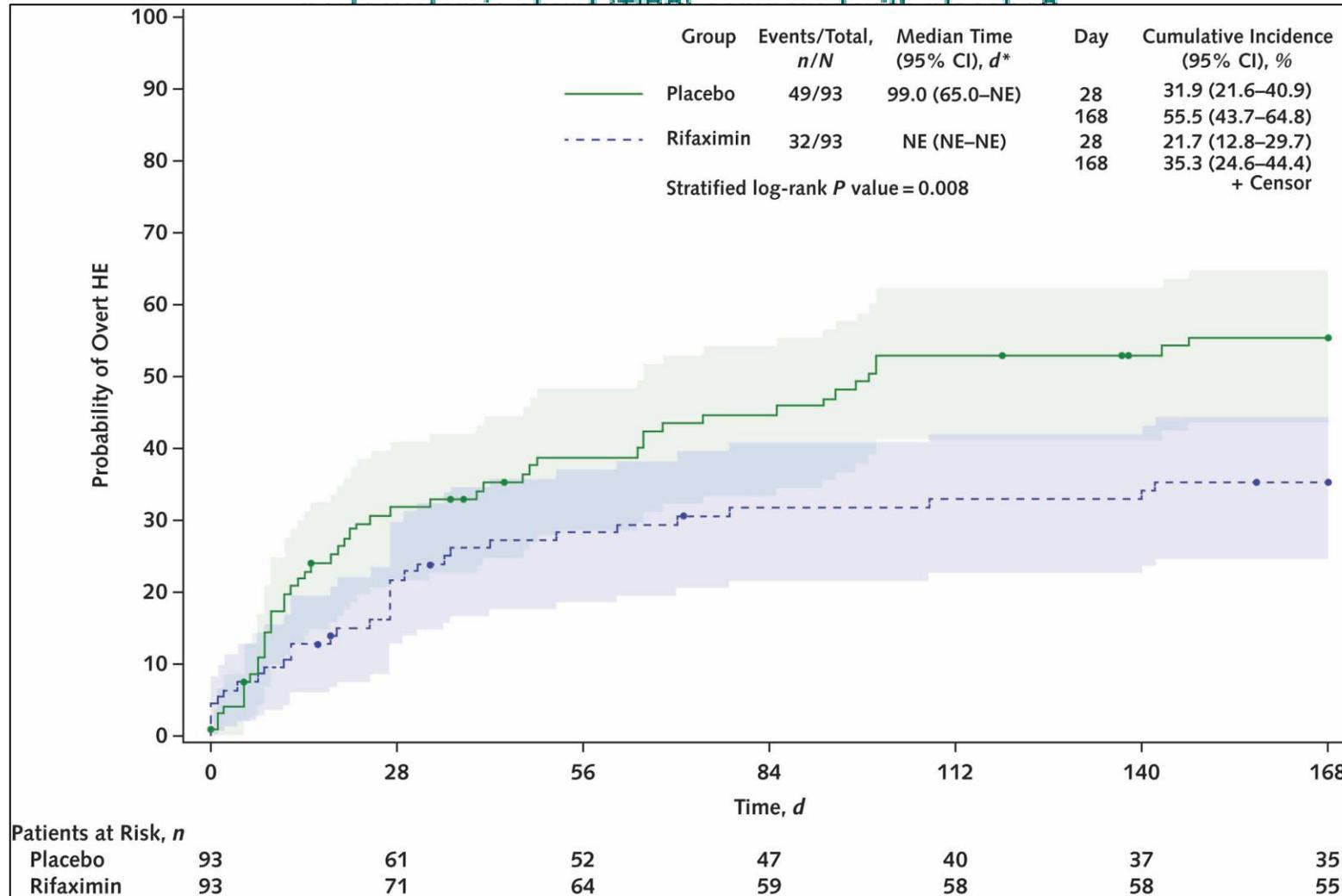
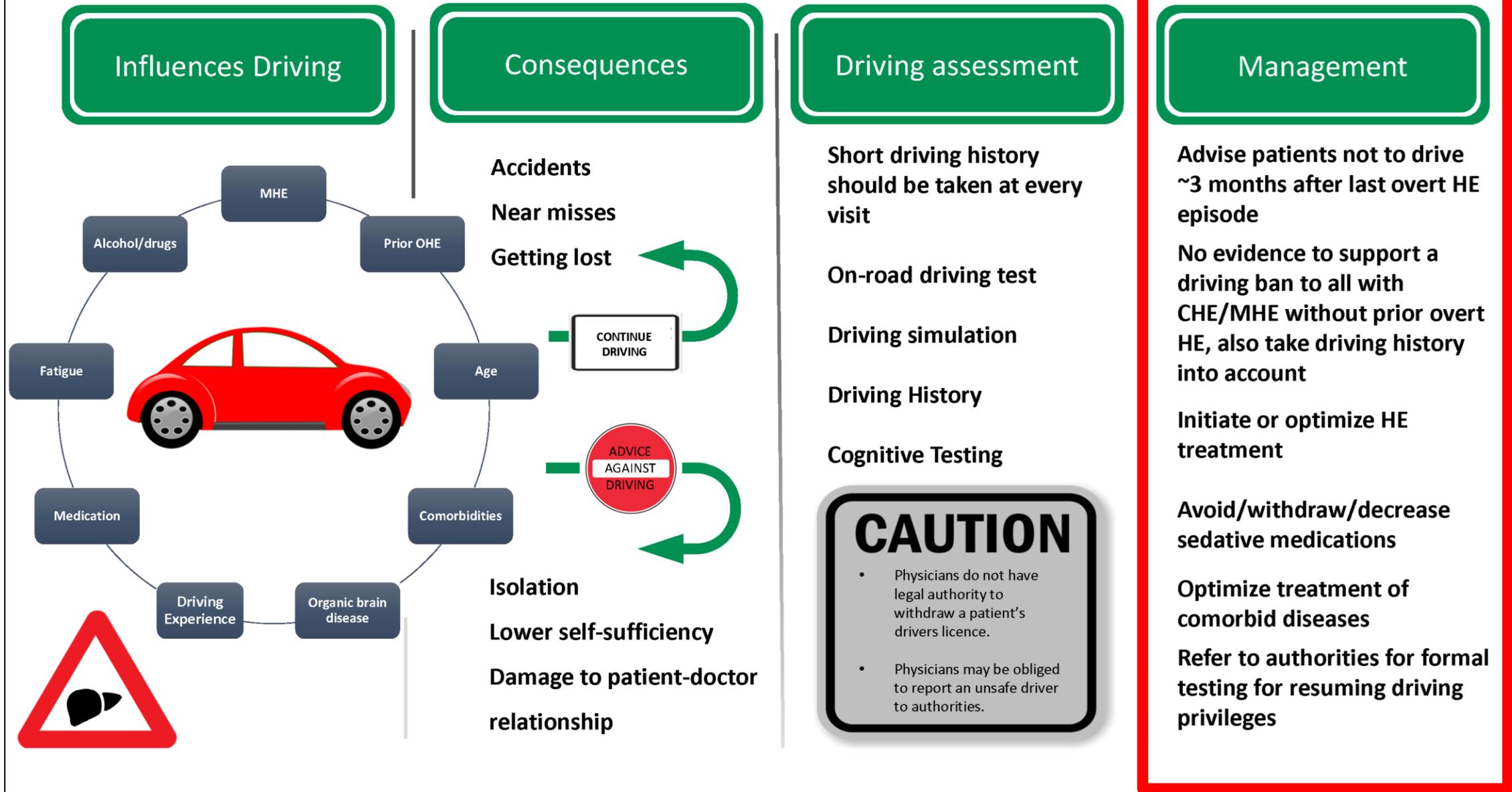


