Meeting del 45° parallelo

IBD and liver hemisphere

30 Maggio 2024

Salone del Grano

Piazza Giuseppe Garibaldi, 2
Rovigo

PREVENTION OF HEPATIC ENCEPHALOPATHY

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IRCCS Istituto di ricovero e cura a carattere scientifico

European Reference Network | Hepatological Diseases (ERN RARE-LIVER)

Hepatic Encephalopathy: DEFINITION

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Guidelines

Hepatic encephalopathy 2018: A clinical practice guideline by the Italian Association for the Study of the Liver (AISF)

Sara Montagnese[a,*,1], Francesco Paolo Russo[b,2], Piero Amodio[a,3], Patrizia Burra[b,3], Antonio Gasbarrini[c,3], Carmela Loguercio[d,3], Giulio Marchesini[e,3], Manuela Merli[f,3], Francesca Romana Ponziani[c,3], Oliviero Riggio[f,3], Carmelo Scarpignato[g,3]

Brain dysfunction caused by liver failure and/or portal-systemic blood shunting

that produces a spectrum of neurological/psychiatric abnormalities

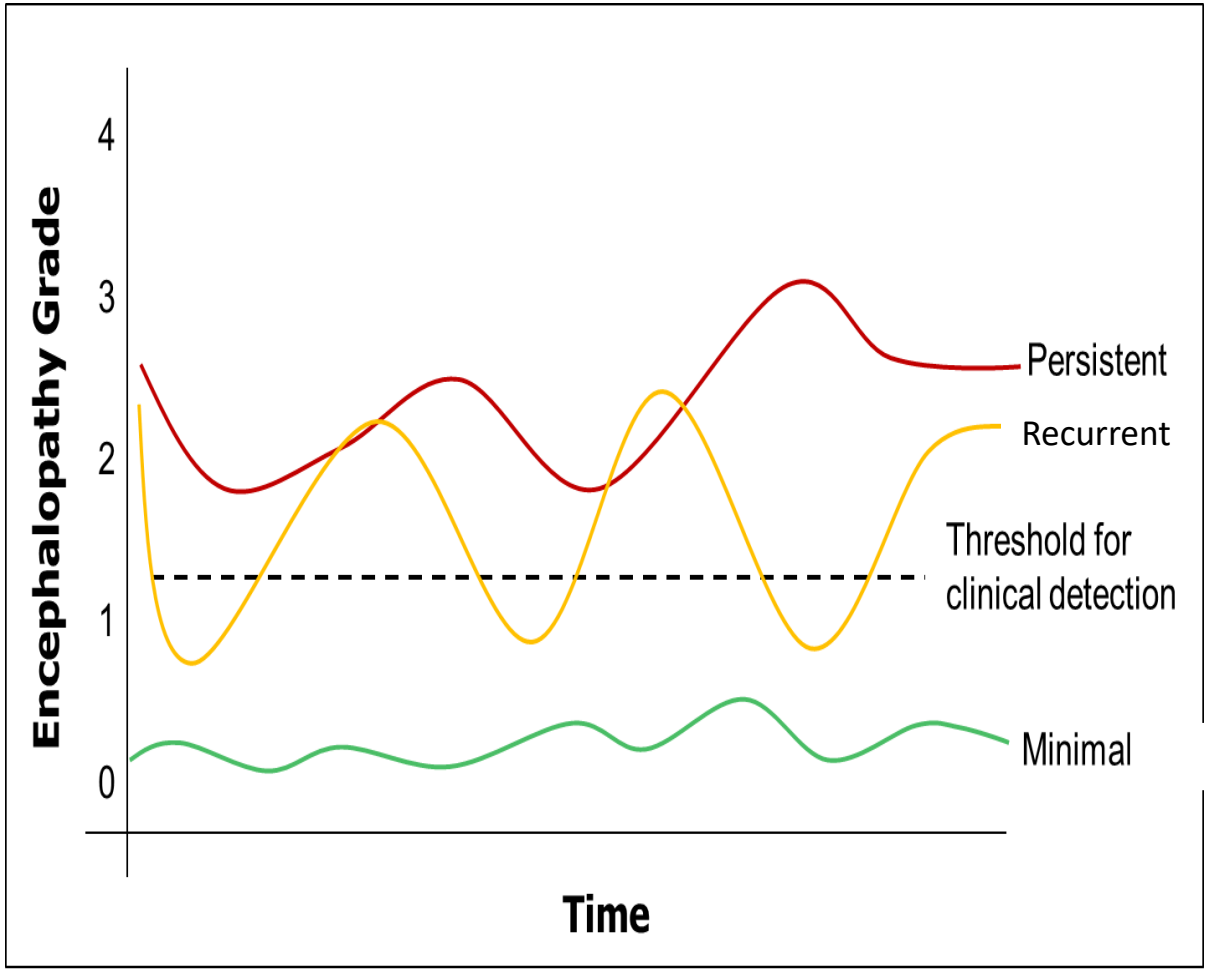
ranging from subclinical alterations to coma

AISF guidelines, Dig Liv Dis, 2018

Hepatic Encephalopathy: CLASSIFICATION

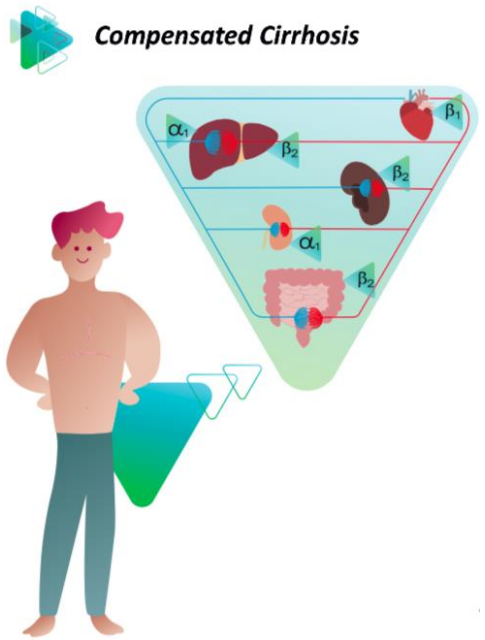
AISF guidelines

Type	Severity	Time course
A Acute liver failure	Quantification/neuromonitoring is closely linked to the expertise	
B Portal-systemic shunt (no significant liver disease)	Covert: minimal HE; grade 1 WH	
C Liver cirrhosis (both liver failure and portal-systemic shunt)	Overt: grade 2 WH; grade 3 WH; grade 4 WH (coma)	episodic; recurrent (≥2 bouts OHE in 6 mo); persistent (dementia or dementia-like)
D Acute on Chronic Liver Failure	*Research area* *Different management, mechanism, and prognostic impact*	



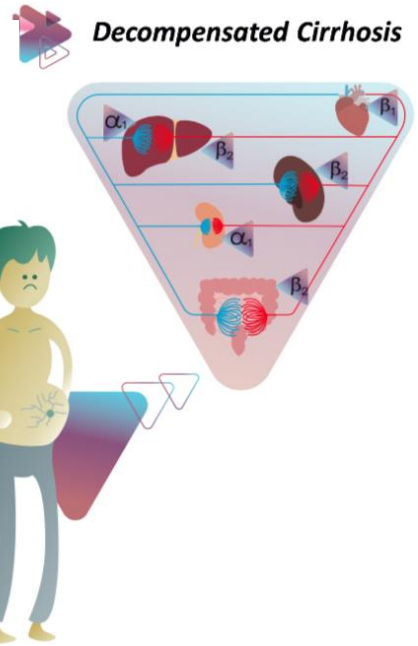
AISF guidelines, Dig Liv Dis, 2018

Disease progression in patients with cirrhosis



- No varices
- Varices

Median survival
> 15 years



- Ascites
- Variceal Bleeding
- H. Encephalopathy

Median survival
2 years

First decompensation

OR Ascites
OR Variceal Bleeding
OR H. Encephalopathy

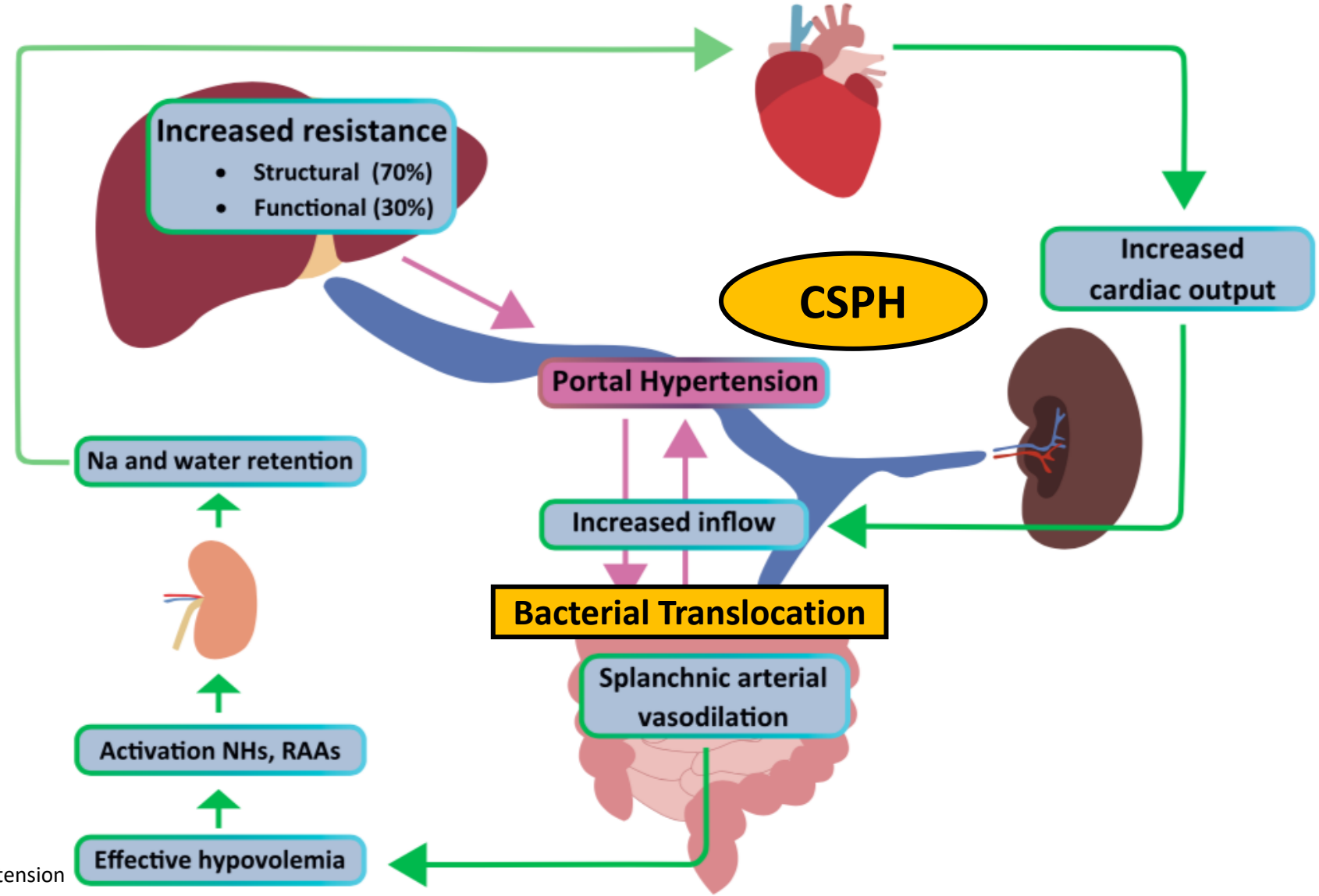
Further decompensation

- Development of a second event
- Recurrent/refractory ascites, recurrent VH/HE
- Spontaneous bacterial peritonitis
- Hepatorenal syndrome (HRS-AKI)
- Jaundice

