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The Brain
(Hepatic Encephalopathy)

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3/4/23

Definition

- Hepatic Encephalopathy is a brain dysfunction caused by liver insufficiency and/or porto-systemic shunting
  - Manifests as a wide spectrum of neurological or psychiatric abnormalities, from subclinical alterations to coma
  - **Overt Hepatic Encephalopathy (OHE):** having noticeable symptoms when evaluated clinically
  - **Covert Hepatic Encephalopathy (CHE):** may not have noticeable symptoms when evaluated clinically

Vilstrup, H. et al. Hepatic Encephalopathy in Chronic Liver disease: 2014 Practice Guideline. Hepatology 2014;60:715-735

Epidemiology

- Prevalence of OHE is:
  - 10-14% at time of diagnosis of cirrhosis
  - 16-21% in decompensated cirrhosis
  - 10-50% in patients with transjugular intrahepatic porto-systemic shunts

- OHE will occur in 30-40% with cirrhosis at some time in their lives
  - Those who have had episodes of OHE nearly always have recurrent episodes

- CHE occurs in 20-80% of patients with cirrhosis

- HE accounts for 110,000 hospitalizations yearly (between 2005-2009)

Vilstrup, H. et al. Hepatic Encephalopathy in Chronic Liver disease: 2014 Practice Guideline. Hepatology 2014;60:715-735

Epidemiology

- From 2010-2014, in USA, there has been a 30% increase in HE-related hospitalizations

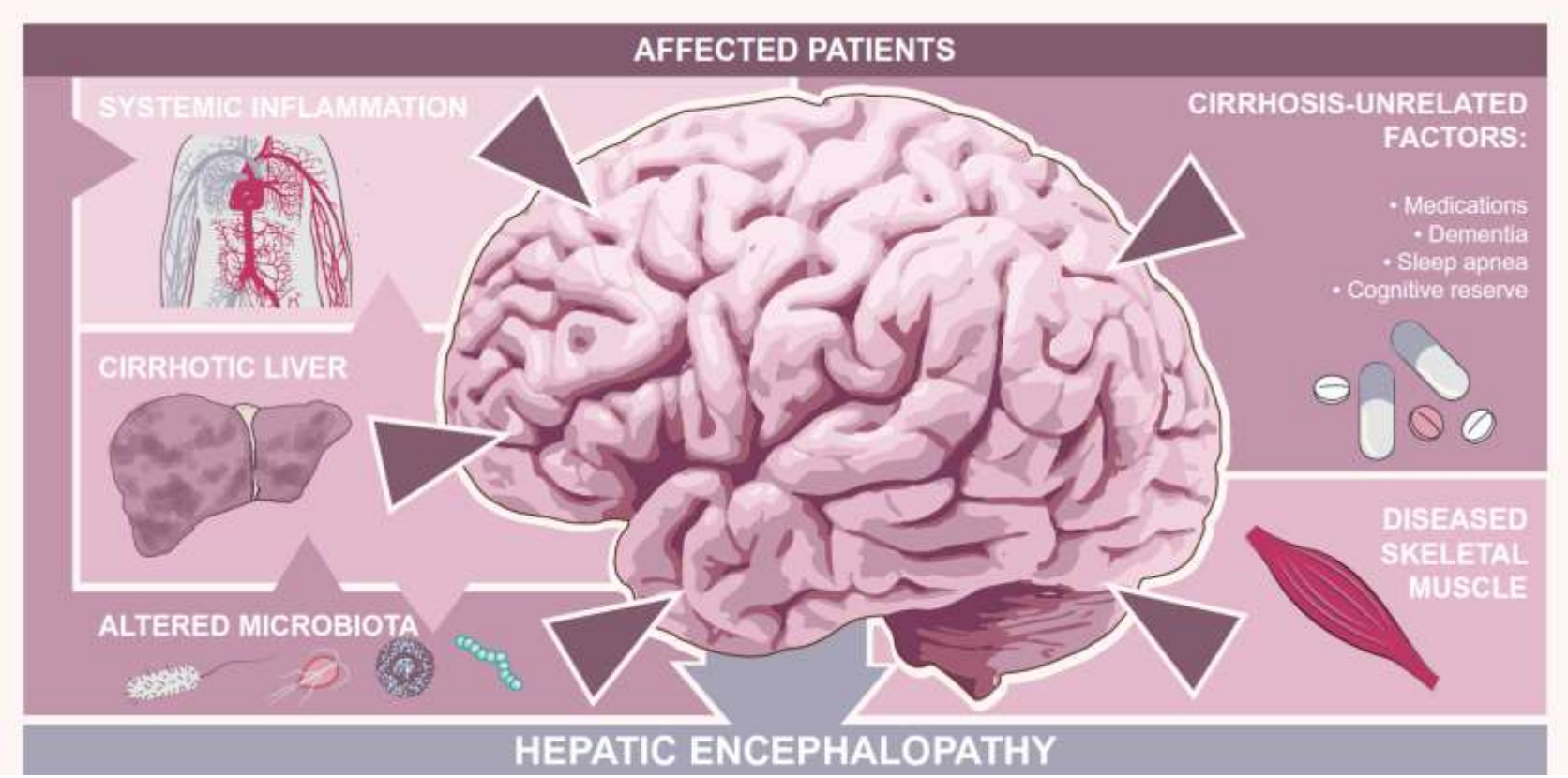
- Patients hospitalized with HE in the US generated charges of about $11.9 billion per year
  - Underestimation, as not taking into account:
    - Primary healthcare
    - Disability
    - Lost productivity
    - Negative impact on patient's family or support network

- Severe HE in patients with cirrhosis is associated with mortality of >50% in the first year

Wijdicks, E. Hepatic Encephalopathy. NEJM 2016; 17: 1660-1670
Rose, C. et al. Hepatic Encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatology 2020;20: 1-22.