Figure 1: Hepatic Encephalopathy and Fitness to Drive

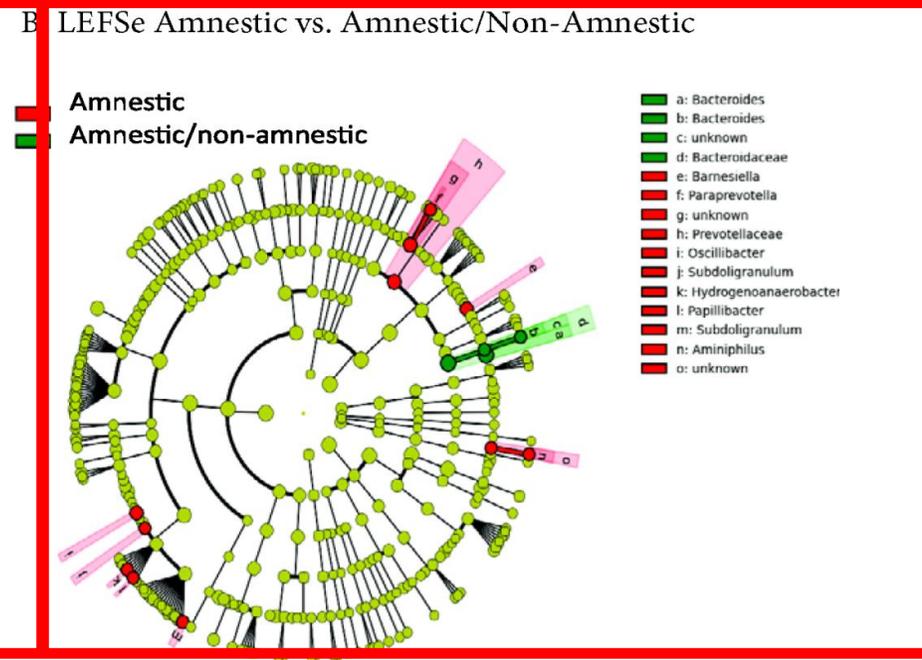
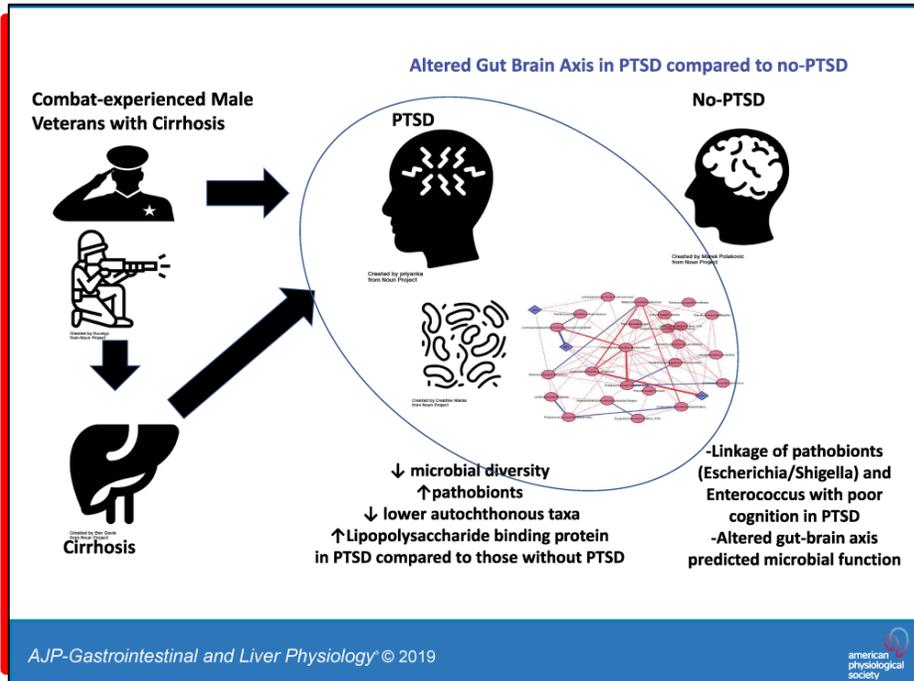
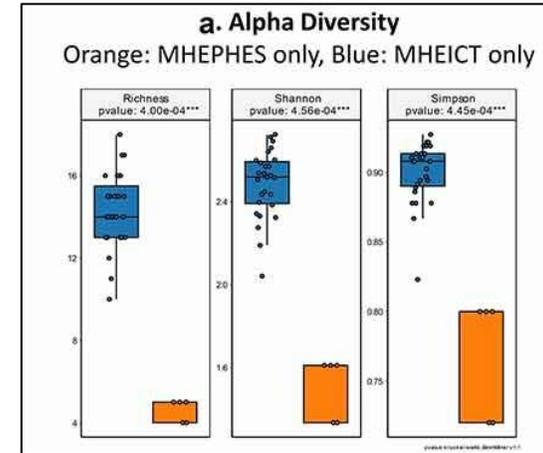
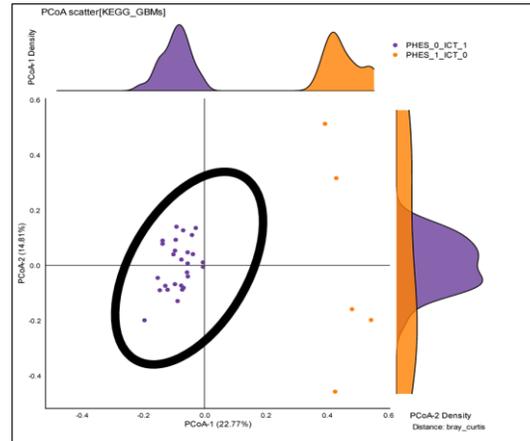
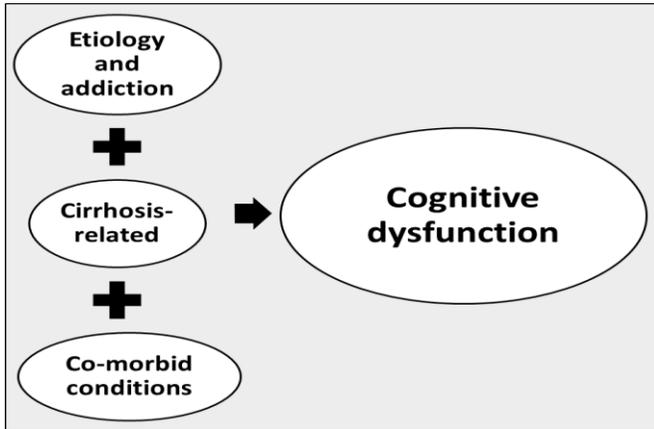