Median survival
9 months

Turco, Liver Intern 2023
D'Amico, J Hep 2018 and Hep 2023

CSPH and Systemic inflammation are key factors in the development of *HEPATIC ENCEPHALOPATHY*



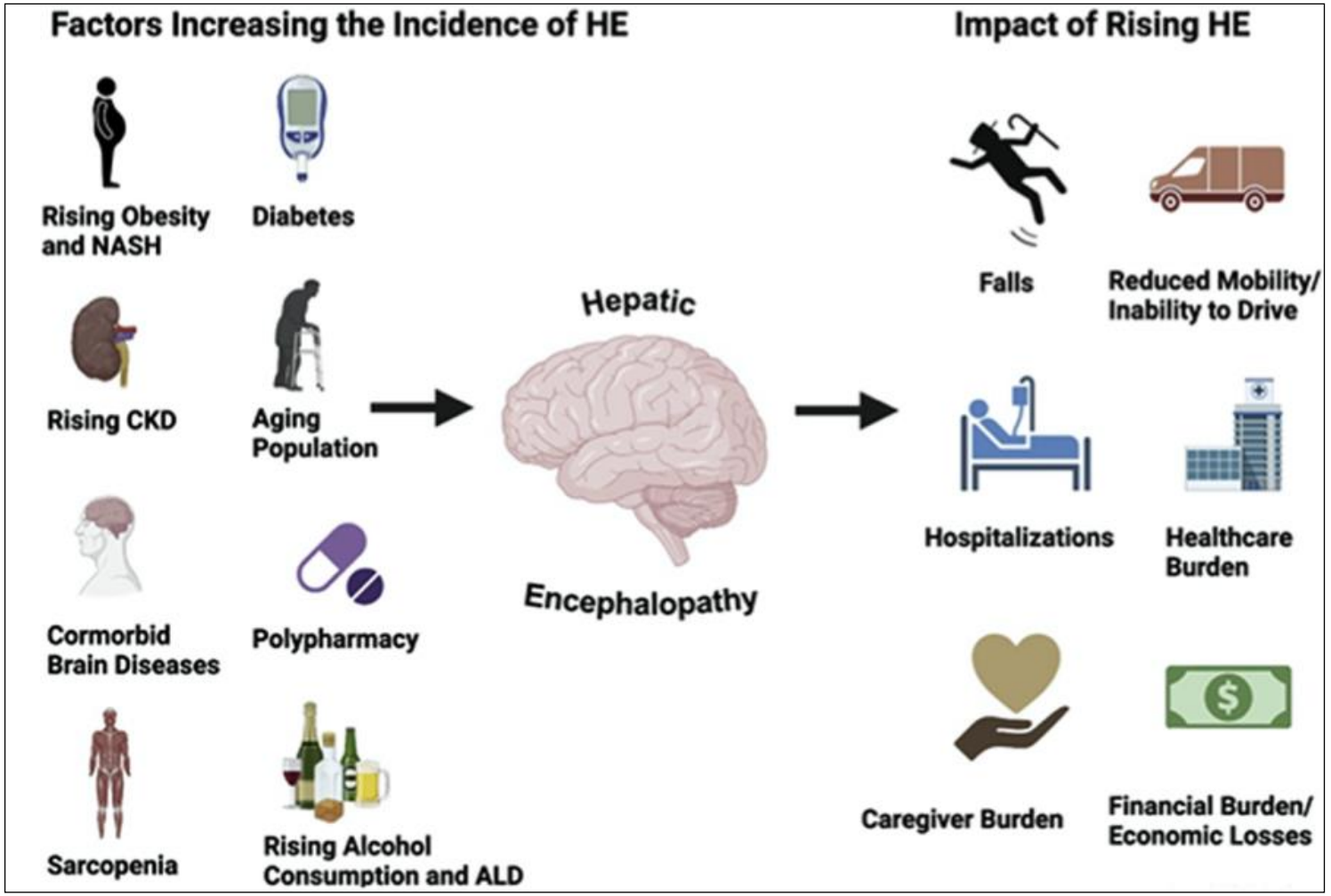
Abbreviations:
CSPH: clinically significant portal hypertension
Na: Sodium;
NHs: Neurohumoral system;
RAAs: renin-angiotensin- aldosterone system

Turco, Liver Intern 2023

Changing Epidemiology of Cirrhosis and Hepatic Encephalopathy

Jeremy Louissaint,[1] Sasha Deutsch-Link,[2] and Elliot B. Tapper[3]

[1]Center for Liver Disease and Transplantation, Columbia University, New York, New York; [2]Division of Gastroenterology and Hepatology, University of North Carolina, Chapel Hill, North Carolina; and [3]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, Michigan



Primary Prophylaxis of Hepatic Encephalopathy

COVERT Hepatic Encephalopathy: How to Manage?

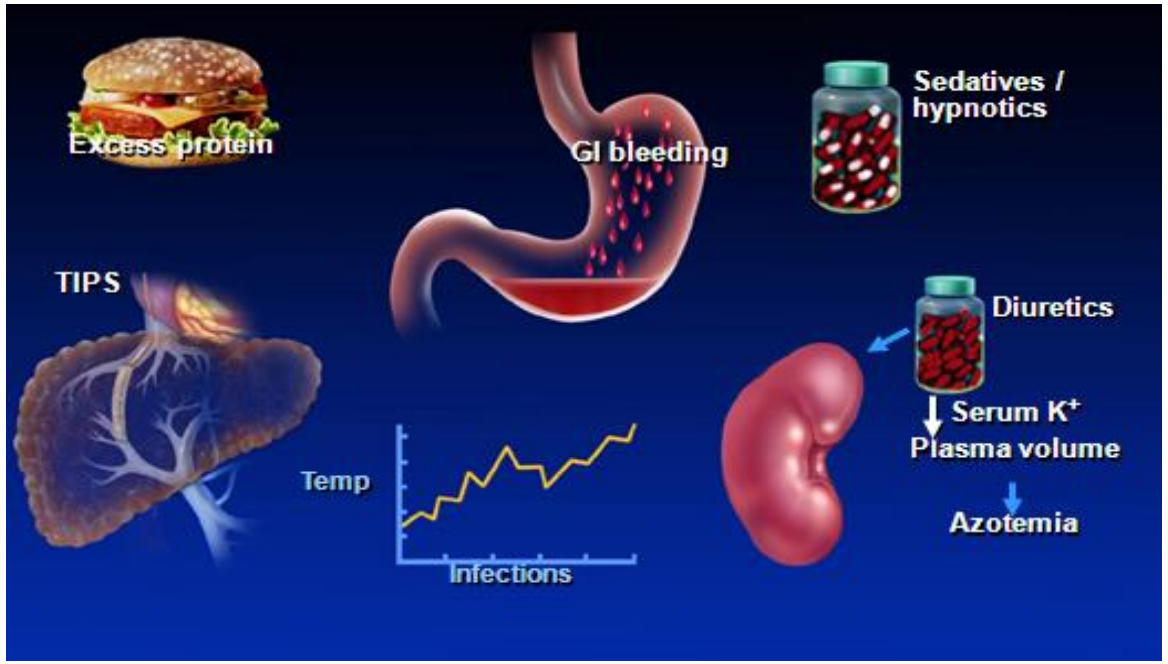
AISF recommendation

Treatment of HE is **not** routinely recommended but can be instituted on a case-by-case basis *(GRADE II-3, A, 1)*

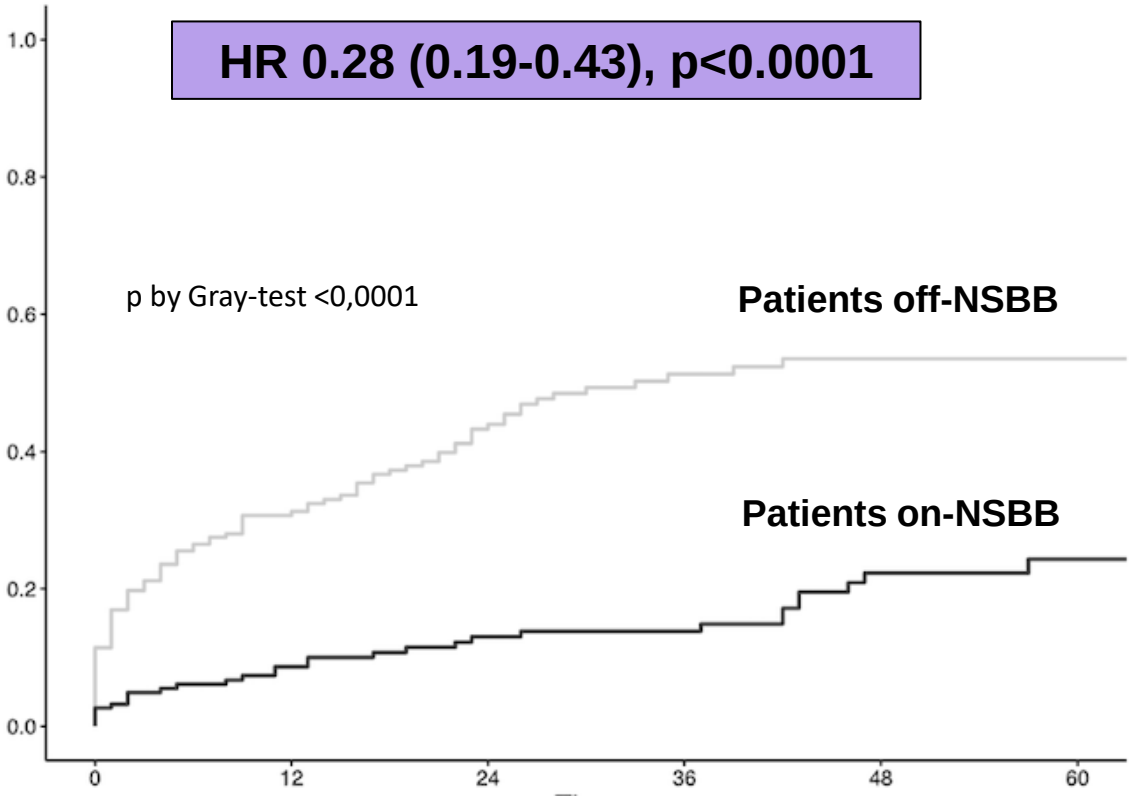
AISF, Dig Liv Dis 2019

No specific pharmacological interventions are currently recommended, but you can:

