10TH ANNUAL

DIGESTIVE DISEASES: NEW ADVANCES

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Hepatic Encephalopathy: New Innovations

Sammy Saab, MD, MPH, AGAF, FACG, FAASLD
Medical Director, Pfleger Liver Institute
Medical Director, Adult Liver Transplant Program at UCLA
Chief, Transplant Hepatology at UCLA
Head, Outcomes Research in Hepatology at UCLA
Professor of Medicine and Surgery, David Geffen School of Medicine
Adjunct Professor of Nursing, UCLA School of Nursing
Professor (Hon), California Northstate University College of Medicine
Associate Editor for Liver, Journal of Clinical Gastroenterology

Disclosures

- Sammy Saab, MD, MPH
  - Speakers Bureau: AbbVie, Gilead, Exelixis, Eisai, Intercept, Takeda, Mallinckrodt, Salix

Educational Objectives

- Review the epidemiology and clinical implications of hepatic encephalopathy (HE), and the role of the provider in treating HE in patients with chronic liver disease
- Discuss the approach and treatment options for medically refractory HE in patients
- Identify prevention and management strategies used in post-TIPS HE

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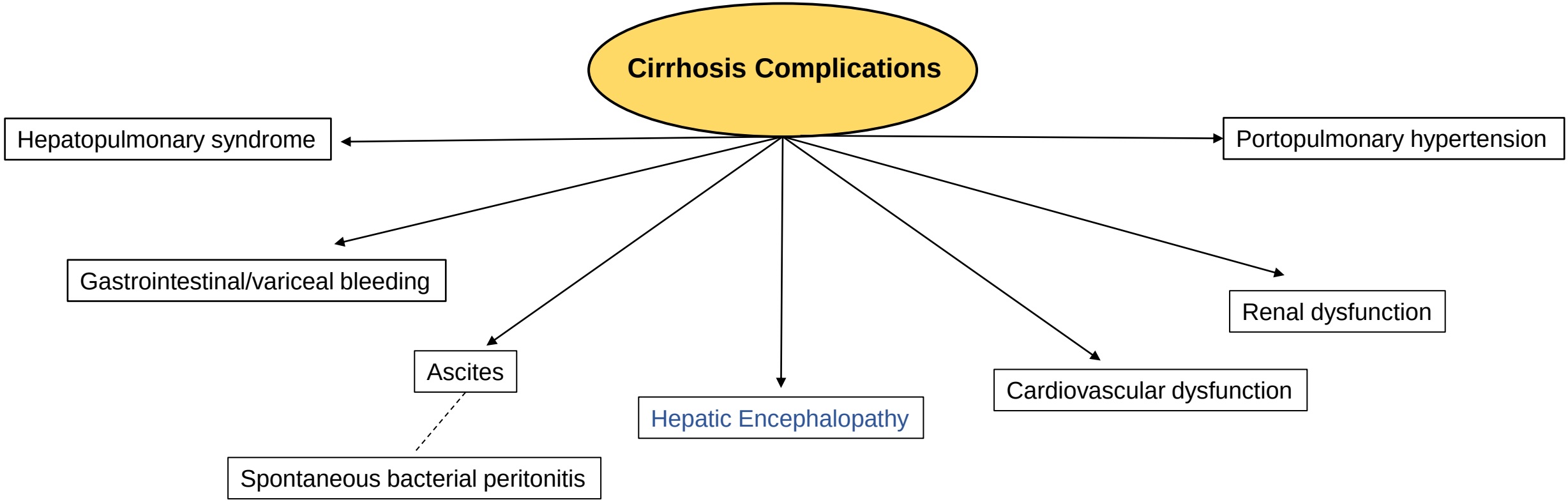
Cirrhosis Is Associated With a Variety of Serious Complications

- Cirrhosis is associated with serious complications due to hepatic insufficiency and portal hypertension
- Hepatic encephalopathy is a primary complication of cirrhosis



James J, Liou IW. *Med Clin North Am*. 2015; Jawaro T et al. *Ann Pharmacother*. 2016; Liu A et al. *World J Hepatol*. 2015; Saab S. *Int J Gen Med.* 2015; Vilstrup H et al. *Hepatology*. 2014; Flamm SL. *Am J Manag Care.* 2018; Nadim MK et al. *J Hepatol*. 2016.