**What's being tested for HE
diagnosis and treatment now?**

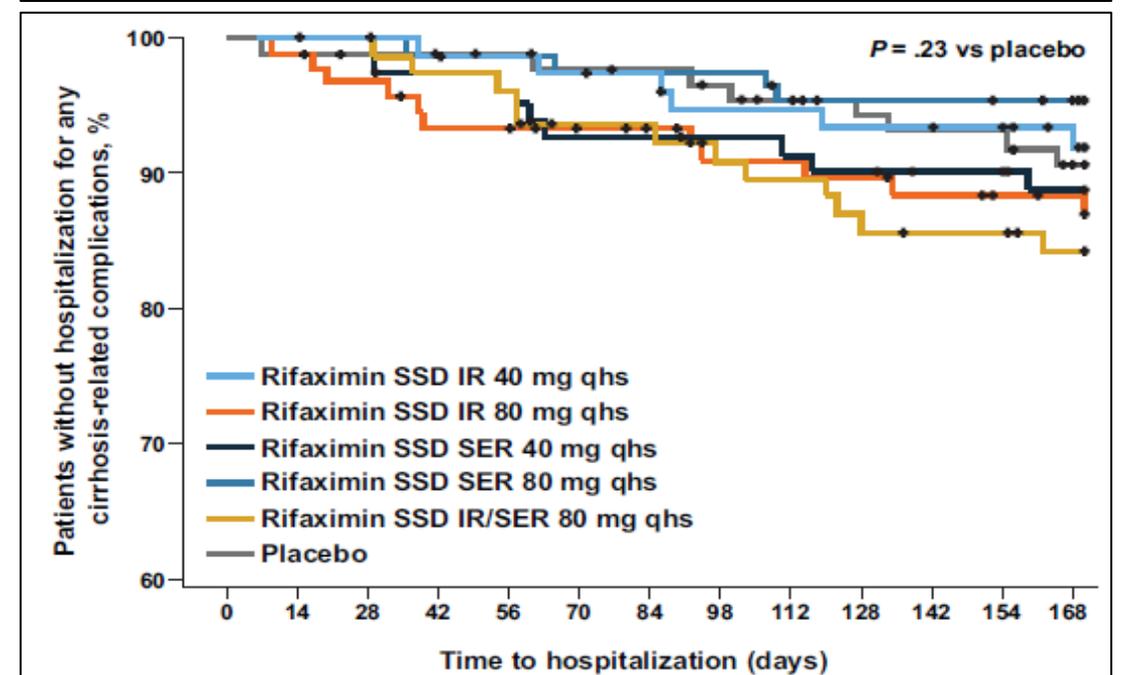
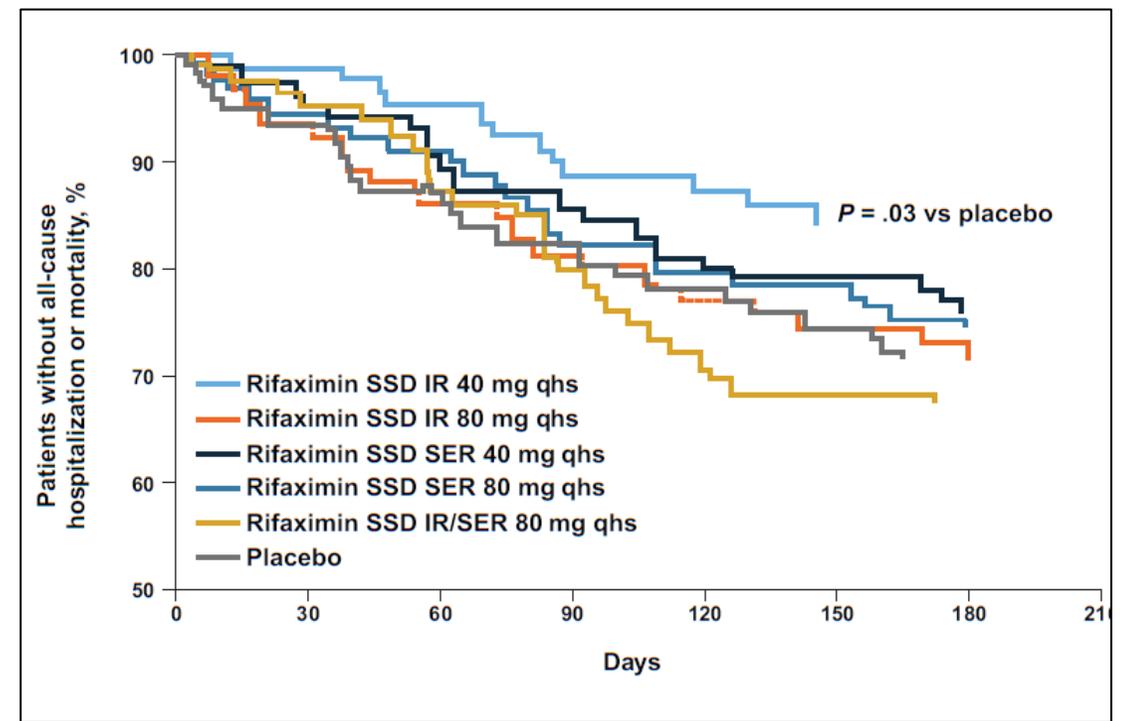
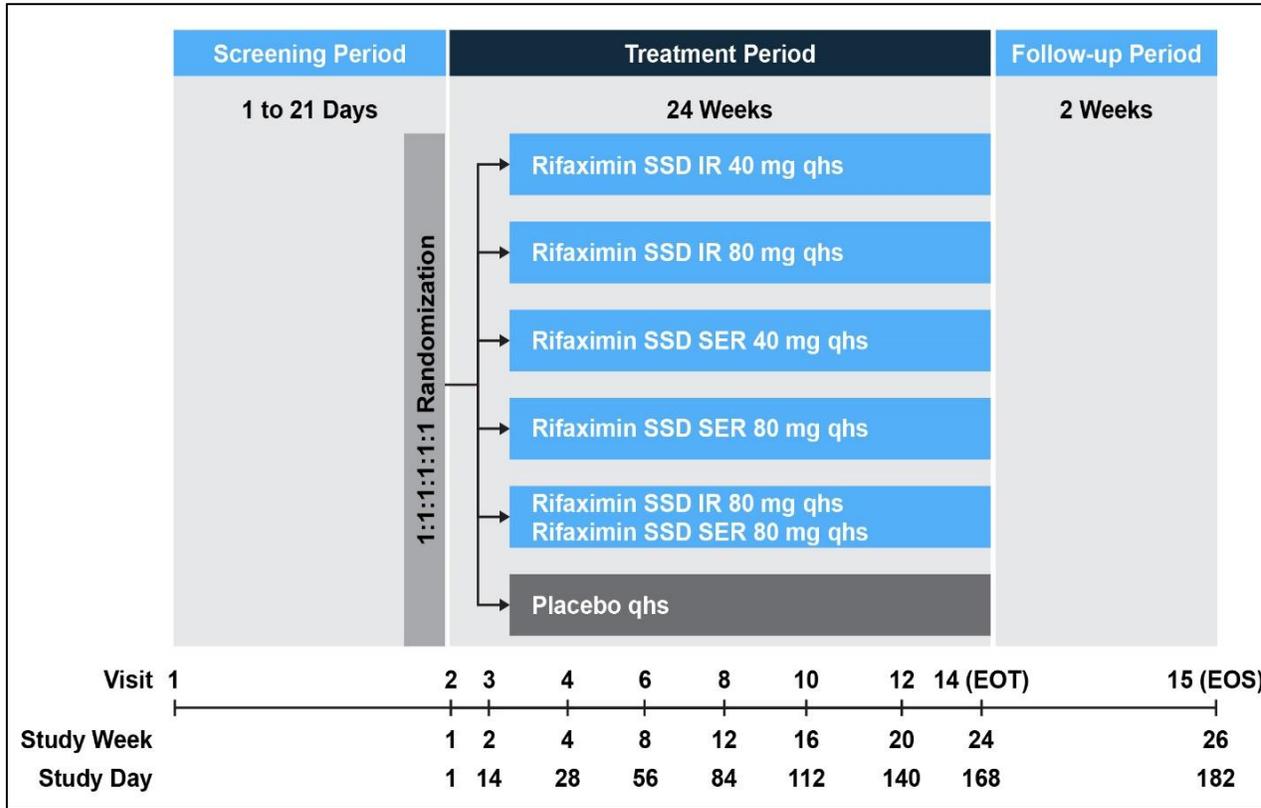
Newer Therapies

- Rifaximin SSD
- Rifamycin SV MMX
 - FMT
- Golexanolone
- Albumin

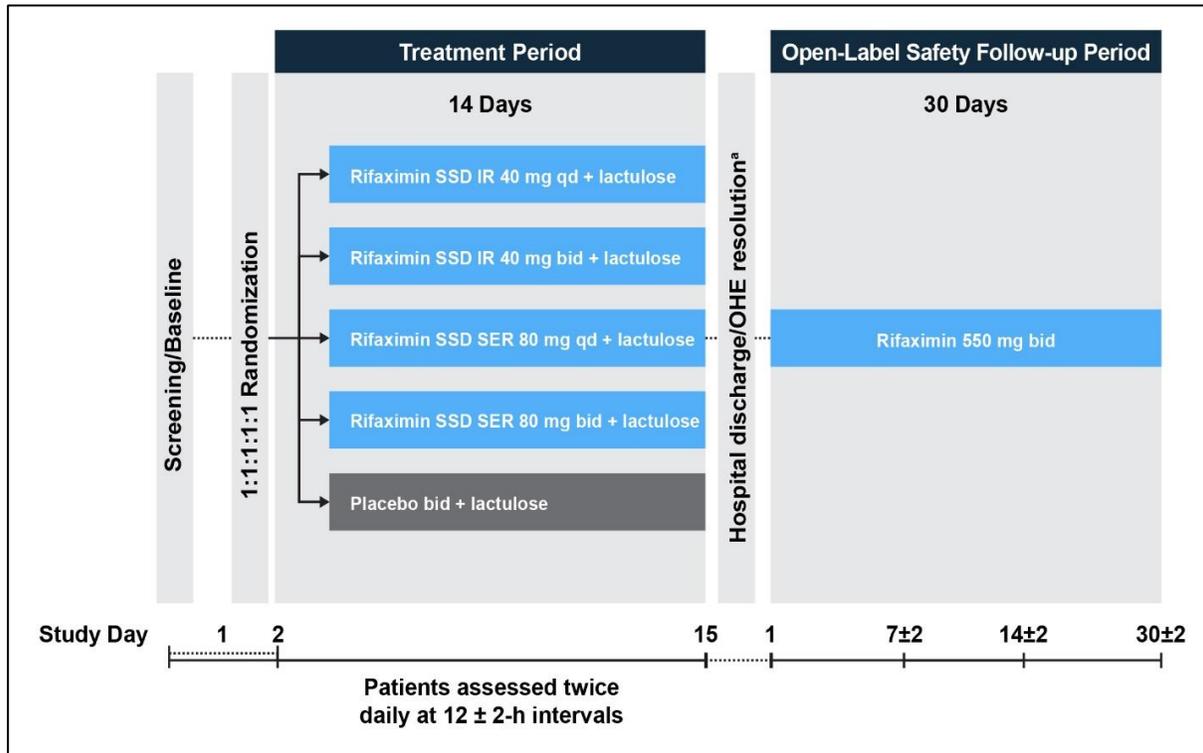
Microbial Profiles Can Exclude MHE and Determine Impact of Addiction, Aging and PTSD