- Educate patient and care-givers on hepatic encephalopathy
- Explain how to avoid constipation
- Provide nutritional counseling



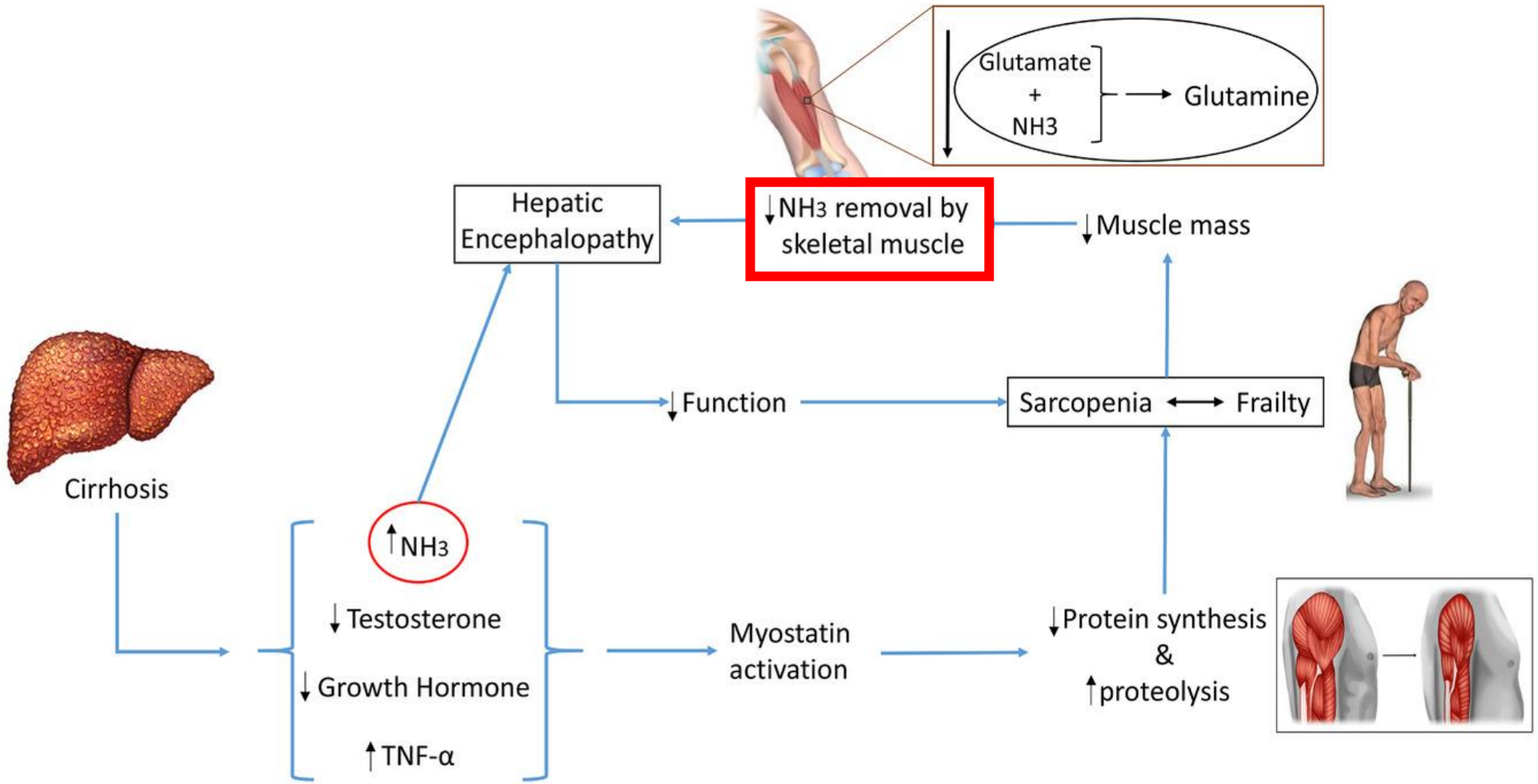
NSBB lower the risk of <u>first</u> decompensation (including HE)



	NSBB-on (n=187)	NSBB-off (n=219)	p
Outcomes			
Decompensation-overall	***30 (16,0%)***	***97 (44,3%)***	***<0,0001***
Decompensation-type			***<0,0001***
Ascites	***22 (11,8%)***	***76 (34,7%)***	
Bleeding	***5 (2,7%)***	***8 (3,7%)***	
H. Encephalopathy	***3 (1,6%)***	***13 (5,9%)***	
PVT (new or worsening)	17 (9,1%)	14 (6,4%)	0,314
HCC (new diagnosis)	26 (13,9%)	20 (9,1%)	0,131
Bacterial Infections	***25 (13,4%)***	***59 (26,9%)***	***0,001***

Turco, SUBMITTED

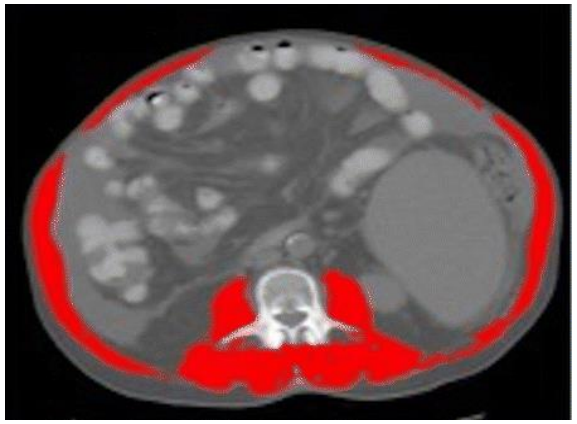
HEPATIC ENCEPHALOPATHY: Relationship with sarcopenia



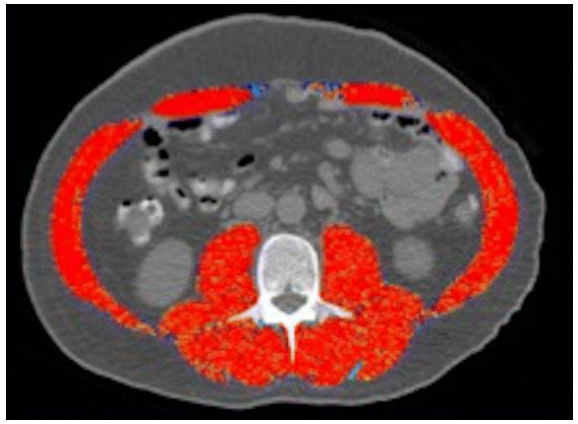
Fallahzadeh MA, Nutr Clin Pract 2021

HEPATIC ENCEPHALOPATHY: IMPACT of sarcopenia

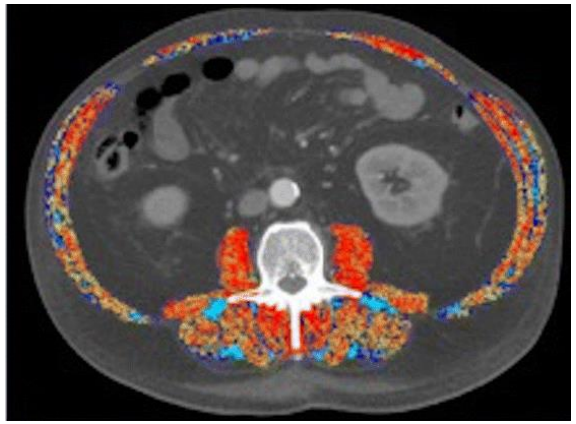
Sarcopenia

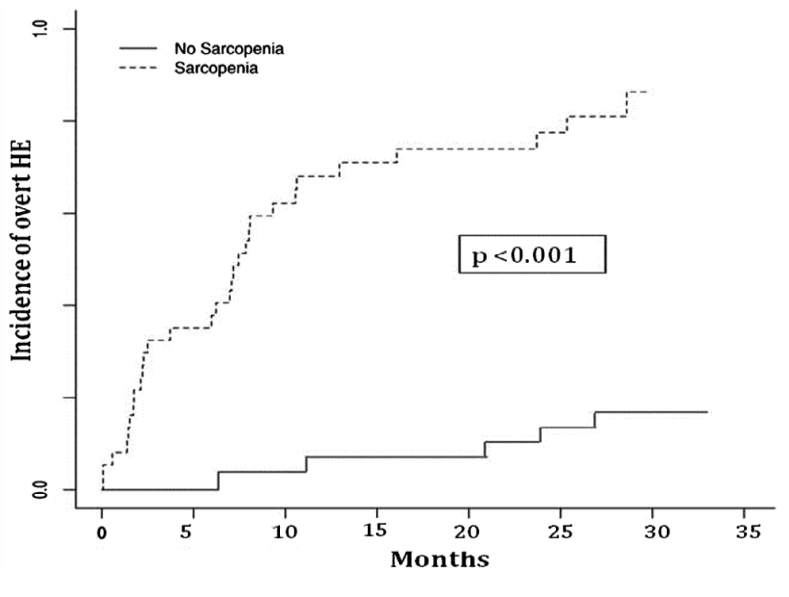


Normal muscle

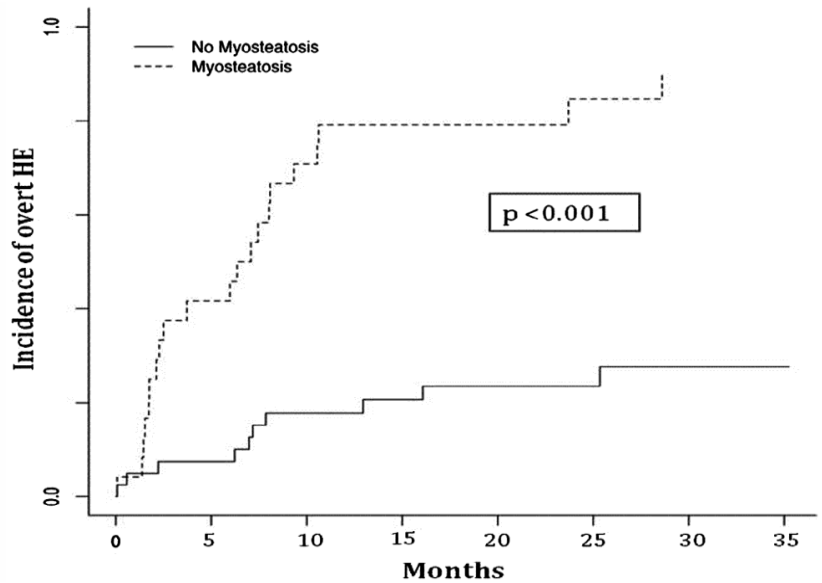


Myosteatosis





Patients with muscle alterations do worse!