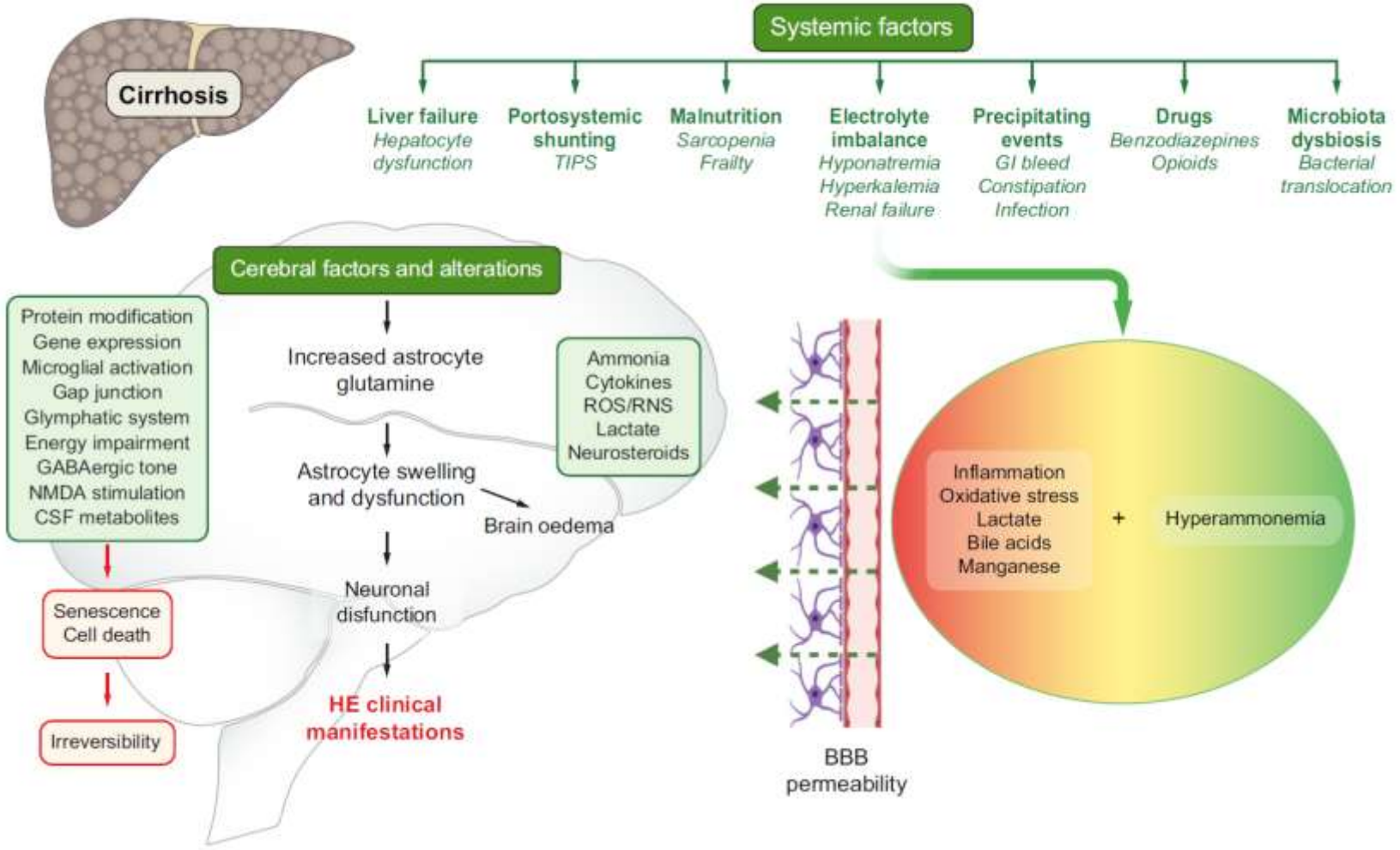
Pathophysiology

- Complex, with multiple components
  - Ammonia
  - Inflammatory cytokines
  - Benzodiazepine-like compounds
  - Altered gut microbiota
  - Oxidative stress



Bajaj, J. Hepatic Encephalopathy: Classification and Treatment. J Hepatology 2018; 68: 838-839.
Patidar K, Bajaj J. Covert and Overt Hepatic Encephalopathy: Diagnosis and Management. *Clin Gastroenterol Hepatol* 2015; 13: 2048-2061.

Pathophysiology



Rose, C. et al. Hepatic Encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatology 2020;20: 1-22.

West Haven Criteria / Glascow Coma Scale

WHC Including MHE	ISHEN	Description	Suggested Operative Criteria	Comment
Unimpaired		No encephalopathy at all, no history of HE	Tested and proved to be normal	
Minimal	Covert	Psychometric or neuropsychological alterations of tests exploring psychomotor speed/executive functions or neurophysiological alterations without clinical evidence of mental change	Abnormal results of established psychometric or neuropsychological tests without clinical manifestations	No universal criteria for diagnosis Local standards and expertise required
Grade I		• Trivial lack of awareness • Euphoria or anxiety • Shortened attention span • Impairment of addition or subtraction • Altered sleep rhythm	Despite oriented in time and space (see below), the patient appears to have some cognitive/behavioral decay with respect to his or her standard on clinical examination or to the caregivers	Clinical findings usually not reproducible
Grade II	Overt	• Lethargy or apathy • Disorientation for time • Obvious personality change • Inappropriate behavior • Dyspraxia • Asterixis	Disoriented for time (at least three of the followings are wrong: day of the month, day of the week, month, season, or year) ± the other mentioned symptoms	Clinical findings variable, but reproducible to some extent
Grade III		• Somnolence to semistupor • Responsive to stimuli • Confused • Gross disorientation • Bizarre behavior	Disoriented also for space (at least three of the following wrongly reported: country, state [or region], city, or place) ± the other mentioned symptoms	Clinical findings reproducible to some extent
Grade IV		Coma	Does not respond even to painful stimuli	Comatose state usually reproducible