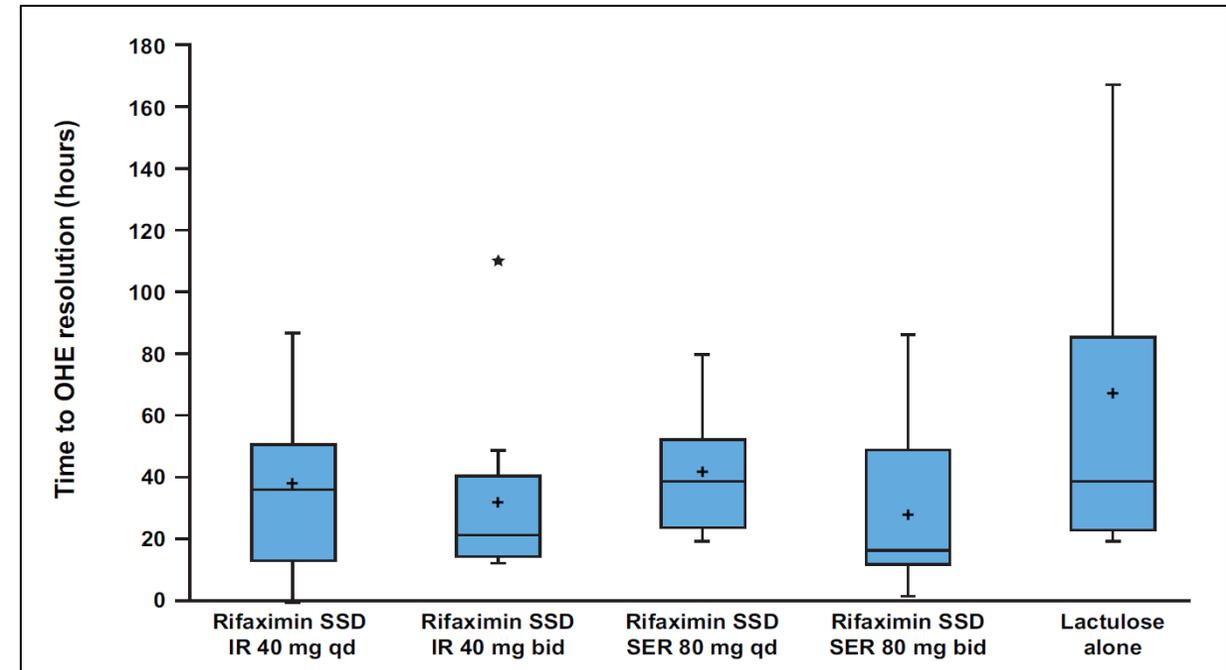
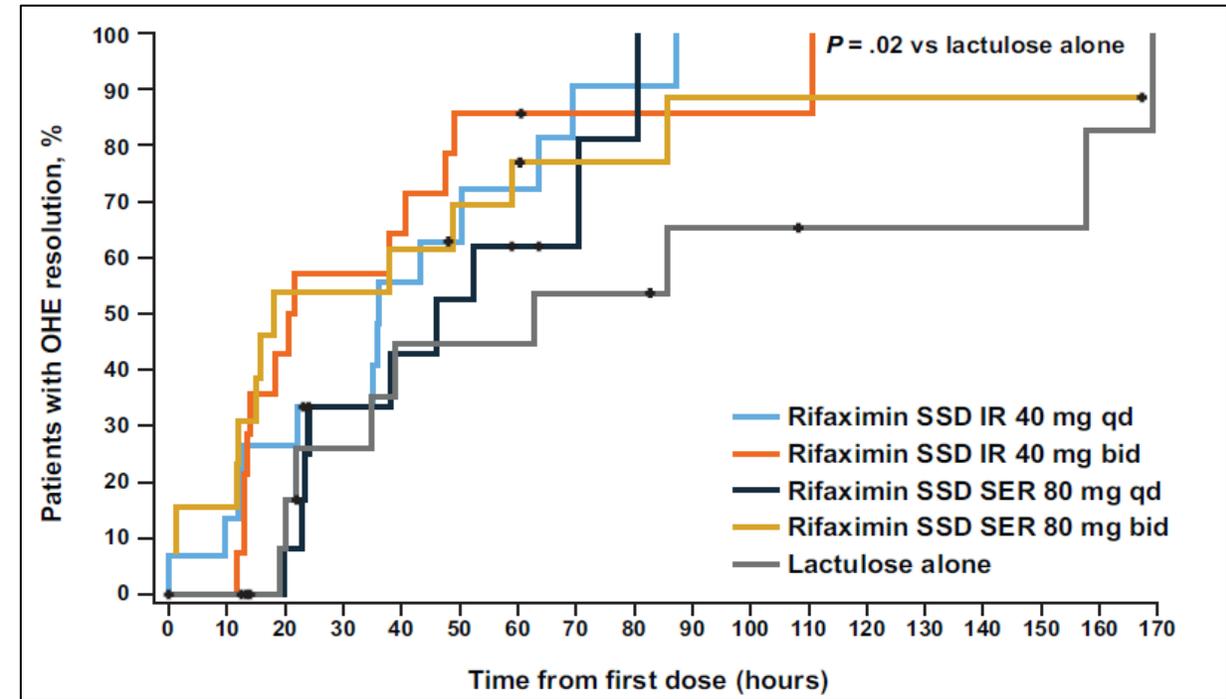
Rifaximin SSD for outpatients with controlled ascites to prevent mortality or hospitalizations