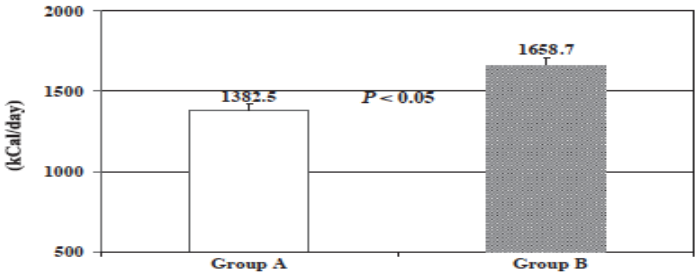


Nardelli et al, Hepatology, 2019

HEPATIC ENCEPHALOPATHY: Practical recommendations for an adequate nutritional intervention

Recommend a daily caloric intake: 35-40 kcal/kg bw

- Expected daily caloric intake for a 70 kg patient: 2450-2800 kCal/day



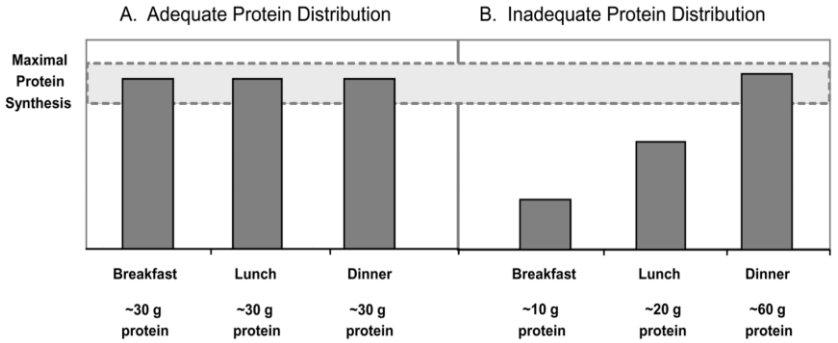
Morando et al, Liv Int, 2015

No hyposodic diets,

but avoid excessive salt intake!

Recommend a daily protein intake: 1.0-1.5 g/kg/bw

- Prefer vegetal and dairy sources of protein
- Aminoacid supplementation (10-20 gr/day), preferably with HMB, can be included
- Micronutrients and vitamin supplementation if deficiency (vitamin D or B1, zinc)



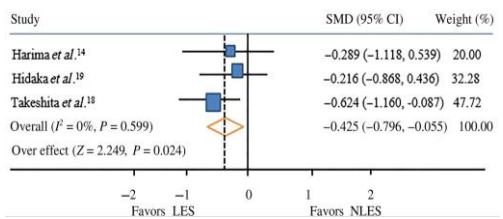
Paddon-Jones D, Curr Opin Clin Nutr Metab Care, 2009

Check
the daily distribution
of protein intake!

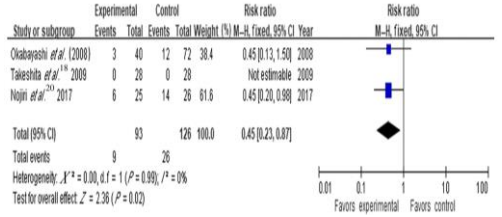
Recommend a late-evening snack

- 60-70 grams of carbohydrates

Benefit on ammonia levels



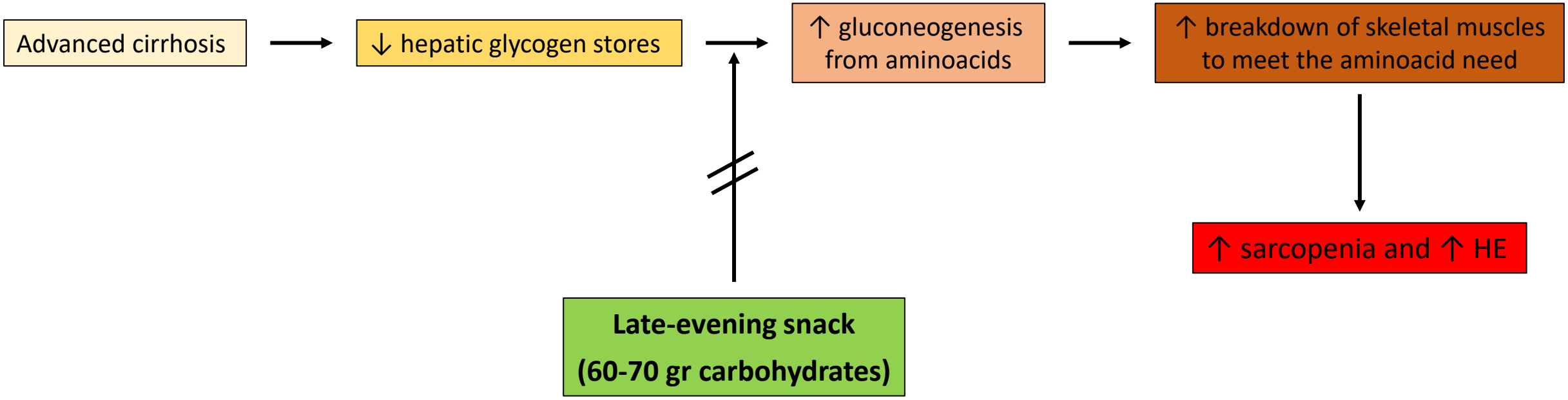
Benefit on hepatic encephalopathy



Chen CJ et al, J Gastroenterol Hepatol, 2019

HEPATIC ENCEPHALOPATHY: Pathophysiological background of the late-evening snacks

Metabolic profile of a patient with advanced cirrhosis **after an overnight fasting** = Metabolic profile of a healthy person **after 3 days starvation**



Hyponatremia Is a Risk Factor of Hepatic Encephalopathy in Patients With Cirrhosis

Hyponatremia induces a reduction in the osmolality of the extracellular fluid

Hyperammonemia cause an increased intracellular content of glutamine

Result in an increased intracellular osmolality

Shift of fluid from the extracellular to the intracellular compartment

ASTROCYTE SWELLING

Astrocyte dysfunction would facilitate development of HE mainly as a result of increased oxidative stress

Table 3. Variables with independent predictive value in the development of overt HE in the multivariate analysis (Prentice, Williams, and Peterson models)

	HR	95% CI	*P* value
Model 1			
Hyponatremia	10.69	(4.39;26.03)	<0.001
Earlier hepatic encephalopathy	2.94	(1.30; 6.61)	0.009
Bilirubin ≥ 2.1 mg/dl	2.4	(0.88;6.60)	0.089
Model 2			
Hyponatremia	9.36	(4.66;18.80)	<0.001
Earlier hepatic encephalopathy	1.78	(1.10; 2.87)	0.018
Creatinine ≥ 1.2 mg/dl	2.31	(1.22;4.38)	0.01
Model 3			
Hyponatremia	8.36	(3.52; 19.82)	<0.001
Earlier hepatic encephalopathy	2.23	(1.09; 4.56)	0.029
Creatinine ≥ 1.2 mg/dl	2.36	(1.11; 5.00)	0.025
Bilirubin ≥ 2.1 mg/dl	2.74	(1.16; 6.47)	0.022

Guevara, AJG 2009

Short-term albumin use leads to HYPONATREMIA resolution in INpatients with decompensated cirrhosis

North America cohort:
-1126 hospitalized cirrhotic patients with hyponatremia (Na<130mmol/L)
-777 patients treated with albumin (total mean amount 225 g).
- Primary indications for albumin were AKI (52%), SBP (15%), post-large volume paracentesis (33%), and hyponatremia (29%)

	Albumin− (*n*=349)	Albumin+ (*n*=777)	*p*-value
Complications of cirrhosis			
Prior ascites	66% (230/347)	85% (658/777)	<0.0001
Variceal bleed	20% (67/339)	23% (171/760)	0.31
Hyponatremia history	53% (175/329)	64% (476/739)	0.0005
Admit MELD score	18.63 (6.98)	22.84 (7.38)	<0.0001
Admit CTP score	9.40 (2.15)	10.54 (1.90)	<0.0001
Admit Na (mmol/L)	129.21 (10.50)	128.66 (4.69)	<0.0001
Admit creatinine (mg/dL)	1.24 (0.94)	1.74 (1.28)	<0.0001
Admit MAP (mmHg)	85.09 (13.88)	81.82 (14.00)	0.0001
Admit GFR (MDRD4)	82.65 (45.41)	59.58 (42.41)	<0.0001
Admit WBC count (/mm^3)	8.5 (6.1)	9.3 (5.9)	0.003
Admit INR	1.70 (0.75)	1.83 (0.67)	<0.0001
Admit total bilirubin (mg/dL)	6.80 (12.47)	8.22 (9.15)	<0.0001
Infection on admission	24% (82/347)	35% (269/771)	0.0002
Resolution of hyponatremia	61% (213/347)	69% (537/774)	0.0085