TABLE 38-2

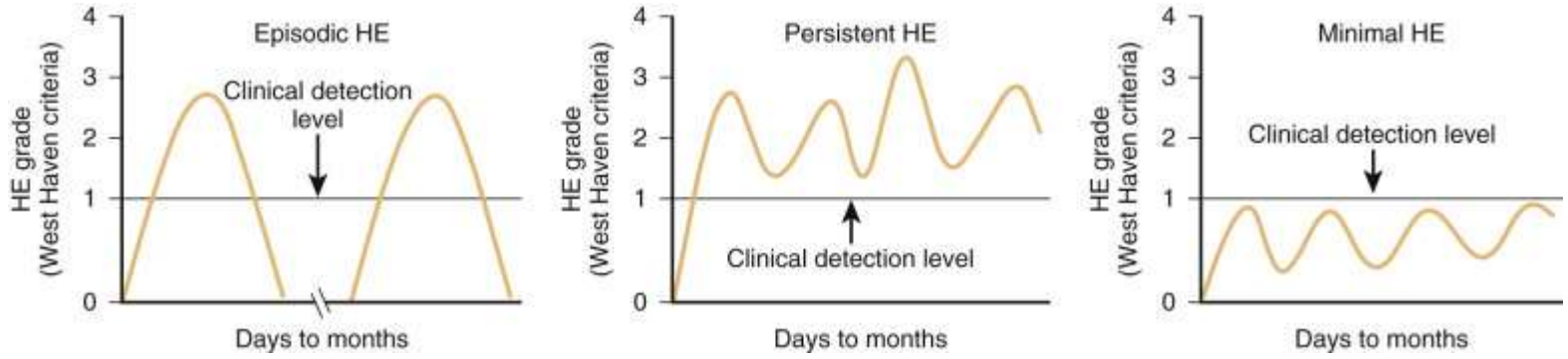
Glasgow Coma Scale

BEHAVIOR	RESPONSE	SCORE
Eye opening response	Spontaneously	4
	To speech	3
	To pain	2
	No response	1
Best verbal response	Oriented to time, place, and person	5
	Confused	4
	Inappropriate words	3
	Incomprehensible sounds	2
	No response	1
Best motor response	Obeys commands	6
	Moves to localized pain	5
	Flexion withdrawal from pain	4
	Abnormal flexion (decorticate)	3
	Abnormal extension (decerebrate)	2
	No response	1
Total score:	*Best response*	15
	Comatose client	8 or less
	Totally unresponsive	3

Vilstrup, H. et al. Hepatic Encephalopathy in Chronic Liver disease: 2014 Practice Guideline. Hepatology 2014;60:715-735
EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. Hepatology 2022;77:807-824

Hepatic Encephalopathy Classification

Type	Grade		Time Course	Spontaneous or Precipitated
A	MHE 1	Covert	Episodic	Spontaneous
B	2	Overt	Recurrent	Precipitated (specify)
	3			
C	4		Persistent	



Vilstrup, H. et al. Hepatic Encephalopathy in Chronic Liver disease: 2014 Practice Guideline. Hepatology 2014;60:715-735
Boyer, T. et al. Zakim and Boyer's Hepatology: A Textbook of Liver Disease. 7th Ed., Elsevier, 2018.

Precipitating Factors for Overt HE

Episodic	Recurrent
Infections*	Electrolyte disorder
GI bleeding	Infections
Diuretic overdose	Unidentified
Electrolyte disorder	Constipation
Constipation	Diuretic overdose
Unidentified	GI bleeding

Vilstrup, H. et al. Hepatic Encephalopathy in Chronic Liver disease: 2014 Practice Guideline. Hepatology 2014;60:715-735

Differential Diagnosis of HE

Overt HE or acute confusional state
Diabetic (hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis)
Alcohol (intoxication, withdrawal, Wernicke)
Drugs (benzodiazepines, neuroleptics, opioids)
Neuroinfections
Electrolyte disorders (hyponatremia and hypercalcemia)
Nonconvulsive epilepsy
Psychiatric disorders
Intracranial bleeding and stroke
Severe medical stress (organ failure and inflammation)
Other presentations
Dementia (primary and secondary)
Brain lesions (traumatic, neoplasms, normal pressure hydrocephalus)
Obstructive sleep apnea

Vilstrup, H. et al. Hepatic Encephalopathy in Chronic Liver disease: 2014 Practice Guideline. Hepatology 2014;60:715-735

Diagnosis of Overt HE

Steps to diagnosis

Step 1

Does the patient have severe enough liver disease for this episode to be HE
- Assess severity of liver disease using Child-Pugh/MELD scores
- In patients with Child-Pugh A disease, consider large portosystemic shunts
- Ammonia levels: if normal, unlikely to be HE

Step 2

Rule out other causes of neurologic/psychiatric diseases
- Alcohol withdrawal
- Psychiatric diseases
- Drug overdose
- Electrolyte disturbances

Evaluation and early management

- Neuropsychiatric profiling. Structured questions aimed at assessing orientation to time/space. Glasgow Coma Scale for uncooperative patients
- Simple but quantitative nutritional assessment and estimate of recent dietary and fluid intake
- History taking, aimed at identifying obvious precipitants and previous episodes of HE, especially if requiring hospitalisation
- Full blood count, liver/kidney function, electrolytes, ammonia, TSH, CRP, glycaemia, vitamin B12 and urine analysis
- Cerebral imaging should be performed if the clinical profile is unusual, the onset of symptoms is abrupt/severe, if there are focal neurological signs and limited or no response to treatment
- Evaluation of the response to treatment (of the precipitant and/or ammonia-lowering strategies)

Rose, C. et al. Hepatic Encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatology 2020;20: 1-22.

Diagnosis of Minimal/Covert HE

Psychometric hepatic encephalopathy score (PHES)	Neuropsychological, paper & pencil	The PHES consists of 5 paper-pencil tests evaluating cognitive/psychomotor processing speed and visuomotor coordination. They are relatively easy to administer, have good external validity and have been translated/validated into several languages and countries.[251]
Animal naming test (ANT)	Neuropsychological, bed-side	The ANT (*i.e.* the number of animals listed in 60 seconds, no equipment required except a stopwatch) has recently been shown to compare favourably with more established mHE measures and to predict overt HE.[186]
Continuous reaction time (CRT)	Neuropsychological, computerised	The CRT test relies on repeated registration of the motor reaction time (pressing a button) to auditory stimuli (through headphones). The most important test result is the CRT index, which measures the stability of the reaction times. Age and sex seem to exert limited influence and there are no learning/tiring effects either.[245]
The inhibitory control test (ICT)	Neuropsychological, computerised	ICT is a computerised test of response inhibition and working memory and is freely downloaded at www.hecme.tv. The ICT test has been judged to have good validity but requires highly functional patients.[246]
Stroop test	Neuropsychological, computerised	The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a coloured field and a written colour name; also available in app form.[26]
SCAN test	Neuropsychological, computerised	The SCAN test is a computerised test that measures speed and accuracy to perform a digit recognition memory task of increasing complexity. It has been shown to have prognostic value.[247]
Electroencephalogram (EEG)	Neurophysiological	The EEG can detect changes in cortical cerebral activity across the spectrum of HE and its reliability increases with quantitative analysis. More recently, a cheap gaming device has been shown to produce similar results compared to a standard EEG machine across the HE spectrum.[248]
Critical flicker frequency (CFF)	Psychophysical	CFF is defined as the frequency at which a flickering light (from 60 Hz downwards) appears to be flickering to the observer. Studies have shown its reduction with worsening cognition and improvement after therapy. It requires specialized equipment.[249]

Rose, C. et al. Hepatic Encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatology 2020;20: 1-22.