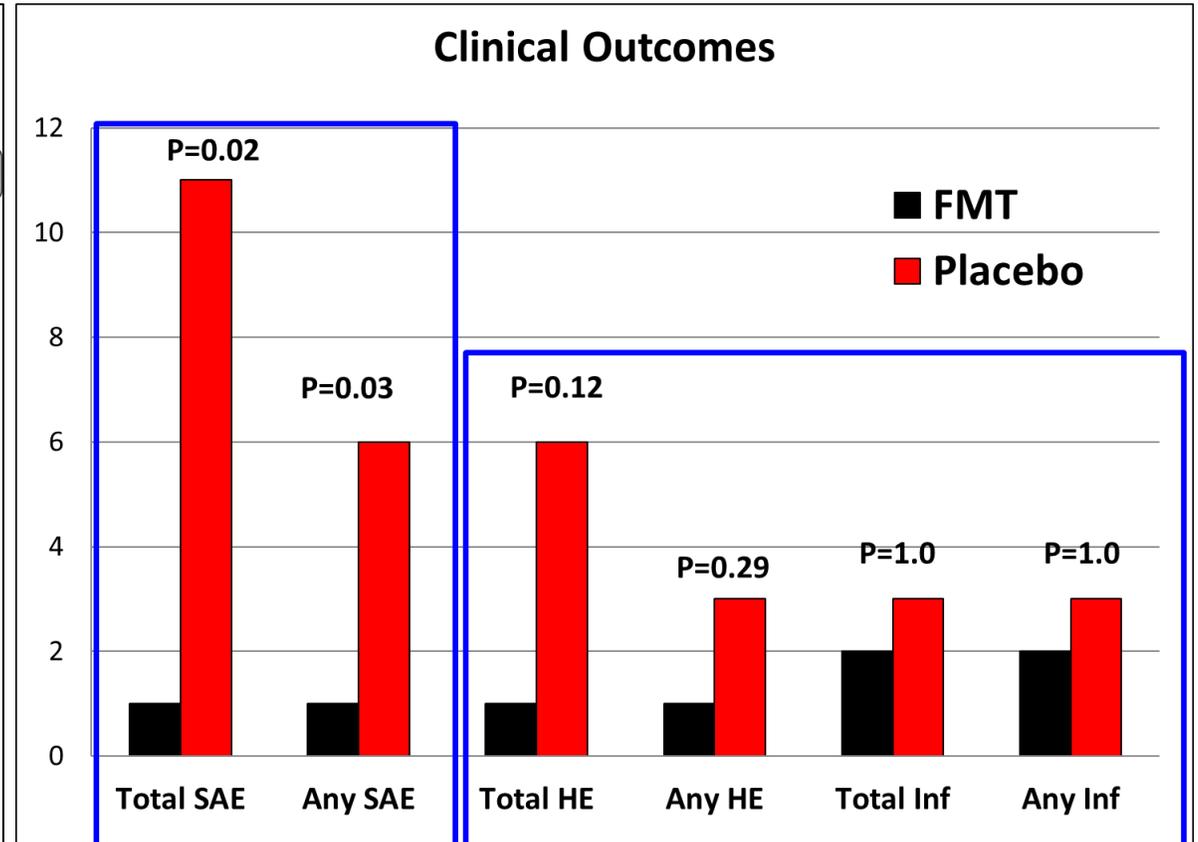
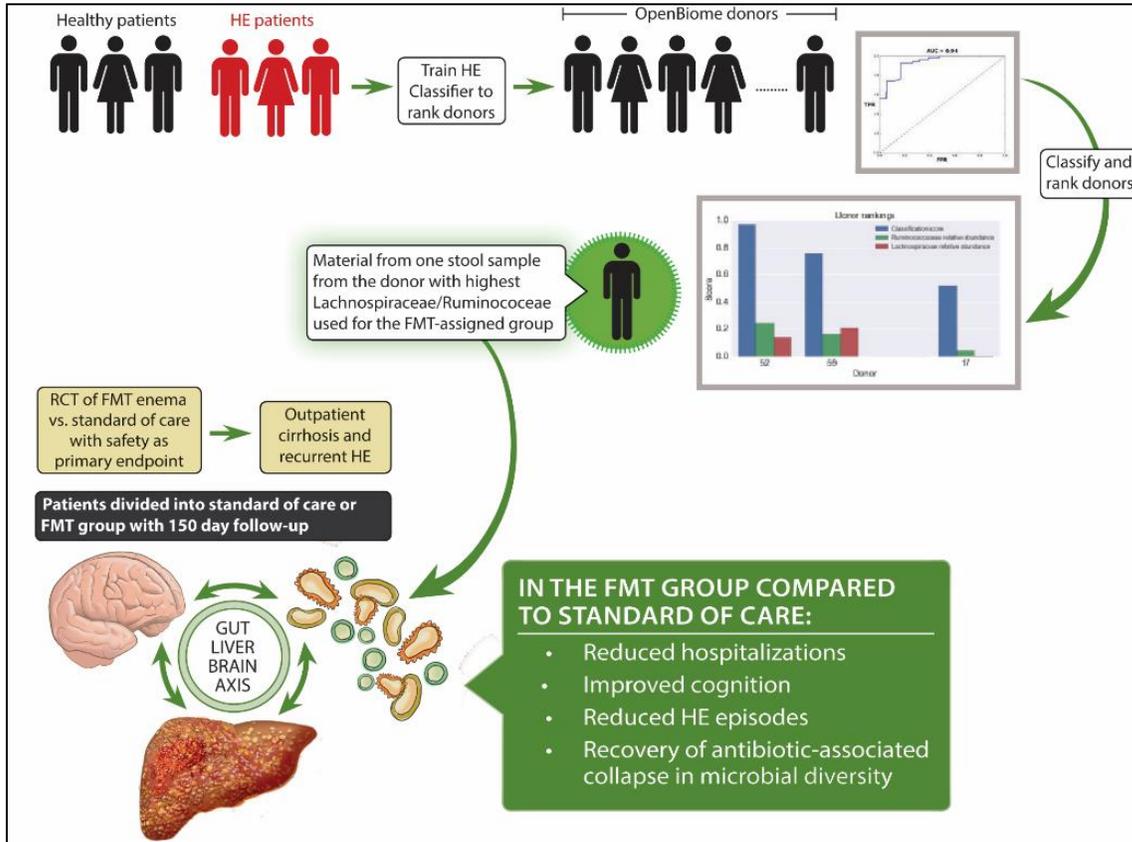
Rifaximin SSD for inpatients with overt HE to hasten resolution of confusion