Hepatic Encephalopathy (HE) is not a Benign Condition

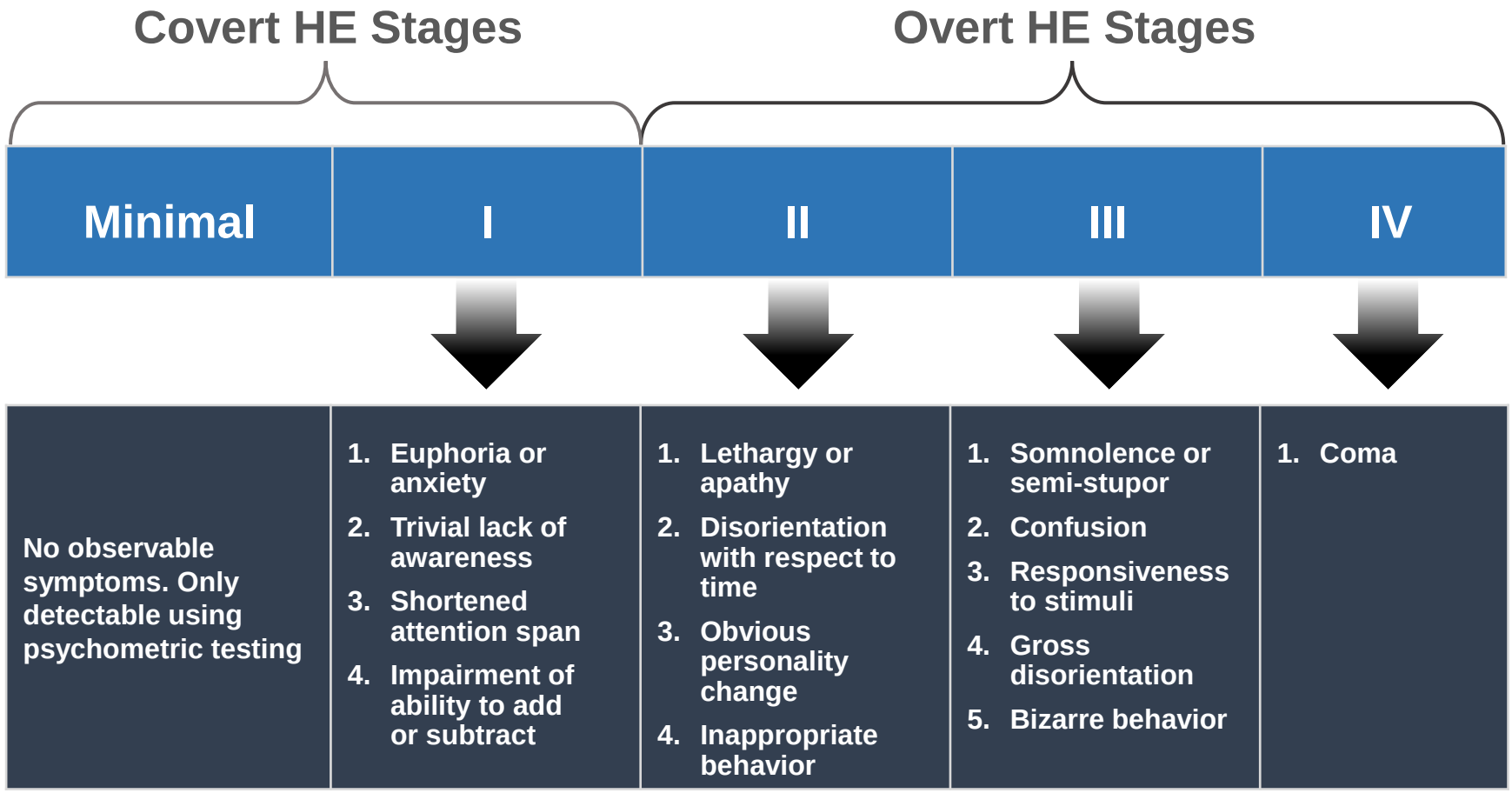
- Common
  - Up to 80% of cirrhosis patients will develop HE, ranging from minimal to overt
- Selfish
  - Huge toll on care givers
- Association with increased mortality
  - Grade 3 and 4 HE
- Leaves a foot print
  - Repeated bouts can cause persistent cognitive deficits despite resolution of HE
  - Cognitive deficits that can persist after liver transplantation
- Destroys quality of life
  - Work, driving, social interaction
- Revolving Door
  - Recurrence common, and readmission rate high
  - Increased health care utilization