Hyponatremia resolution

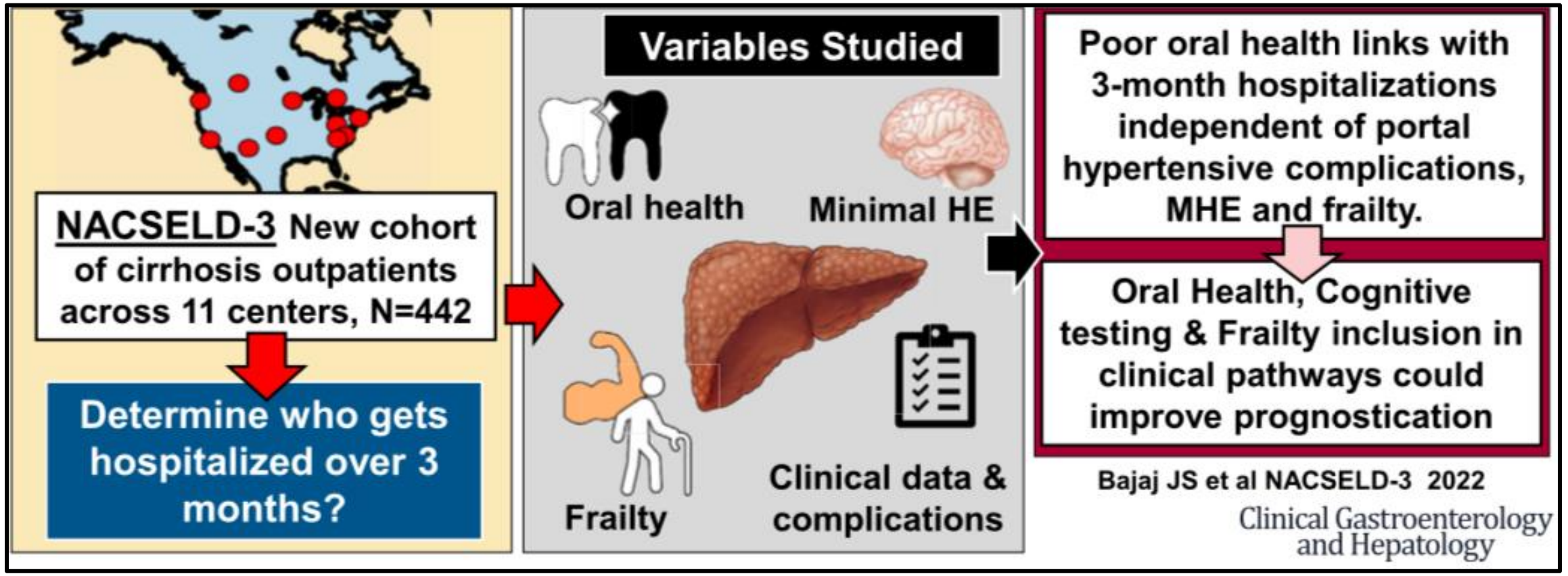
Variable	Estimate	Std err	Wald X^2	*p*-value	OR (95% CI)
Admission Na	0.1149	0.0148	60.51	<0.0001	1.12 (1.09, 1.16)
Admission GFR	−0.0063	0.0015	16.67	<0.0001	0.99 (0.99, 1.00)
Albumin use	0.4063	0.1470	7.64	0.0057	1.50 (1.13, 2.00)

30-days mortality

Variable	Estimate	Std err	Wald X^2	*p*-value	OR (95% CI)
Age	−0.0218	0.0096	5.19	0.0227	0.978 (0.960, 0.997)
Admission GFR	0.0065	0.0027	5.89	0.0153	1.007 (1.001, 1.012)
NACSELD-ACLF	−1.8470	0.2192	70.98	<0.0001	0.158 (0.103, 0.242)
Resolution of hyponatremia	0.4021	0.2016	3.98	0.042	1.495 (1.017, 2.219)

Bajaj, AJG 2018

Periodontitis as an indipendent prognostic factor in patients with decompensated cirrhosis



Periodontitis OR 3.68; 95% CI, 1.36–10; P < 0.01

Bajaj, CGH 2022

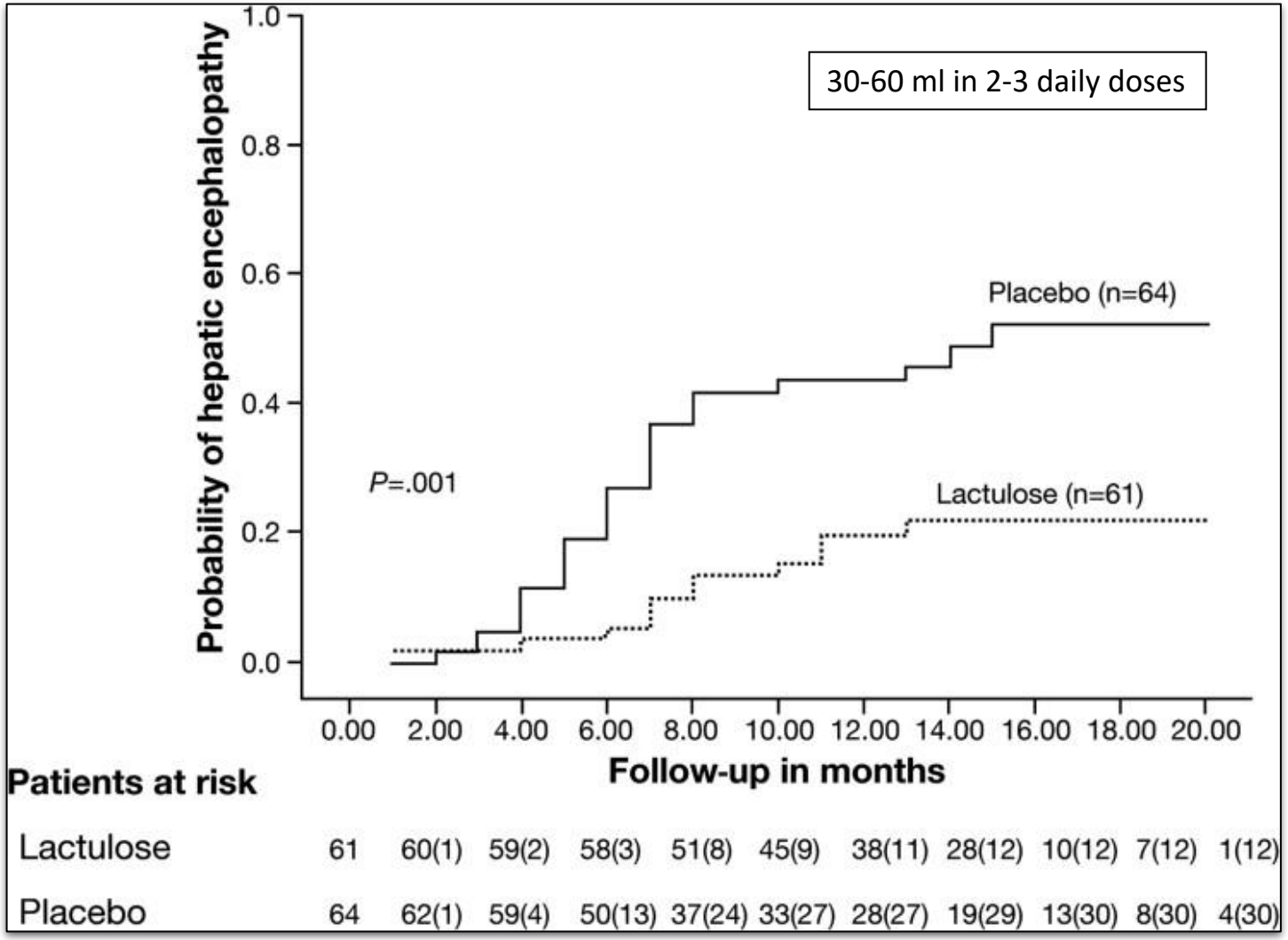
Secondary Prophylaxis of Hepatic Encephalopathy

Secondary Prophylaxis of Overt HE: Lactulose

Lactulose is metabolized by the bacteria in the colon to short chain fatty acids, which lowers the colonic pH to about 5.0.

↓

Acid pH favors formation of non-absorbable NH4 from NH3



Sharma et al. Gastroenterology 2009

Secondary Prophylaxis of Overt HE: Rifaximin

The NEW ENGLAND JOURNAL of MEDICINE

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

Rifaximin Treatment in Hepatic Encephalopathy

Nathan M. Bass, M.B., Ch.B., Ph.D., Kevin D. Mullen, M.D., Arun Sanyal, M.D., Fred Poordad, M.D., Guy Neff, M.D., Carroll B. Leevy, M.D.,* Samuel Sigal, M.D., Muhammad Y. Sheikh, M.D., Kimberly Beavers, M.D., Todd Frederick, M.D., Lewis Teperman, M.D., Donald Hillebrand, M.D., Shirley Huang, M.S., Kunal Merchant, Ph.D., Audrey Shaw, Ph.D., Enoch Bortey, Ph.D., and William P. Forbes, Pharm.D.

Microbiota modulation by Rifaximin

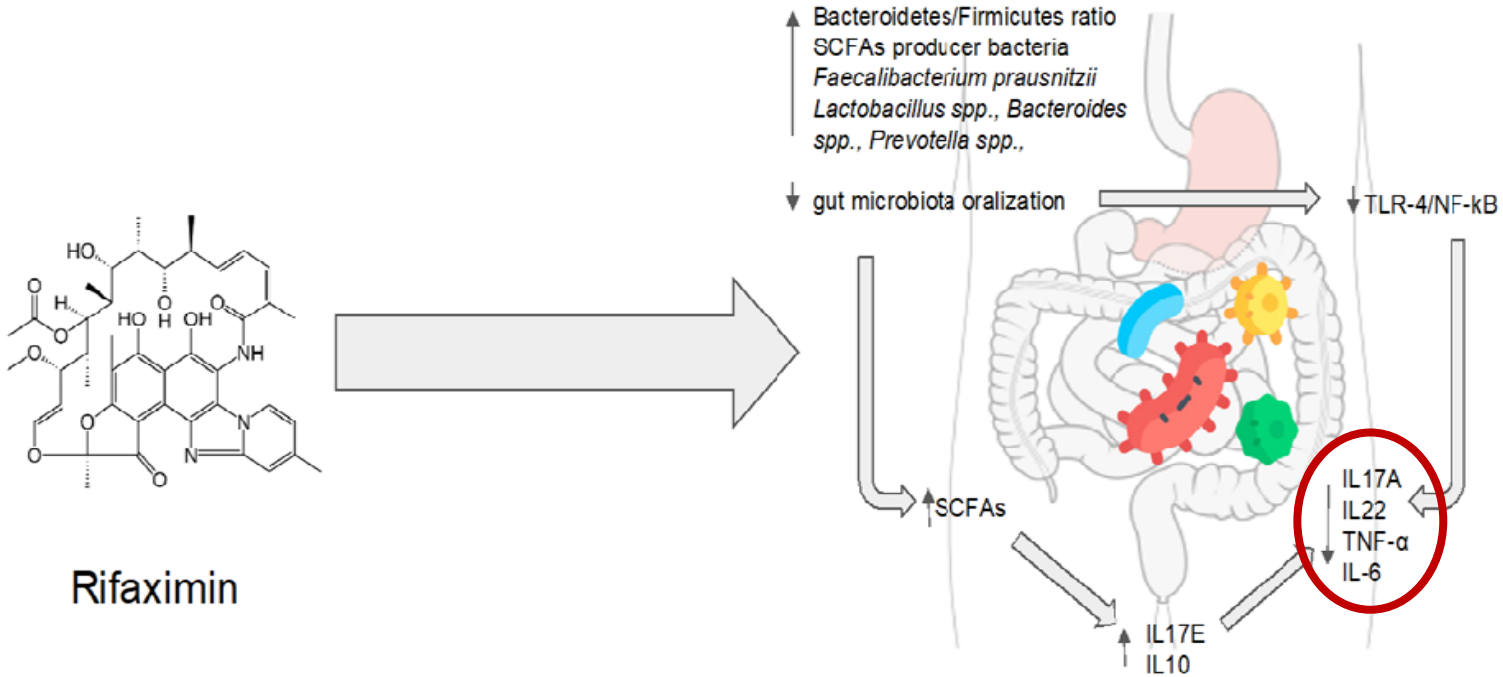


Figure 2. Rifaximin's eubiotic effects. IL17A: interleukin 17A; IL22: interleukin 22; TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6; IL10: interleukin 10; IL17E: interleukin 17E.