Bajaj JS et al Clin Gastro Hep 2022

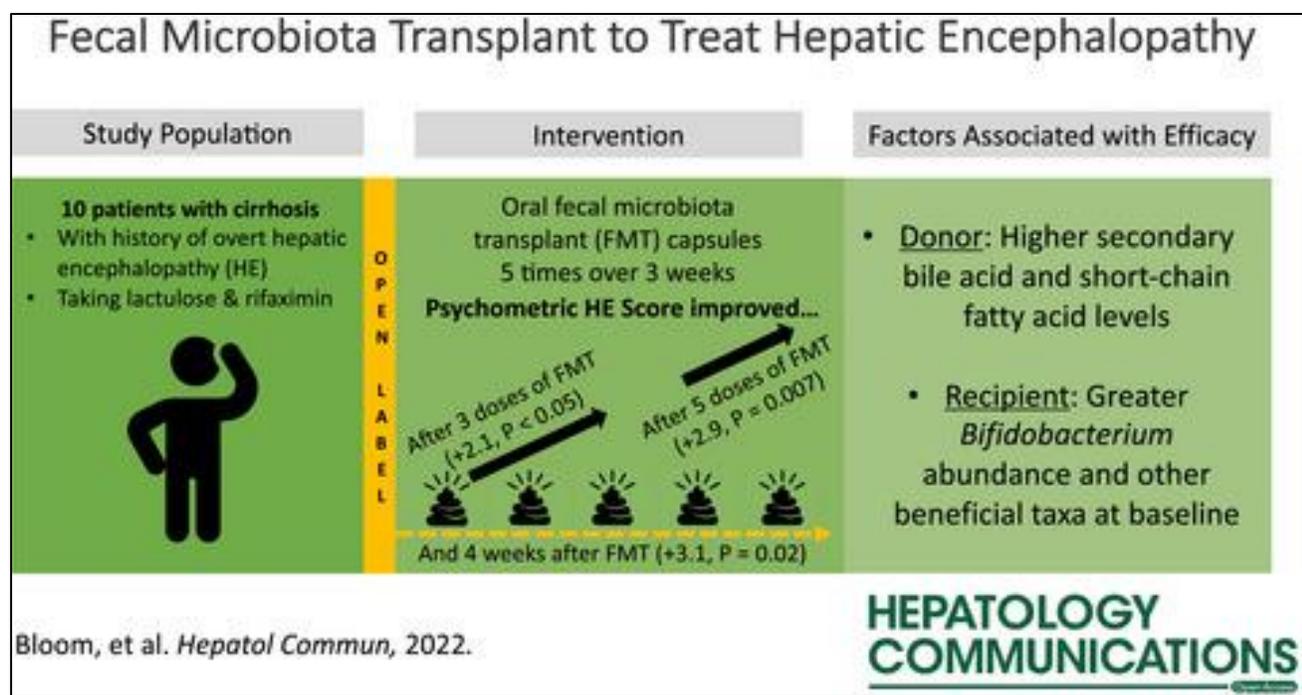


Gut Microbiota modulation for HE prevention using FMT

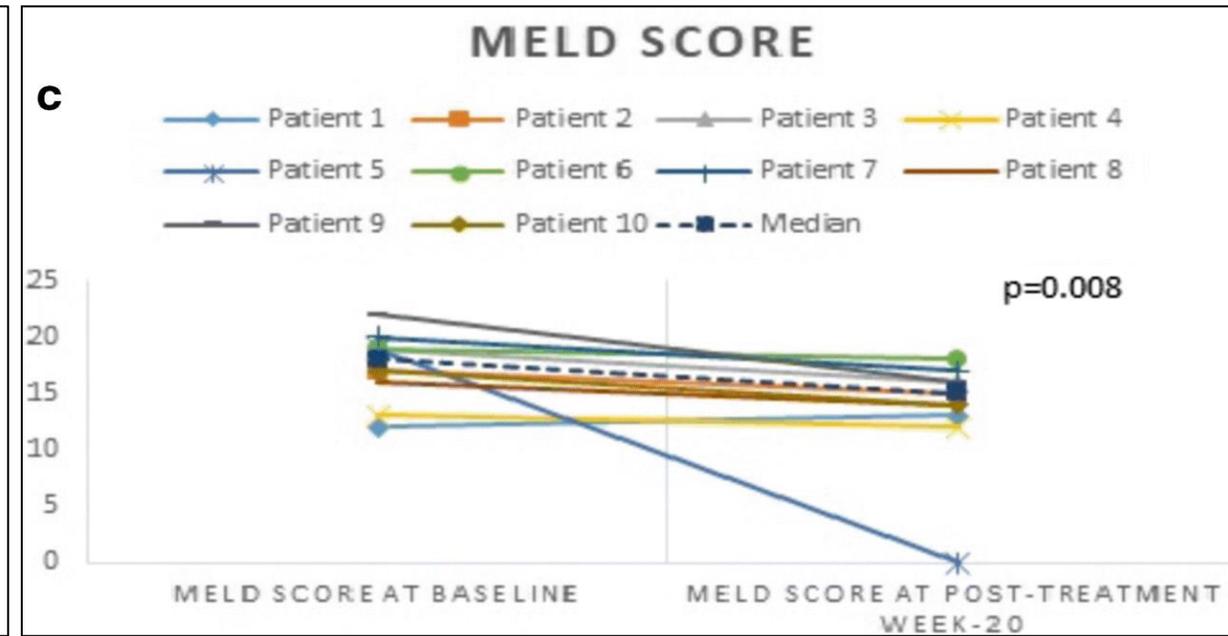
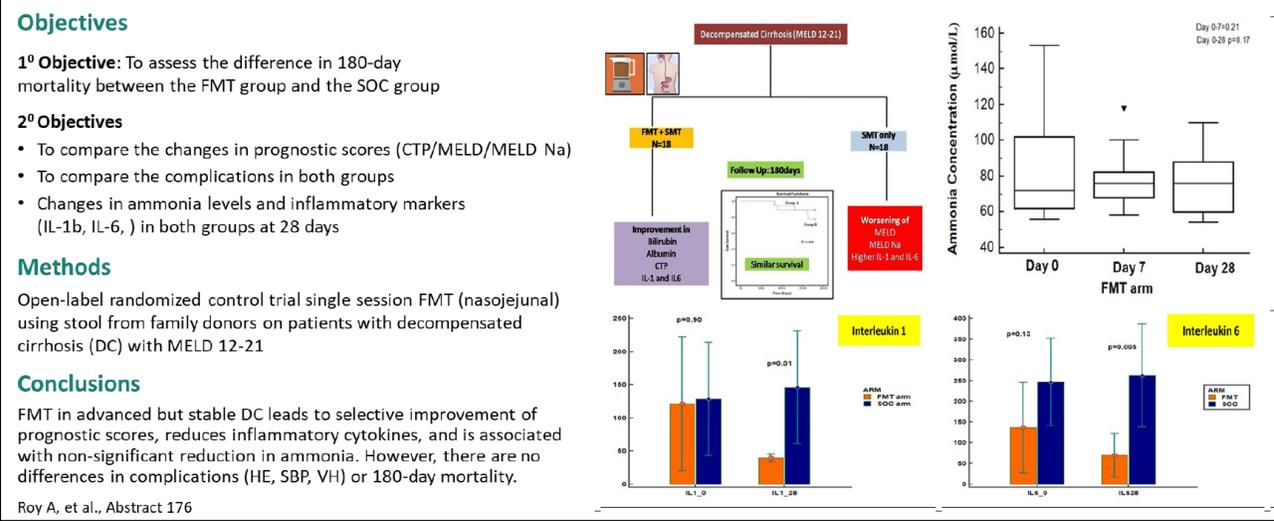


Enema and capsules are both safe with potential for improvement in 2 small RCTs
 Large RCT in HE underway

Further Studies on HE using FMT

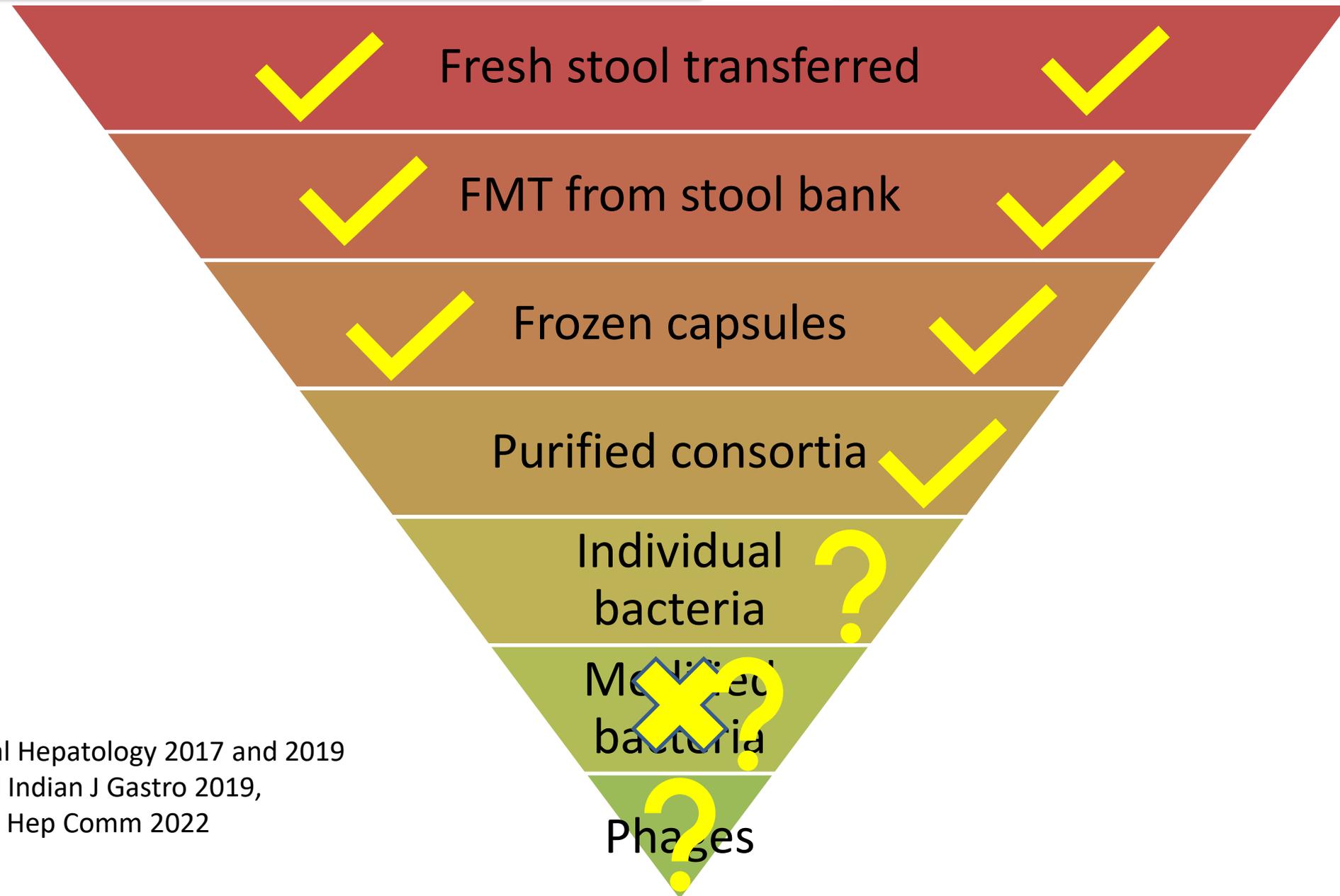


Single session fecal microbiota transplantation in decompensated cirrhosis: an initial experience of clinical endpoints