Bajaj JS et al. *Clin Gastroenterol Hepatol.* 2017; Vilstrup H et al. *Hepatology*. 2014. Bajaj JS et al. *Aliment Pharmacol Ther*. 2019; Bass et al. *N Engl J Med*. 2010; Guevara et al. *Am J Gastroenterology*. 2009; Mas. *Digestion*. 2006; Bajaj et al. *Gastroenterology*. 2010; Mullen et al. *Semin Liver Dis*. 2007. Conn HO, Bircher J. *Medi-Ed Press* 1994; Riggio et al. *Clin Gastroenterol Hepatol.* 2011. Bajaj et al. *Gastroenterology.* 2010. Garcia-Martinez et al. *Liver Transpl.* 2011; Bajaj et al. *Am J Gastroenterol* 2011. Rakoski et al. *Hepatology* 2012; Nardelli S et al. *Dig Dis Sci* 2017.

Hepatic Encephalopathy Symptoms Can be Subtle; Should be Considered in Any Patient With Cirrhosis

Diagnosis of Overt Hepatic Encephalopathy

- Clinical recognition of the distinctive neurologic features of HE
- Knowledge that underlying cirrhosis is present
- Exclusion of all other etiologies of neurologic and/or metabolic abnormalities
- Identification of precipitating factors
- Grading systems to evaluate mental status
- Portal-systemic encephalopathy score to evaluate overall severity



HE = hepatic encephalopathy

Vilstrup H, et al. *Hepatology* 2014; Mullen KD. *Semin Liver Dis* 2007. Lawrence KR, Klee JA. *Pharmacotherapy* 2008.

Precipitating Factors for Hepatic Encephalopathy

Increased ammonia production

GI hemorrhage

Excessive dietary protein

Blood transfusion

Electrolyte disorder (eg, hypokalemia)

Constipation

Portosystemic shunts

Spontaneous

Iatrogenic (eg, TIPS)

Other

Drugs (eg, opioids, benzodiazepines)

Infections (eg, SBP)

Malignancy (eg, hepatoma)

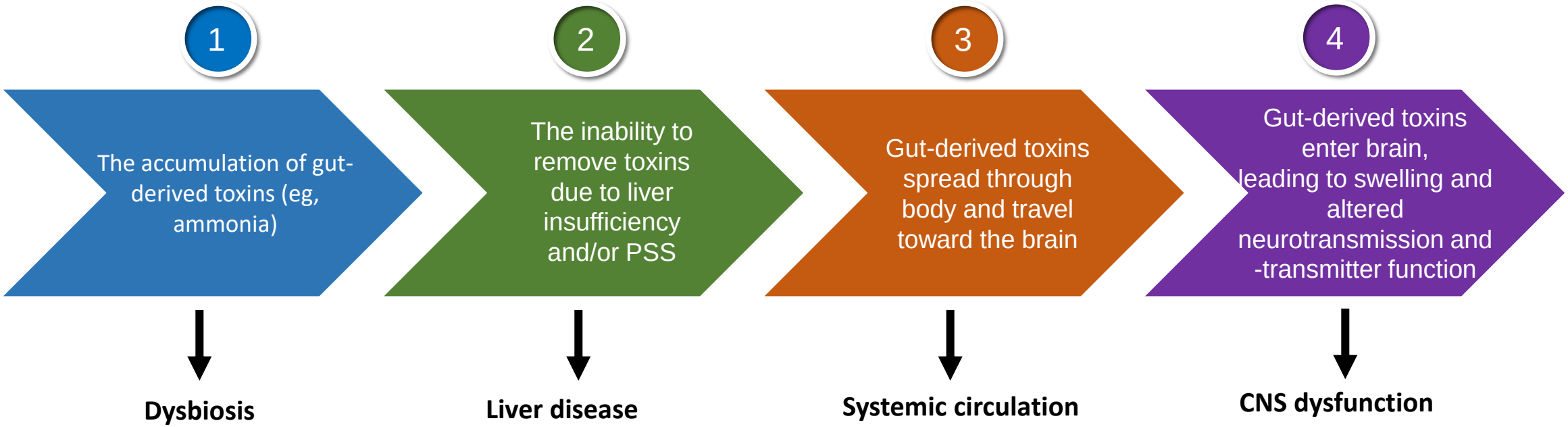
Dehydration

Sarcopenia

Vilstrup H et al. *Hepatology*. 2014; Bellafante D et al. *J Clin Med* 2023.