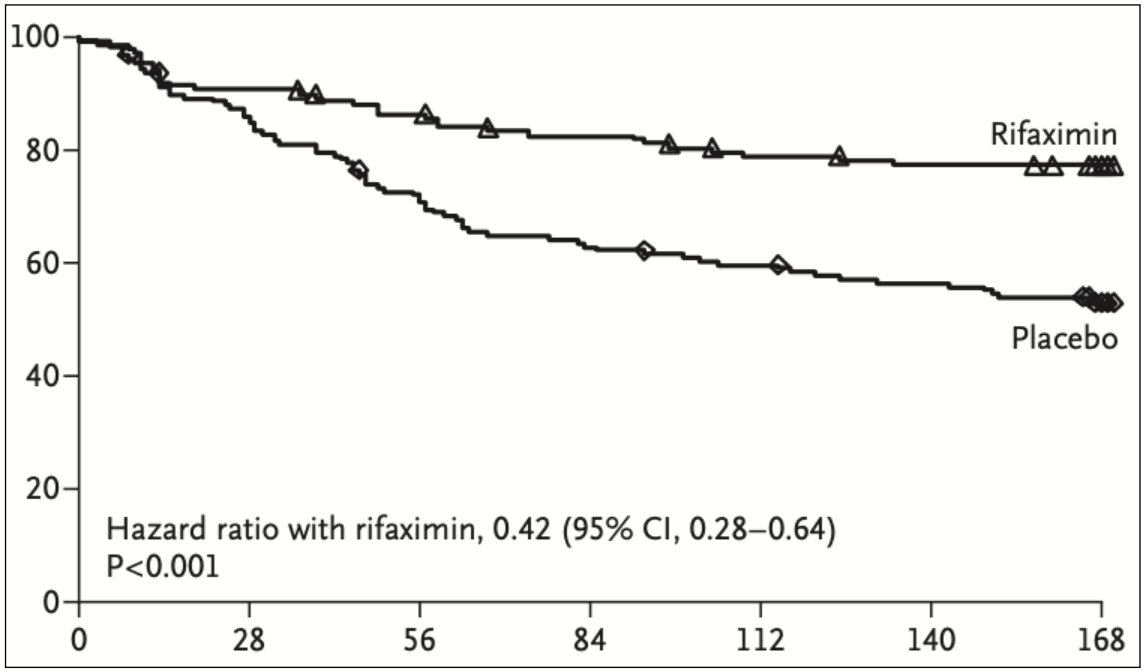
Bass et al. NEJM 2010

Airola et al. Antibiotics 2023

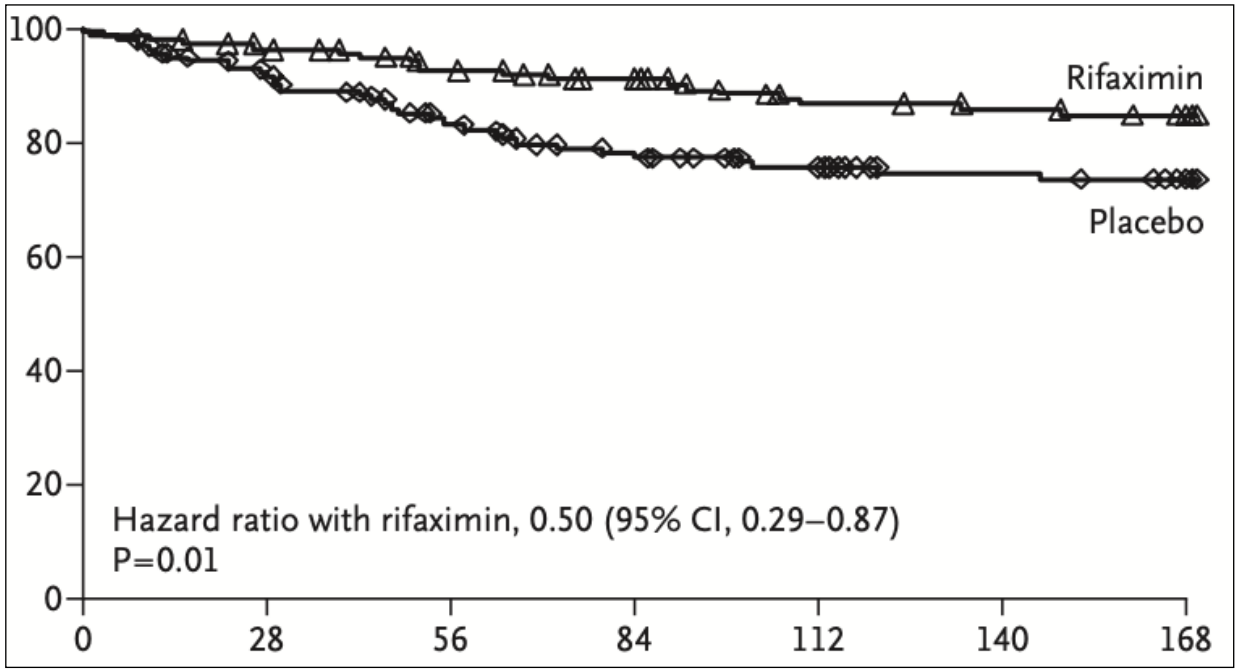
Secondary Prophylaxis of Overt HE: Rifaximin

Rifaximin 550 mg twice daily vs Placebo for 6 months

First Breakthrough HE Episode (Primary End Point)



First HE-Related Hospitalization (Key Secondary End Point)



Bass et al. NEJM 2010

Secondary Prophylaxis of Overt HE: AISF reccomendation

AISF recommendations

- **Non-absorbable disaccharides** represent the first-choice treatment for the secondary prophylaxis of overt HE, at a dose that guarantees 2/3 soft stools per day. *PEG may represent an alternative for patients who are intolerant to non-absorbable disaccharides*

- **Rifaximin** (550 mg twice daily or 400 mg three times daily) should be added to non-absorbable disaccharides in patients with recurrent OHE (i.e. those who have developed a second episode of overt HE within 6 months of the first one)

- Rifaximin may be used as first-line agent for the secondary prophylaxis of overt HE in patients who are truly intolerant to non-absorbable disaccharides, after their tapering has been tested and shown not to be beneficial

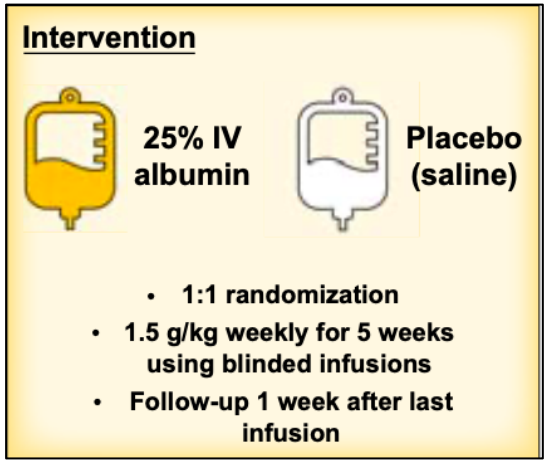
AISF, Dig Liv Dis 2019

HEAL study: A double-blind randomized placebo-controlled trial of albumin in OUTpatients with hepatic encephalopathy

Problem:
Even after recovery from clinically evident episodes of HE, most patients experience minimal hepatic encephalopathy (MHE) despite maximal therapy (Rifaximin+Lactulose)

Evidences:
1) Persistent cognitive impairment is accompanied by a sustained pro-inflammatory and endothelial dysfunctional state that is not quenched by current standard of care.

2) Albumin can bind metabolites that precipitate HE in individuals with advanced cirrhosis



Fagan, JHep 2023

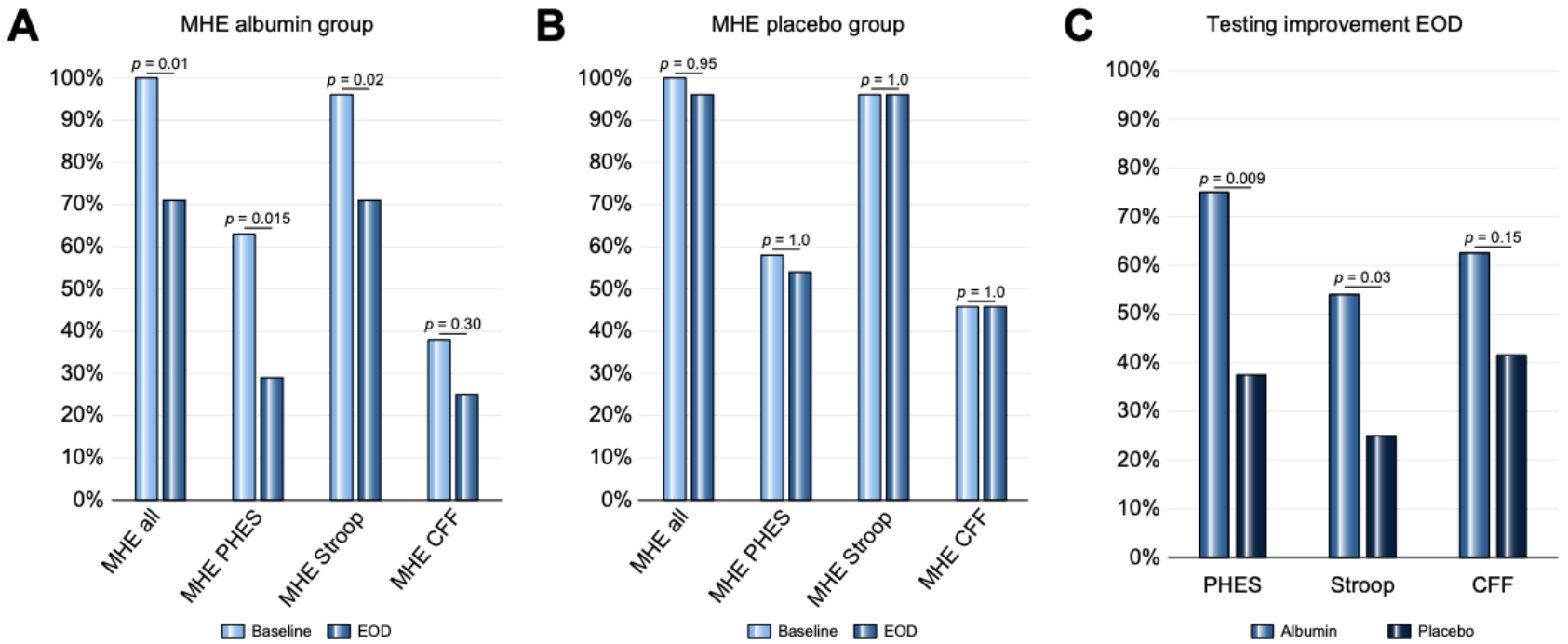
Outcomes

Primary:

Cognitive performance

Secondary:

Quality of life
Inflammatory cytokines
Endothelial dysfunction



	Placebo baseline	Placebo EOD	Placebo EOS	Albumin baseline	Albumin EOD	Albumin EOS
IL-1β (pg/ml)	0.53 ± 0.57	0.50 ± 0.47	0.47 ± 0.50	0.42 ± 0.39	0.37 ± 0.29*	0.35 ± 0.37*
IL-6 (pg/ml)	3.61 ± 2.67	3.80 ± 2.23	4.94 ± 7.52	3.71 ± 2.56	3.91 ± 2.61	3.18 ± 1.73
TNFα (pg/ml)	15.55 ± 8.34	15.09 ± 6.23	16.88 ± 7.32	16.34 ± 14.46	14.46 ± 7.06	15.06 ± 7.94
IL-10 (pg/ml)	3.69 ± 3.09	2.93 ± 3.17*	3.08 ± 3.02*	4.01 ± 4.07	3.83 ± 2.96	3.28 ± 1.81
LBP (ng/ml)	1,784.9 ± 1,557.3	1,714.8 ± 1,255.5	1,931.2 ± 316.7	1,651.1 ± 952.1	1,669.8 ± 1,010.4	1,659.7 ± 931.6
ICAM-1 (ng/ml)	298.1 ± 97.1	341.6 ± 118.8*	343.6 ± 125.9*	316.7 ± 140.3	271.1 ± 134.1*,†	313.1 ± 125.6
ADMA (μM)	0.65 ± 0.12	0.72 ± 0.13*	0.65 ± 0.14	0.69 ± 0.13	0.63 ± 0.09*,†	0.63 ± 0.10*
IMA (IU/ml)	831.7 ± 1,335.6	997.2 ± 1,529.3*	1,604.9 ± 3,082.3*	1,491.5 ± 3,125.9	1,144.1 ± 2,812.6*	1,042.9 ± 2,753.9*

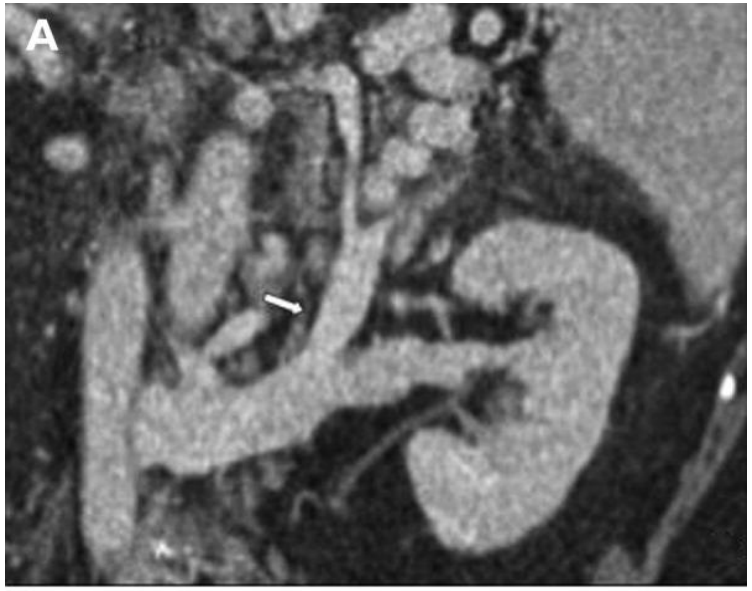
Fagan, JHep 2023

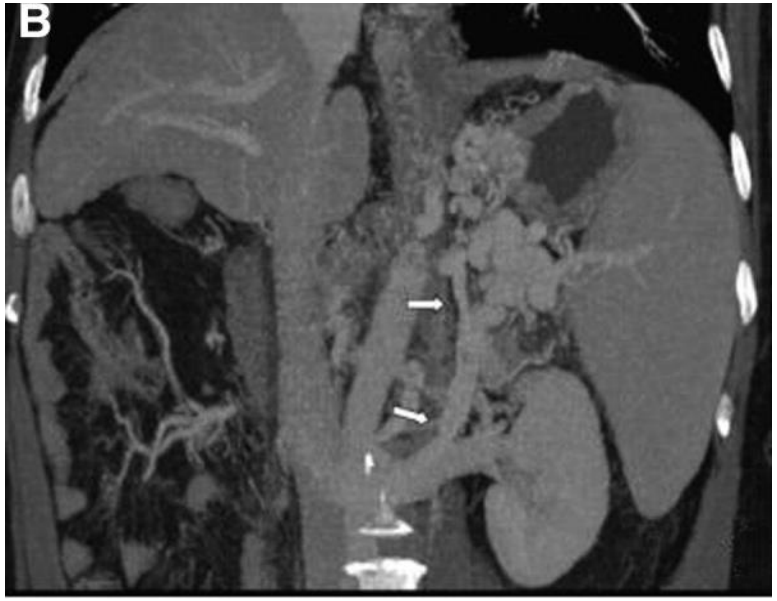
PERSISTENT OR HIGHLY RECURRENT HEPATIC ENCEPHALOPATHY: Consider SHUNT reduction

AISF recommendations

- In patients with persistent or highly recurrent HE spontaneous portal-systemic shunts should be sought for by Doppler ultrasound and, should this be negative, by angio-CT abdomen *(GRADE III, A, 1)*
- Persistent or highly recurrent OHE is an indication for interventional shunt reduction/obliteration *(GRADE II-3, A, 1)*

AISF, Dig Liv Dis 2019





Riggio et al., Hepatology 2005

Prophylaxis of Hepatic Encephalopathy after TIPS

Under-dilated TIPS Associate With Efficacy and Reduced Encephalopathy in a Prospective, Non-randomized Study of Patients With Cirrhosis