Treatment

- 4-pronged approach to treatment
  - Initiation of care for patients with altered mental status
  - Evaluate/treat for alternative causes of altered mental status
  - Identify precipitating factors and correct them
  - Start empirical HE treatment

Vilstrup, H. et al. Hepatic Encephalopathy in Chronic Liver disease: 2014 Practice Guideline. Hepatology 2014;60:715-735

Treatment - Lactulose

- Non-absorbable disaccharide
- 1st line therapy for HE
- Catabolized by colonic bacteria to short chain fatty acids
  - Lowering colonic pH to ~ 5
    - Results in formation of ammonium (NH4+, non-absorbable) from ammonia
      - Lost in cathartic effect
  - Displaces urease-producing bacteria with non-urease-producing lactobacillus
  - Hyperosmolar stool composition in colon improves GI transit time
- Used in treatment and prevention of recurrence of HE (covert and overt)
- Dose is usually 20-30gm 2-4x/day, with goal of 2-3 BMs/day
- Can be given orally or via NGT/rectal enema
- AE: abdominal cramping, diarrhea, flatulence

Mahpour N. et al. Pharmacologic Management of Hepatic Encephalopathy. *Clin Liver Dis* 2020; 24: 231-242.
Rose, C. et al. Hepatic Encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatology 2020;20: 1-22.
EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. Hepatology 2022;77:807-824

Treatment - Lactulose

Cochrane Library

Cochrane Database of Systematic Reviews

Non-absorbable disaccharides versus placebo/no intervention a
lactulose versus lactitol for the prevention and treatment of he
encephalopathy in people with cirrhosis (Review)

Cochrane Database of Syst

Showed beneficial effect on:

HE severity (NNT=4)

Prevention of HE (NNT=6)

Analysis 2.3. Comparison 2 Prevention trials: non-absorbable disaccharides versus placebo/no intervention, Outcome 3 Hepatic encephalopathy.

Study or subgroup	Disaccharide n/N	Control n/N	Risk Ratio IV, Random, 95% CI	Weight	Risk Ratio IV, Random, 95% CI
2.3.1 Primary					
Riggio 2005	9/25	8/25		16.02%	1.13[0.52,2.44]
Sharma 2011	5/35	14/35		12.64%	0.36[0.14,0.88]
Sharma 2012	6/60	14/60		13.09%	0.43[0.18,1.04]
Wen 2013	2/65	11/65		5.61%	0.18[0.04,0.79]
Subtotal (95% CI)	**185**	**185**		**47.36%**	**0.48[0.23,0.98]**
Total events: 22 (Disaccharide), 47 (Control)					
Heterogeneity: Tau^2=0.29; Chi^2=6.62, df=3(P=0.09); I^2=54.68%					
Test for overall effect: Z=2.02(P=0.04)					
2.3.2 Secondary					
Agrawal 2012	18/80	37/78		29.34%	0.47[0.3,0.76]
Sharma 2009	12/70	30/70		23.3%	0.4[0.22,0.72]
Subtotal (95% CI)	**150**	**148**		**52.64%**	**0.44[0.31,0.64]**
Total events: 30 (Disaccharide), 67 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=4.36(P<0.0001)					
Total (95% CI)	**335**	**333**		**100%**	**0.47[0.33,0.68]**
Total events: 52 (Disaccharide), 114 (Control)					
Heterogeneity: Tau^2=0.06; Chi^2=7.18, df=5(P=0.21); I^2=30.31%					
Test for overall effect: Z=4.02(P<0.0001)					
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.86), I^2=0%					

Favours disaccharide 0.005 0.1 1 10 200 Favours control

Test for overall effect: Z=6.44(P<0.0001)

Favours disaccharide 0.005 0.1 1 10 200 Favours control

Gluud L, Vilstrup H, Morgan M. Non-absorbable disaccharides versus placebo/no intervention and lactulose versus lactitol for the prevention and treatment of hepatic encephalopathy in people with cirrhosis. *Cochrane Database of Systematic Reviews* 2016; 5: CD003044.

Treatment - Rifaximin

- Synthetic antibiotic with activity against gram (+), gram (-), aerobic and anaerobic bacteria
- Has minimal systemic absorption
- Destroys gut bacteria producing ammonia
- Majority of data is for use in prevention of recurrence of HE
- Dosing is 550mg twice daily

- Other antibiotics used
  - Neomycin
  - Metronidazole
  - Vancomycin

Mahpour N. et al. Pharmacologic Management of Hepatic Encephalopathy. *Clin Liver Dis* 2020; 24: 231-242.
Rose, C. et al. Hepatic Encephalopathy: Novel insights into classification, pathophysiology and therapy. J Hepatology 2020;20: 1-22.