HE is brain dysfunction, thought to involve the accumulation of gut-derived neurotoxins

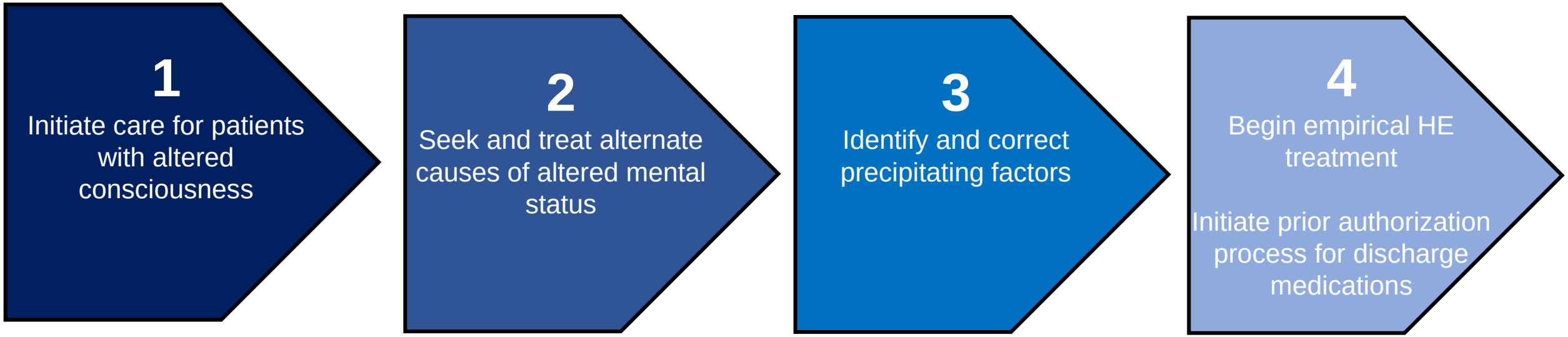
HE is caused by liver insufficiency and/or PSS. The pathophysiology of HE is complex and is thought to involve accumulation of gut-derived toxins (eg, ammonia), inflammation, and oxidative stress



NH_3, ammonia; PSS, portal systemic shunting.

Vilstrup H, et al. *Hepatology*. 2014; Elwir S, et al. *J Clin Transl Hepatol.* 2017; DuPont HL. *Mayo Clin Proc.* 2015; Bajaj JS, et al. *Am J Physiol Gastrointest Liver Physiol.* 2012; Oikonomou T, et al. *World J Gastroenterol.* 2018; Basile AS, et al. *Pharmacol Rev.* 1991.

AASLD Recommends 4-Pronged Approach to Treating Overt Hepatic Encephalopathy



Vilstrup H et al. *Hepatology*. 2014

FDA Approved Treatment Options and Goals for Hepatic Encephalopathy

Immediate goals:

- Provide supportive care
- Prior authorization for discharge medications upon admission
- Identification and removal of precipitating factors
- Reduction of nitrogenous load from gut
- Correction of electrolyte abnormalities

Long-term goals

- Control of potential precipitating factors
- Discharge on medications due to higher likelihood of recurrent encephalopathy
- Assessment of need for liver transplantation

Drug Name	Drug Class	Mechanism of Action
Lactulose	Poorly absorbed disaccharide	• Decreases blood ammonia concentration - Promotes elimination of NH_3 - Fermentation by bacteria acidify colon and prevent absorption - Reduces urease-producing bacteria
Rifaximin	Non-aminoglycoside semi-synthetic, nonsystemic antibiotic	• Decreases blood ammonia concentration - Broad spectrum antibiotic; results in a change in bowel flora - May cause downregulation of intestinal glutaminase activity

Blei AT, et al. *Am J Gastroenterol*. 2001.