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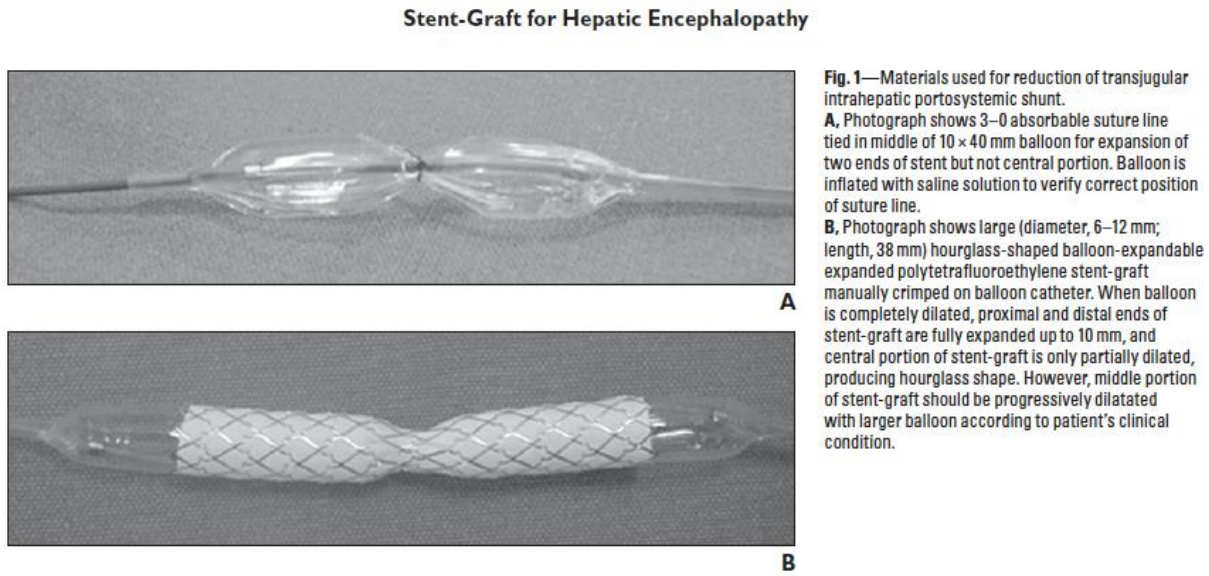
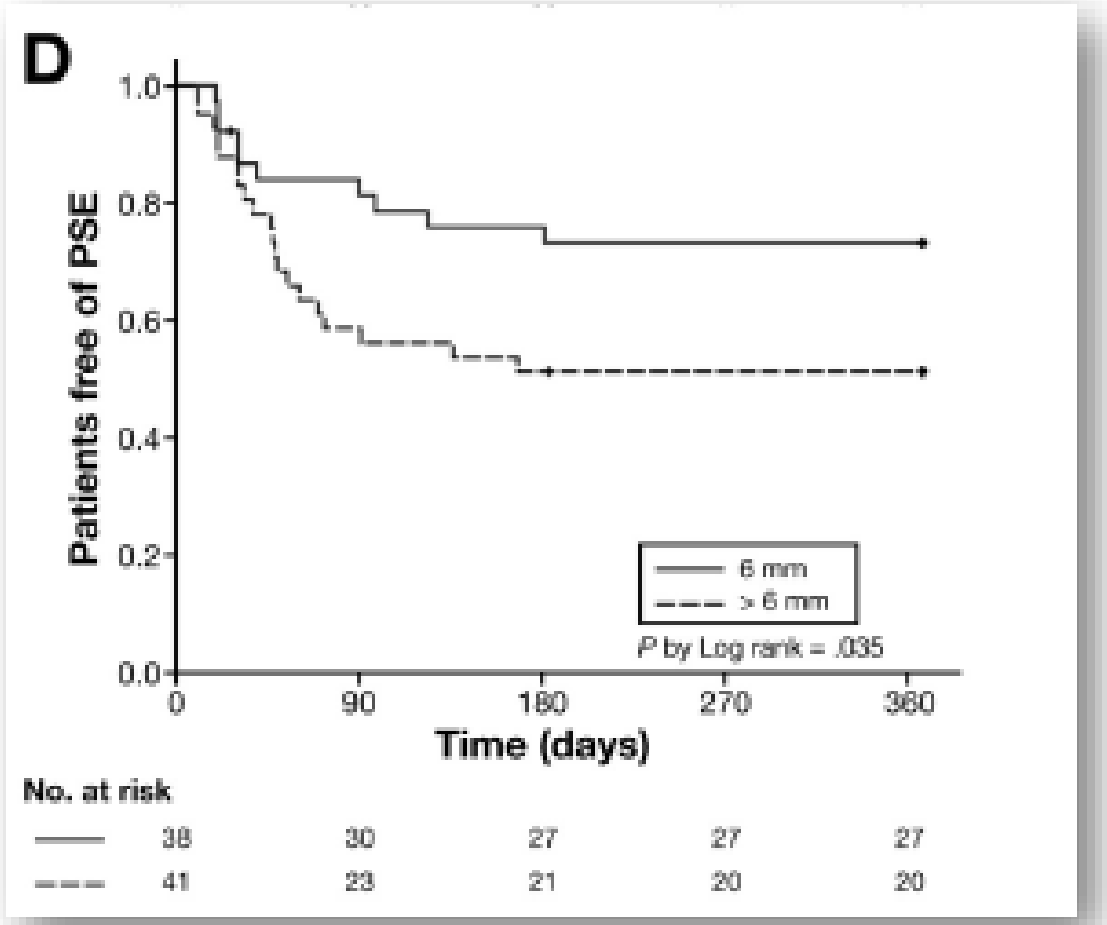
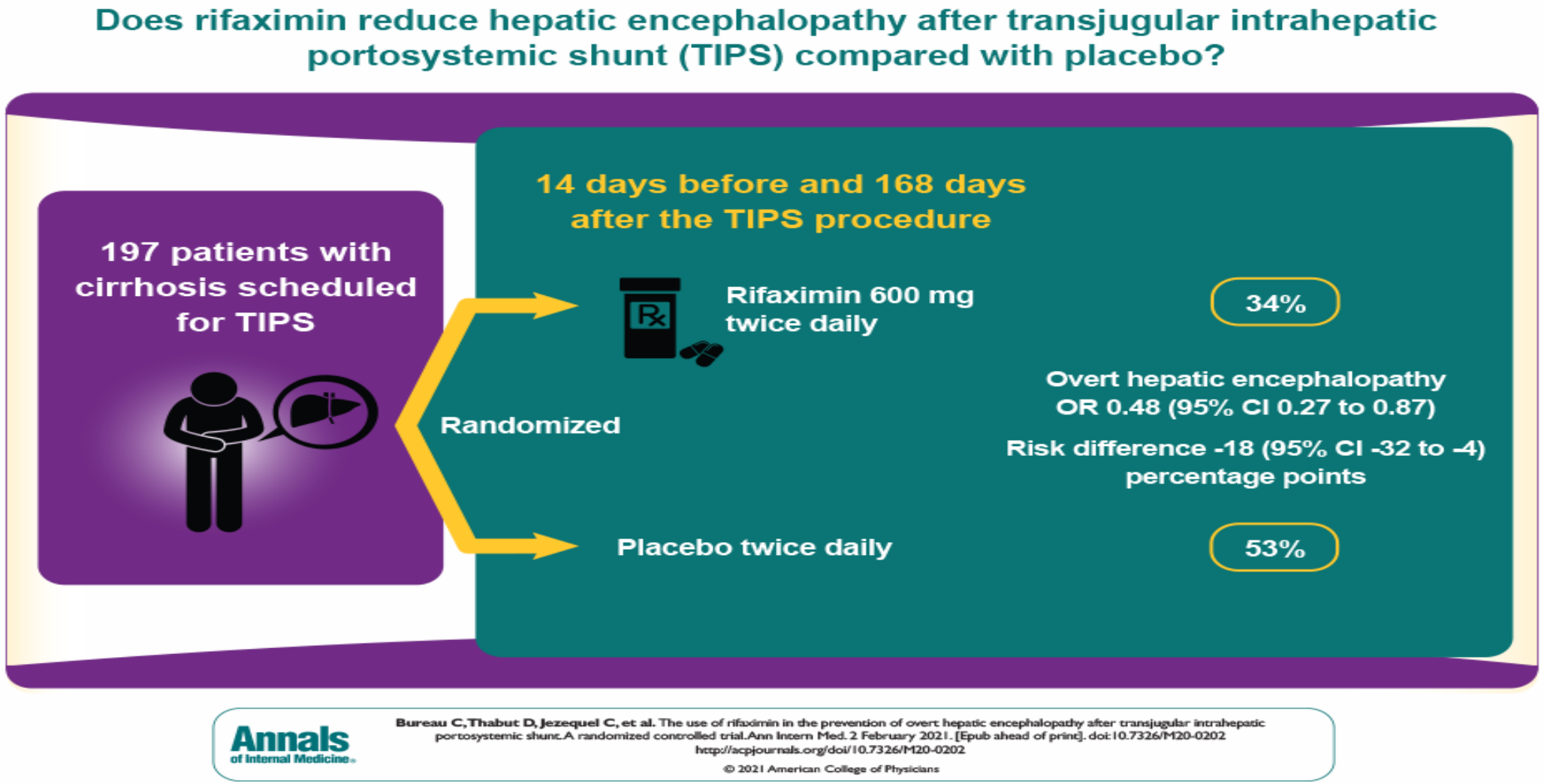


Fig. 1—Materials used for reduction of transjugular intrahepatic portosystemic shunt.
A, Photograph shows 3–0 absorbable suture line tied in middle of 10 × 40 mm balloon for expansion of two ends of stent but not central portion. Balloon is inflated with saline solution to verify correct position of suture line.
B, Photograph shows large (diameter, 6–12 mm; length, 38 mm) hourglass-shaped balloon-expandable expanded polytetrafluoroethylene stent-graft manually crimped on balloon catheter. When balloon is completely dilated, proximal and distal ends of stent-graft are fully expanded up to 10 mm, and central portion of stent-graft is only partially dilated, producing hourglass shape. However, middle portion of stent-graft should be progressively dilatated with larger balloon according to patient's clinical condition.

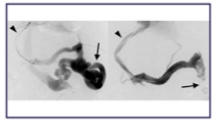


Schepis et al., CGH 2018

Rifaximin reduces the risk of Post-TIPS Hepatic Encephalopathy



Bureau, Annals of Internal Medicine 2021



Combined Spontaneous Portosystemic Shunt Embolization and Transjugular Intrahepatic Portosystemic Shunt Creation for Treatment of Hepatic Encephalopathy

Rajangad S. Gurtatta, BS, Ron C. Gaba, MD, MS, and Josi L. Herren, DO

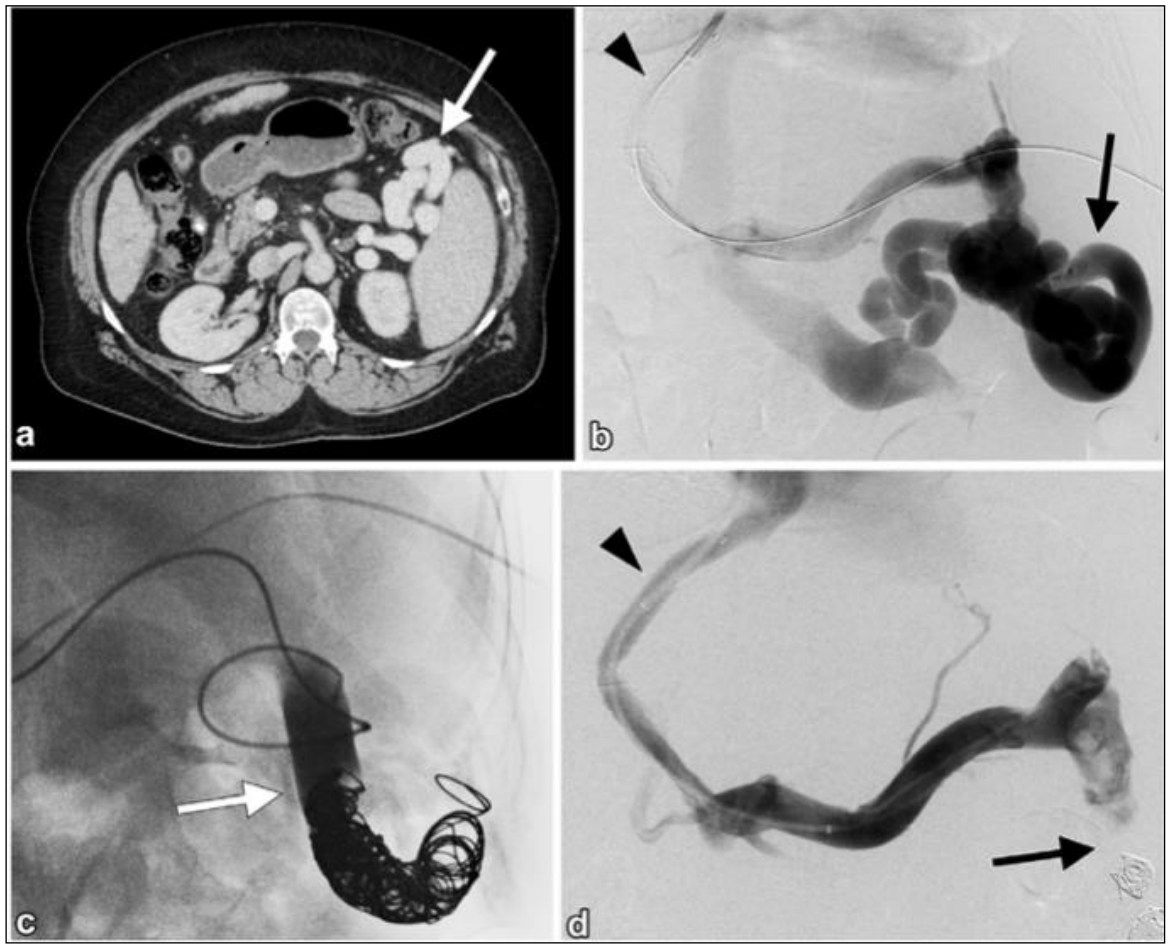


Table 3. Spontaneous Portosystemic Shunt Embolization and Transjugular Intrahepatic Portosystemic Shunt Creation Clinical Outcomes

Measure	Before the procedures	After the procedures	*P* value
HE	8/8 (100%)	3/8 (37.5%)	.026
HE severity			.010
Overt (WH Grades 2–4)	7 (87.5%)	1 (12.5%)	
Covert (WH Grade 1)	1 (12.5%)	7 (87.5%)	
90-d HE hospitalizations (mean)	3 (37.5%)	1 (12.5%)	.569

RESEARCH HIGHLIGHTS

- In 8 patient with refractory hepatic encephalopathy related to cirrhosis and spontaneous portosystemic shunts, transjugular intrahepatic portosystemic shunts were created and the spontaneous shunts were embolized.
- Seven patients exhibited improvement in encephalopathy, and none developed new complications of ascites.

Gurtatta, J Vasc Interv Radiol, MAY 2024

THANKS