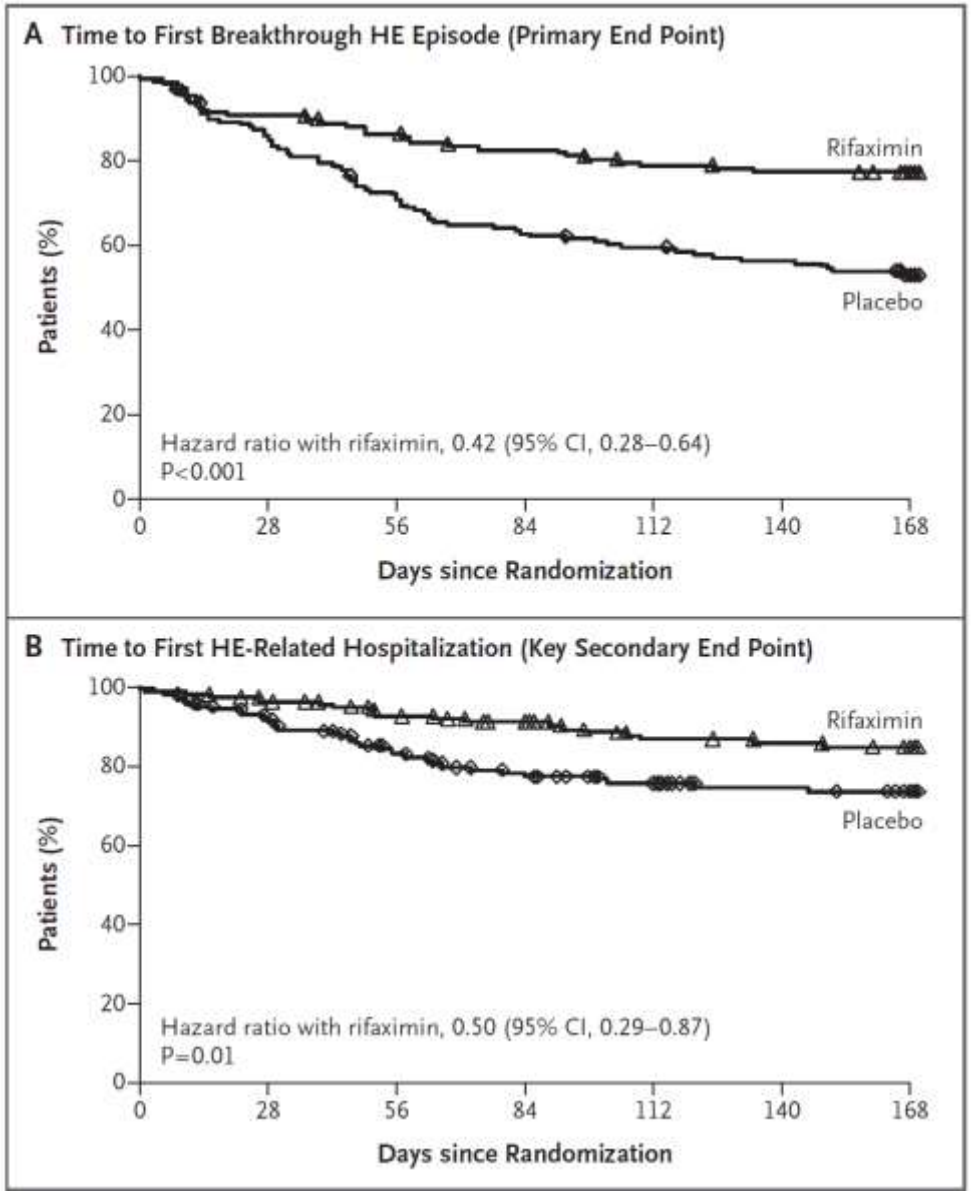
Treatment - Rifaximin

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 25, 2010 VOL. 362 NO. 12

Rifaximin Treatment in Hepatic Encephalopathy

- Randomized, double-blind placebo-controlled trial
- N: 299 in remission from recurrent HE
- >90% of patients in study were receiving concomitant lactulose



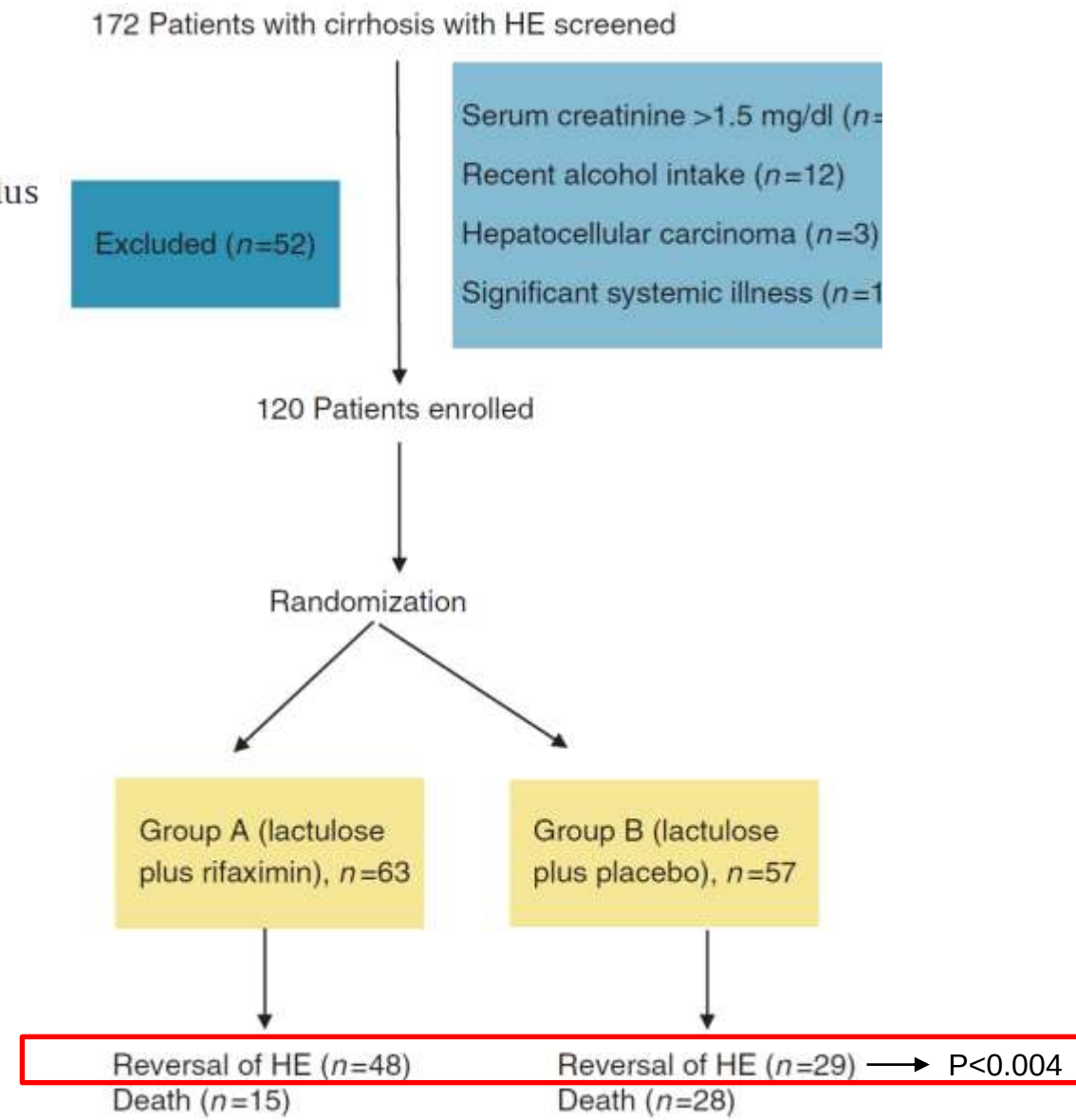
Bass N, Mullen K, Sanyal A, et al. Rifaximin Treatment in Hepatic Encephalopathy. *N Engl J Med* 2010; 362(**12**): 1071-1081.