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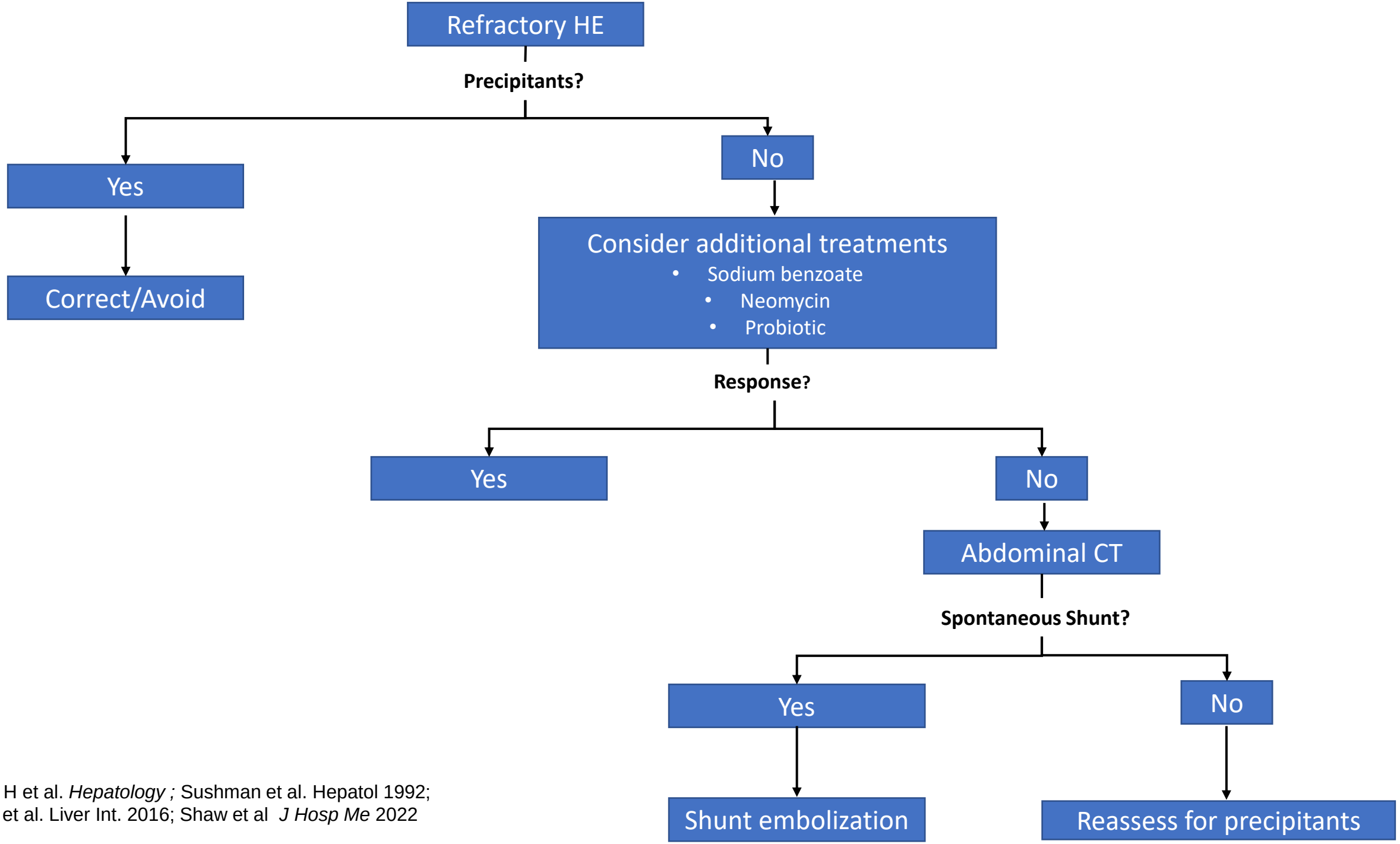
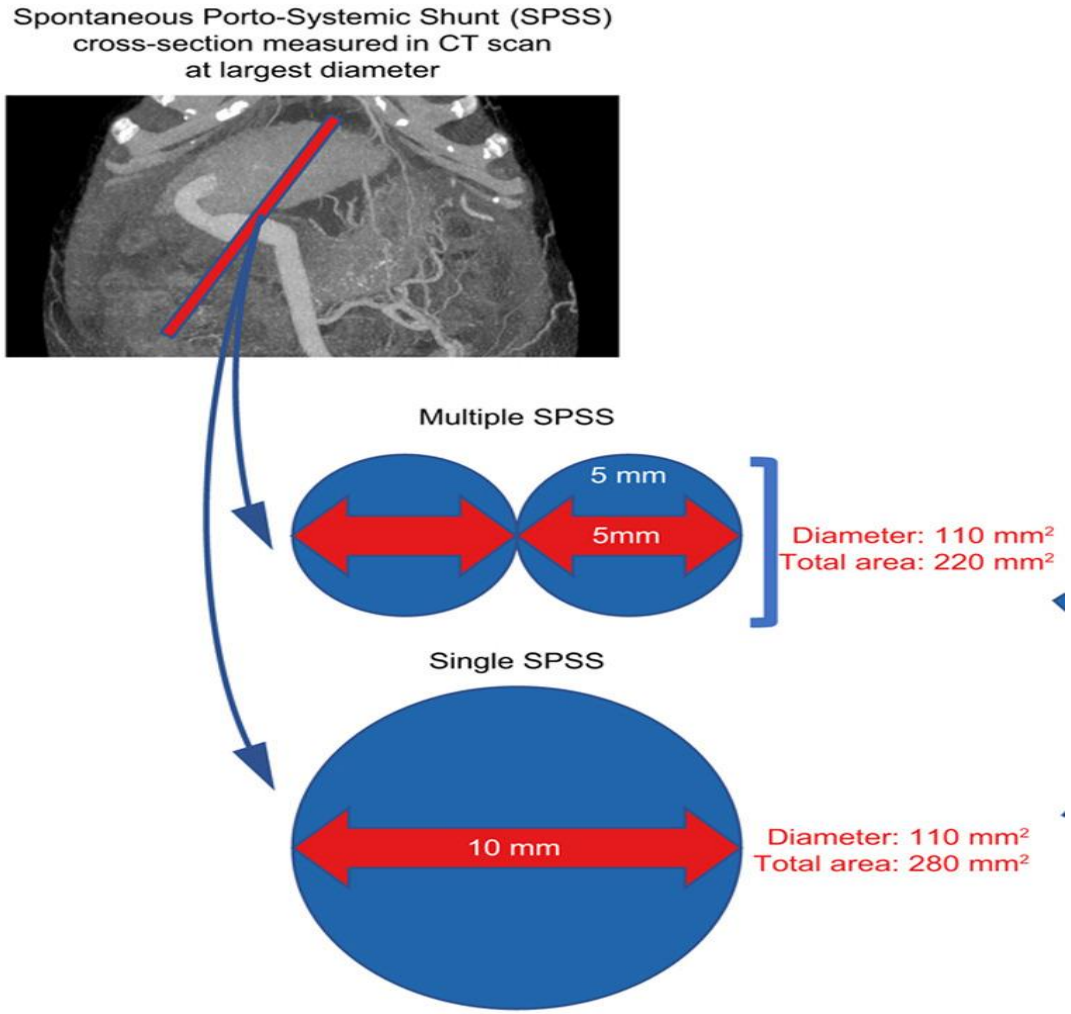