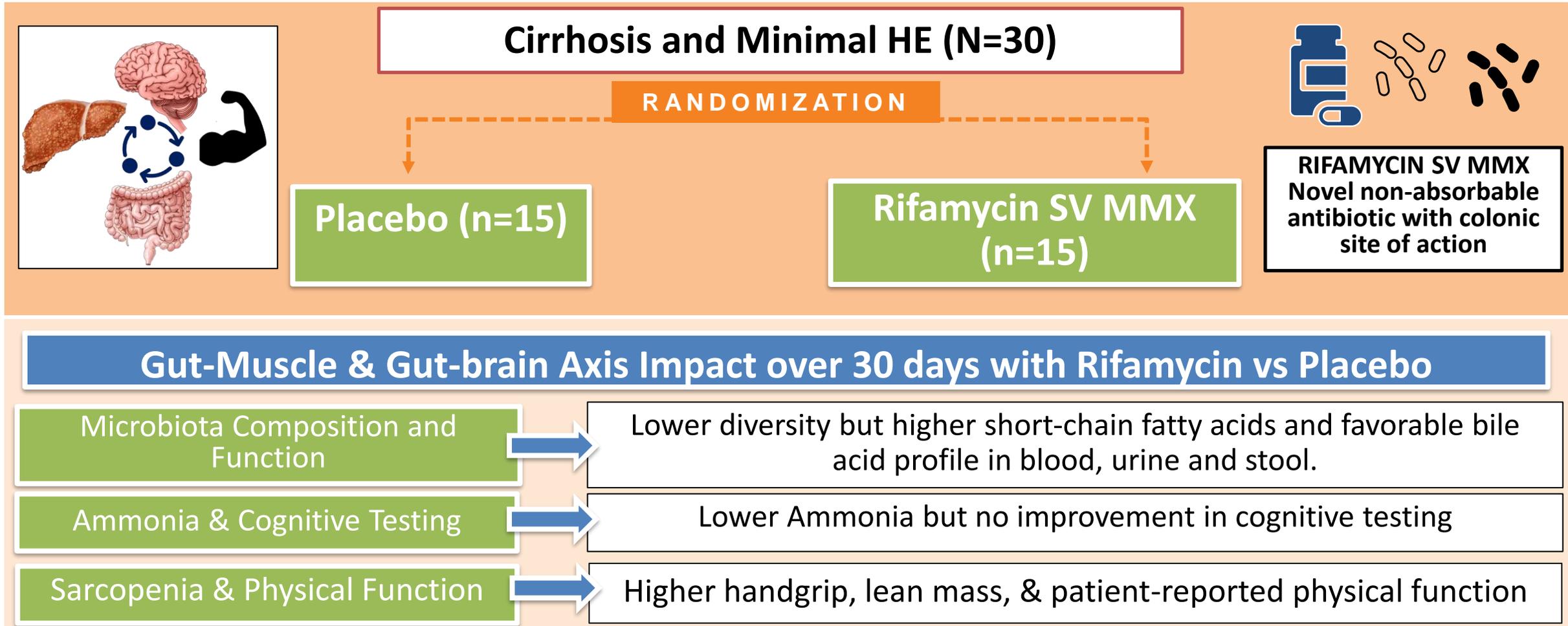
Hepatic Encephalopathy

C. Difficile

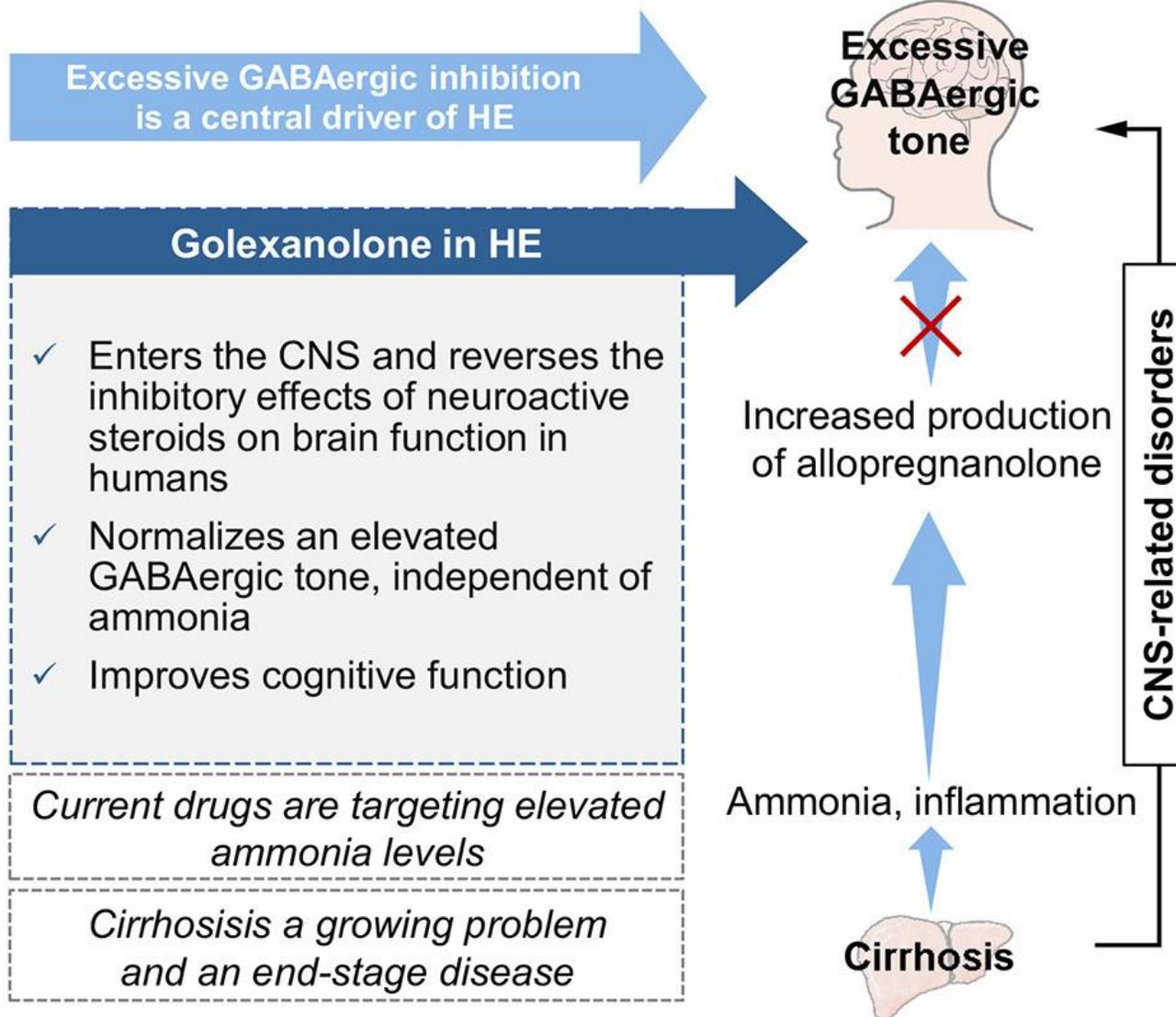


Bajaj JS et al Hepatology 2017 and 2019
Mehta et al Indian J Gastro 2019,
Bloom et al Hep Comm 2022

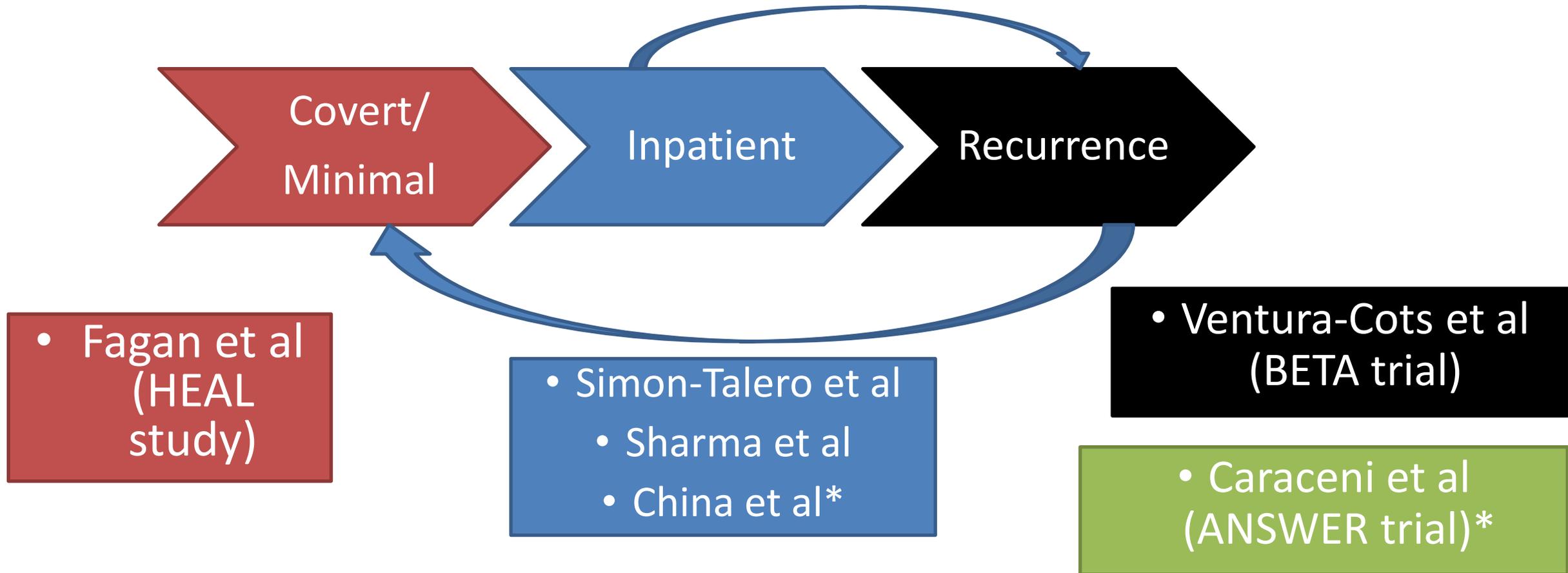
RIVET Trial: Impact of Rifamycin SV MMX on gut-brain and gut-muscle axis in patients with cirrhosis