Treatment - Rifaximin

A Randomized, Double-Blind, Controlled Trial Comparing Rifaximin Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy

Article in The American Journal of Gastroenterology · July 2013

- Prospective, double-blind, randomized controlled trial
- N: 120



Sharma B et al. A Randomized , Double-Blind, Controlled Trial Comparing Rifaximin Plus Lactulose With Lactulose Alone in Treatment of Overt Hepatic Encephalopathy. *Am J Gastroenterol* 2013; 108: 1458–1463.

Treatment – L-Ornithine L-aspartate (LOLA)

- Stable salt of amino acids ornithine and aspartate
  - Not FDA approved
  - Ammonia scavenger
  - Promotes hepatic removal of ammonia by:
    - stimulating residual hepatic urea cycle activity (via carbamoyl phosphate synthetase activation)
    - promoting glutamine synthesis, particularly in skeletal tissue (via glutamine synthetase activation)
  - Has IV and oral formulations

Mahpour N, Pioppo-Phelan L, Reja M, et al. Pharmacologic Management of Hepatic Encephalopathy. *Clin Liver Dis* 2020; 24: 231-242.
Goh E, Stokes C, Sidhu S, et al. L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. *Cochrane Database of Systematic Reviews* 2018; 5: CD012410.

Treatment – L-Ornithine L-aspartate (LOLA)

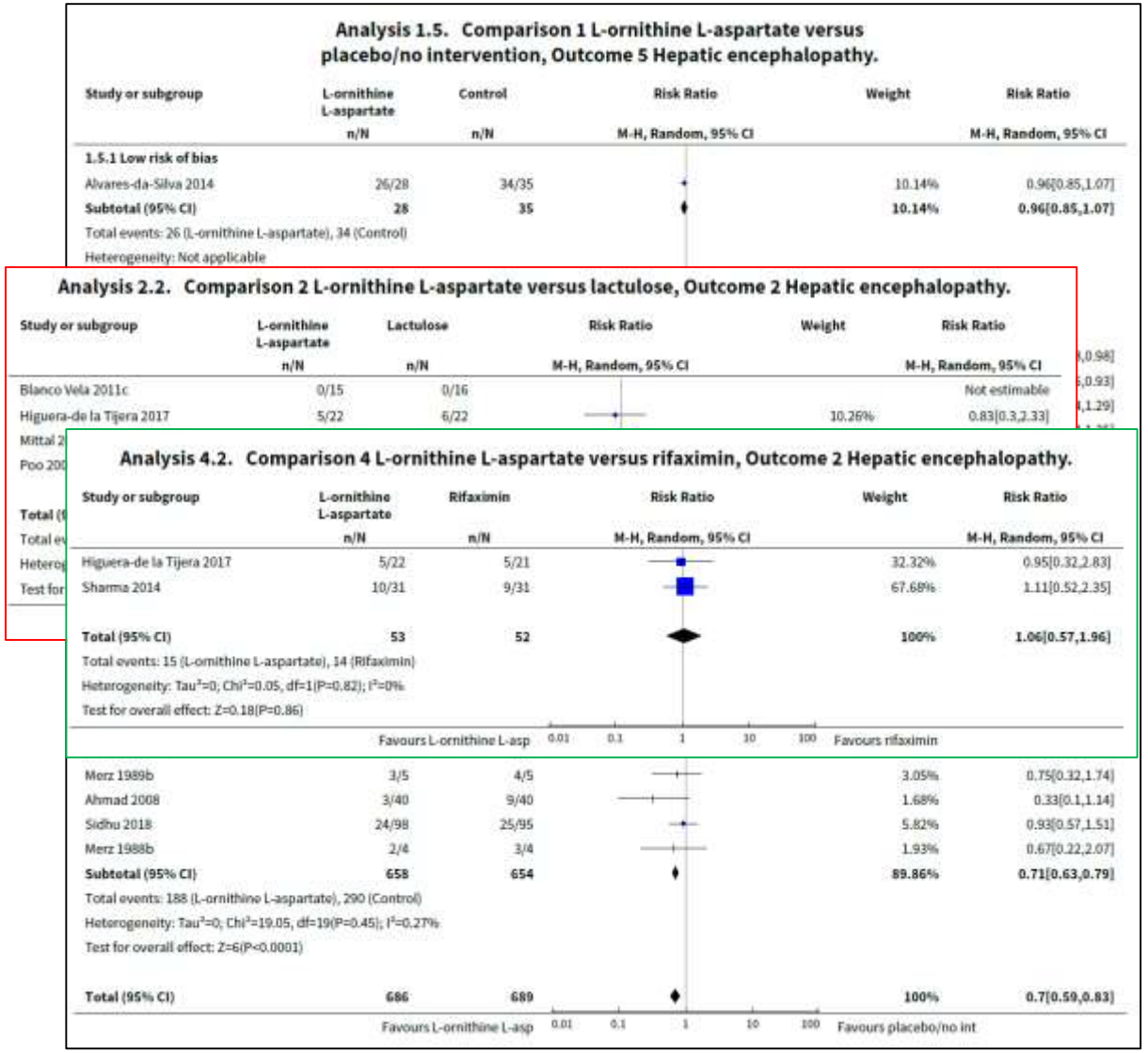
Cochrane Library

Cochrane Database of Systematic Reviews

L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis (Review)

Cochrane Database of Systematic Reviews 2018

- Looked at 29 trials involving 1891 patients
- Improvement in HE when compared to placebo/no treatment (RR:0.7)
- No benefit compared to other HE meds
- Higher risk of bias in papers



Goh E, Stokes C, Sidhu S, et al. L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis. *Cochrane Database of Systematic Reviews* 2018; 5: CD012410.