Vilstrup H et al. *Hepatology ;* Sushman et al. Hepatol 1992;
Saab S et al. Liver Int. 2016; Shaw et al *J Hosp Me* 2022

Measuring Spontaneous Porto-Systemic Shunt (SPSS)



"MELD score was the strongest positive predictive factor of HE recurrence, with a cut-off of 11 used for patient selection to ensure safe embolisation without an increase in *de novo* development or aggravation of pre-existing varices, portal hypertensive gastropathy, or ascites".

Praktiknjo et al. *J Hepatol* 2020; EASL *J Hepatol* 2022

Presence of Spontaneous Portosystemic Shunt Associated with Hepatic Encephalopathy

Comparison Between the Two Groups of Patients Included in the Study

Demographics

	Cases (n = 14)	Controls (n = 14)	p value
Age (y)	65.4 ± 9.3	65.1 ± 9.4	NS
Sex	9M/5F	12M/2F	NS
Etiology (alcohol/virus)	5/9	3/11	NS
Plasma sodium	135.4 ± 6.4	137.4 ± 3.2	NS
INR	1.42 ± 0.1	1.37 ± 0.3	NS
Creatinine (mg/dl)	0.98 ± 0.68	0.99 ± 0.78	NS
Bilirubin (mg/dl)	2.7 ± 1.5	2.1 ± 2.1	NS
Albumin (g/dl)	2.8 ± 0.7	2.9 ± 0.8	NS
MELD (score)	10.7 ± 4.0	10.2 ± 4.9	NS

Mean± SD.