Golexanolone: the only HE drug directly targeting CNS



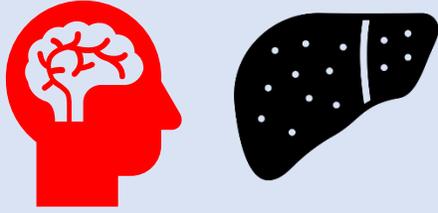
Stages of HE and where albumin has been used



*HE was not the primary focus of inclusion

HEAL RCT: Albumin in Hepatic encephalopathy

Population

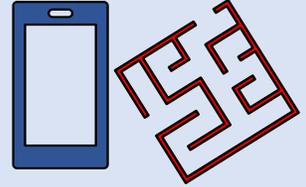


Created by Flowicon

Patients with cirrhosis and prior HE who have cognitive impairment or minimal HE despite standard of care

Outcomes

Primary: Cognitive Performance

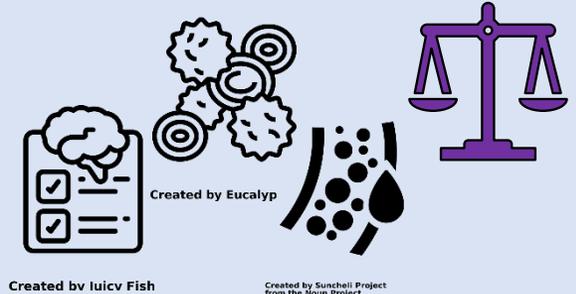


Secondary:

Quality of life

Inflammatory cytokines

Endothelial dysfunction



Created by luicy Fish

Created by Sunchell Project from the House Project

Intervention



25% IV albumin



Placebo (saline)

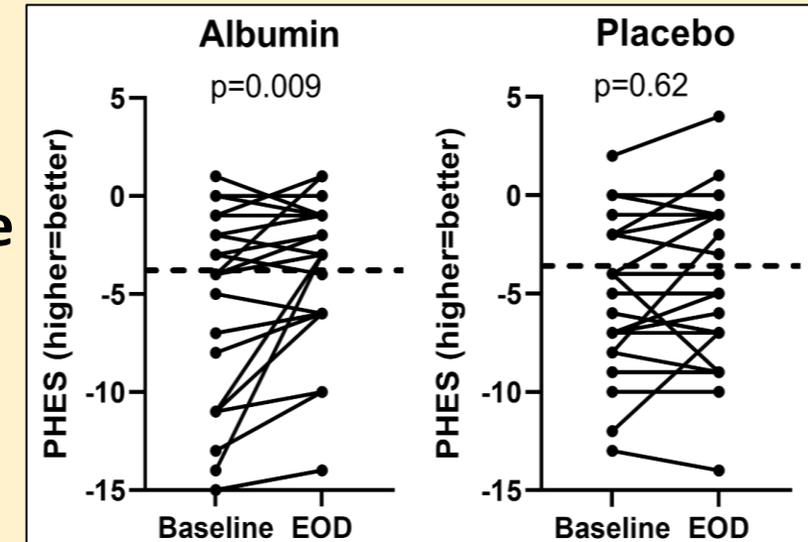
- 1:1 randomization
- 1.5g/kg weekly for 5 weeks using blinded infusions
- Follow-up 1 week after last infusion

Findings

In Albumin vs placebo

- ↑ Minimal HE Reversal
- ↑ Psycho-social quality of life
- ↓ endothelial dysfunction & inflammation
- Effect persisted even after albumin discontinuation

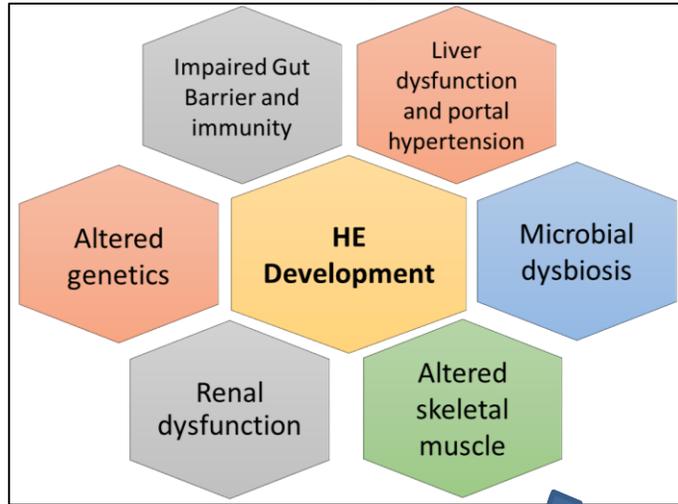
PHES: Primary Cognitive Outcome



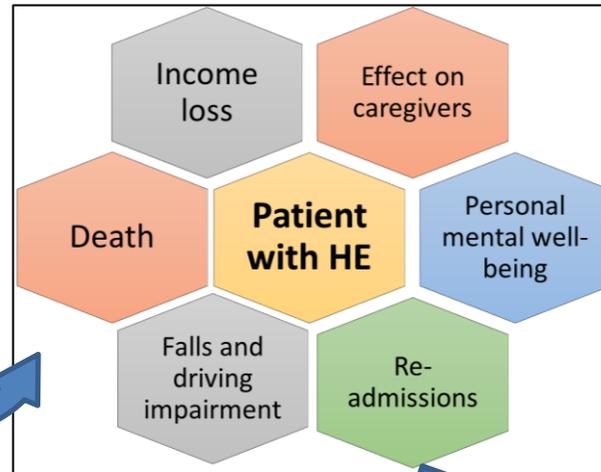
Fagan et al Journal of Hepatology 2022

The Three Villages of Hepatic Encephalopathy

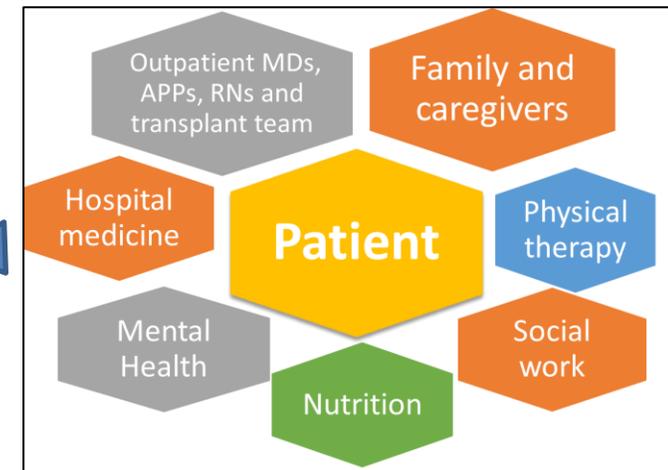
The Village Within for HE Development



The Village Affected by HE



The Village Required to Manage HE



Take-home messages

- Hepatic Encephalopathy is a complex syndrome **which requires several specialties** in management
- Overt HE **staging along 4 axes** during inpatient settings to improve treatment and prevent readmissions is important
- Appropriate use of **therapies** to prevent recurrence with adequate patient contact, improving **nutrition**, optimizing **medications** and ensuring contact with **caregivers** are needed
- **Checklists** on discharge may be helpful, especially if included in the EMR
- **Microbial alterations** as prognosticators and FMT are potential emerging fields of management and **quality vs quantity of** stools may be important.

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