Treatment – Branched Chain Amino Acids

- Patients with cirrhosis have decreased concentration of BCAAs

- BCAAs aid in detoxification of ammonia via effects on skeletal tissue
  - Skeletal muscle detoxifies ammonia via conversion to glutamine
  - In cirrhosis, hyperammonemia impairs skeletal muscle protein synthesis via mTor signaling alterations
  - BCAAs counteract this pathway

- Not FDA approved

Mahpour N, Pioppo-Phelan L, Reja M, et al. Pharmacologic Management of Hepatic Encephalopathy. *Clin Liver Dis* 2020; 24: 231-242.

Treatment – Branched Chain Amino Acids

Cochrane Library

Cochrane Database of Systematic Reviews

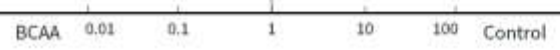
Branched-chain amino acids for people with hepatic encephalopathy (Review)

Cochrane Database of Systematic Reviews 2017

- Reviewed 16 RCTs including 827 patients
- Showed beneficial effect on:
  - HE treatment (NNT: 5) with RR: 0.73

Analysis 1.7. Comparison 1 Branched-chain amino acids (BCAA) versus control, Outcome 7 Hepatic encephalopathy.

Study or subgroup	BCAA n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Calvey 1985	3/10	11/16		2.76%	0.44[0.16,1.19]
Cerra 1985	14/40	13/35		5.8%	0.94[0.52,1.72]
Egberts 1985	4/11	10/11		3.91%	0.4[0.18,0.89]
Fiaccadori 1984	1/32	6/16		0.78%	0.08[0.01,0.63]
Hayashi 1991	21/35	30/32		11.3%	0.64[0.48,0.85]
Horst 1984	12/17	19/20		10.49%	0.74[0.54,1.03]
Hwang 1988	8/27	15/28		5.01%	0.55[0.28,1.09]
Les 2011	4/18	11/22		2.96%	0.44[0.17,1.16]
Marchesini 1990	6/30	22/34		4.27%	0.31[0.14,0.66]
Marchesini 2003	21/33	57/79		11.15%	0.88[0.66,1.18]
Michel 1985	24/36	24/34		10.62%	0.94[0.69,1.3]
Muto 2005	10/27	5/12		3.72%	0.89[0.39,2.04]
Plauth 1993	11/12	10/11		11.99%	1.01[0.78,1.3]
Rossi-Fanelli 1986	8/20	12/20		5.33%	0.67[0.35,1.27]
Strauss 1986	2/16	2/16		0.94%	1[0.16,6.25]
Vilstrup 1990	21/38	22/39		8.99%	0.98[0.66,1.46]
Total (95% CI)	**402**	**425**		**100%**	**0.73[0.61,0.88]**
Total events: 170 (BCAA), 269 (Control)					



Gluud L, Dam G, Les I, et al. Branched-chain amino acids for people with hepatic encephalopathy (Review). *Cochrane Database of Systematic Reviews* 2017; 5: CD001939.

Treatment - Zinc

- Element that is often found to be deficient in cirrhotic patients
- Zinc is necessary as a co-factor:
  - to convert ammonia into urea via ornithine transcarbamylase
  - to activate muscle glutamine synthetase to convert ammonia and glutamate into glutamine
- Dosing is usually 220mg BID (50mg elemental Zn BID)
- AE: nausea/vomiting, abdominal cramps, diarrhea
- Not FDA approved

Mahpour N, Pioppo-Phelan L, Reja M, et al. Pharmacologic Management of Hepatic Encephalopathy. *Clin Liver Dis* 2020; 24: 231-242.
Takuma Y et al. Clinical trial: oral zinc in hepatic encephalopathy. *Aliment Pharmacol Ther* 2010; 32: 1080–1090

Treatment - Zinc

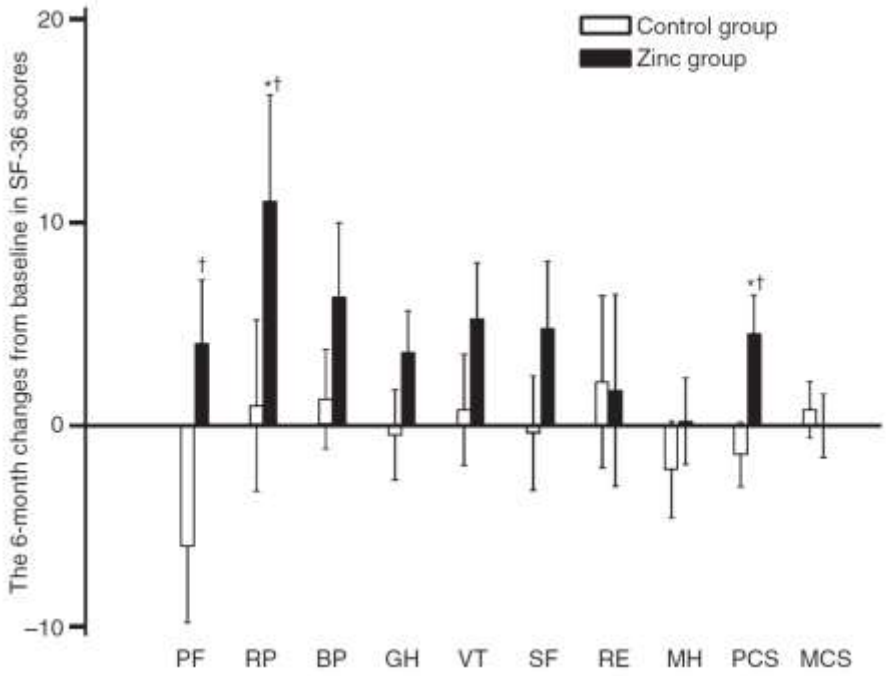
AP&T Alimentary Pharmacology and Therapeutics

Clinical trial: oral zinc in hepatic encephalopathy

Aliment Pharmacol Ther 2010

- randomized, prospective trial of 79 patients who either received zinc therapy in addition to standard therapy of BCAA and lactulose, v. standard therapy alone

- HE improved in 21 patients in the zinc group compared to 10 patients in the the control group (54% v. 26%, P=0.03)



Takuma Y et al. Clinical trial: oral zinc in hepatic encephalopathy. *Aliment Pharmacol Ther* 2010; 32: 1080–1090

Treatment – Shunt Obliteration

- Up to 1/3 of patients with cirrhosis have large (>8mm) or smaller porto-systemic shunts on imaging
  - ~50% are splenorenal shunts

- HE has been reported in:
  - 48% of patients with large porto-systemic shunts
  - 34% of patients with small porto-systemic shunts

- Porto-systemic shunts with total surface area > 83mm^2 increase the risk of overt HE and mortality in cirrhosis

- Obliteration of accessible porto-systemic shunts in patients with recurrent/persistent HE (despite appropriate medical treatment) can be considered in stable patients with MELD <11

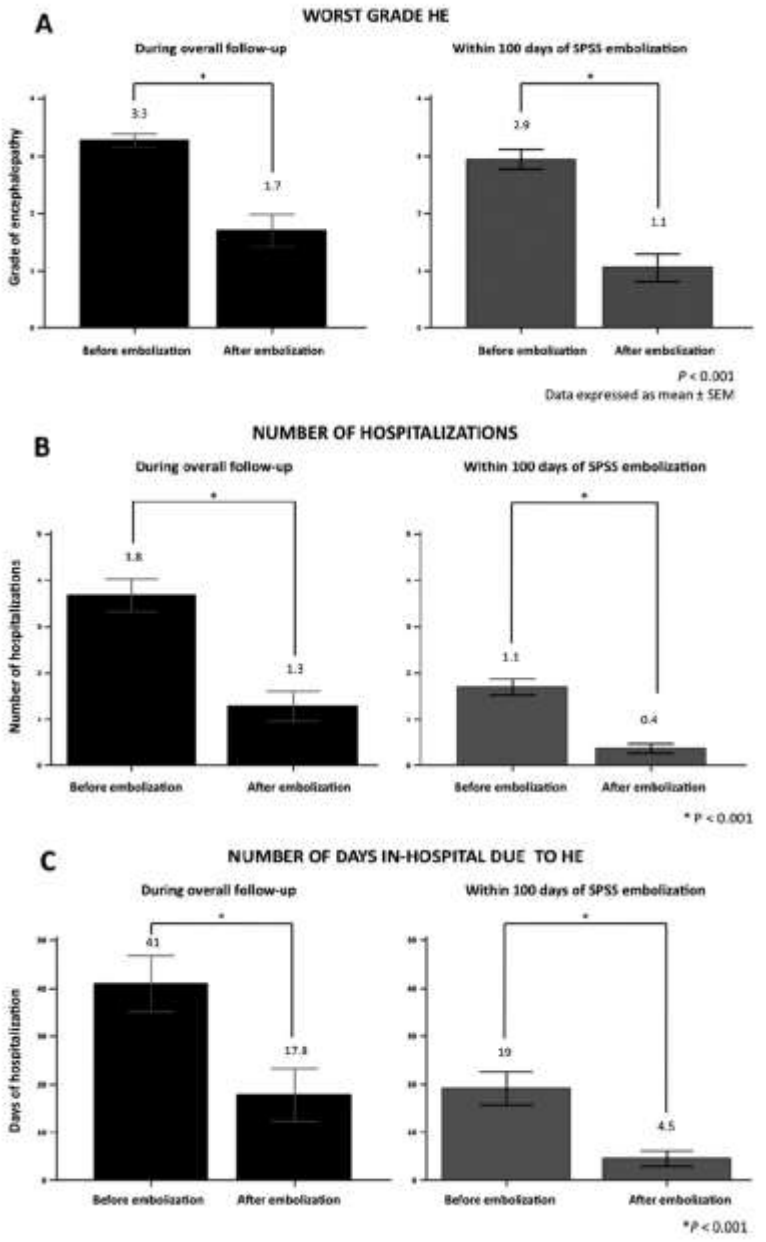
EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. Hepatology 2022;77:807-824

Treatment – Shunt Obliteration

Embolization of Large Spontaneous Portosystemic Shunts for Refractory Hepatic Encephalopathy: A Multicenter Survey on Safety and Efficacy

HEPATOLOGY, Vol. 57, No. 6, 2013

- Multicenter, retrospective cohort study of 37 patients with refractory HE who were diagnosed with single large porto-systemic shunts eligible for embolization
- 22/37 (59.4%) patients without HE for 100 days after embolization (P<0.001 v. prior to embolization)
- 18/37 (48.6%) patients remained HE free over mean follow up period of 697+/- 157 days (P<0.001 v. prior to embolization)



Novel Therapies

Table 1
Novel agents for treatment of hepatic encephalopathy with their mechanisms of action and clinical effects

Agent	Theorized Mechanism of Action	Clinical Effect
Acetyl carnitine	Supporting neuronal clearance of ammonia and free radicals	No clinical benefit observed despite reduced ammonia levels
Albumin	Reducing oxidation stress and inflammatory cascade	No improvement in overt HE; however, overall improvement in 3 mo mortality
AST-120	Preventing absorption of gut ammonia and toxins	No improvement in covert HE despite reduced ammonia levels
Flumazenil	Reducing GABAnergic response in neurons	Limited data suggest clinical benefit of short-term use
Fecal microbiota transplantation	Reducing peripheral inflammation through gut microbiome modification	Small trials demonstrate reduced hospitalizations for HE, but clinical applicability remains under investigation
Glycerol phenylbutyrate	Increasing urinary excretion of ammonia	Reduction in ammonia levels in phase II trials with reduced incidence of HE in follow-up studies
L-Ornithine L-aspartate	Increasing skeletal muscle use of ammonia	Reduction in HE grade in combination with lactulose
Polyethylene glycol	Increasing gut clearance of ammonia producing organisms	Improves mentation and reduces length of admission in patients hospitalized for HE compared with lactulose alone
Probiotics	Reducing peripheral inflammation through gut microbiome modification	Cochrane review found no benefit but overall poor data quality limited review

Alimirah M, Sadiq O, Gordon S. Novel Therapies in Hepatic Encephalopathy. *Clin Liver Ds* 2020; 24: 303-315.

Thank You!