Prevalence of Spontaneous Portosystemic Shunts, Ascites, Large Varices, and Portal Gastropathy

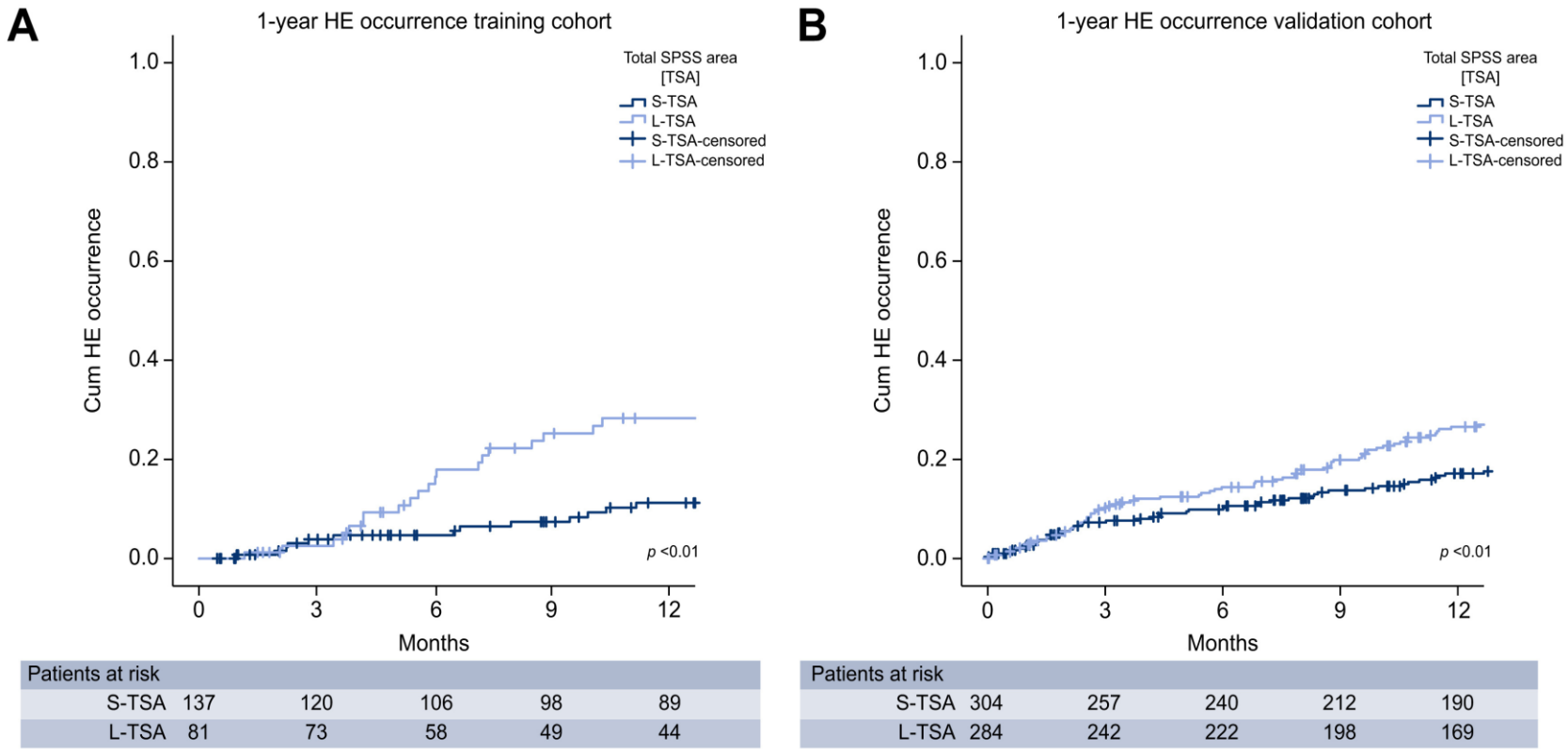
	Cases (n = 14)	Controls (n = 14)	p value
Shunts	10 (71%)	2 (14%)	.002
History of ascites	3(21%)	11 (78%)	.002
Large varices (F2-F3)	1 (7%)	6(42%)	.02
Presence of portal gastropathy	4(29%)	12 (86%)	.0007

Riggio et al. *Hepatology*, 2005

Spontaneous Portosystemic Shunt Size Associated with Hepatic Encephalopathy Risk

Cumulative hazard function for the occurrence of overt hepatic encephalopathy (HE) in the training and validation cohorts

- Small total area (S-TSA) SPSS defined as **<83 mm²**
- Large total area (L-TSA) SPSS area defined as **≥83 mm²**

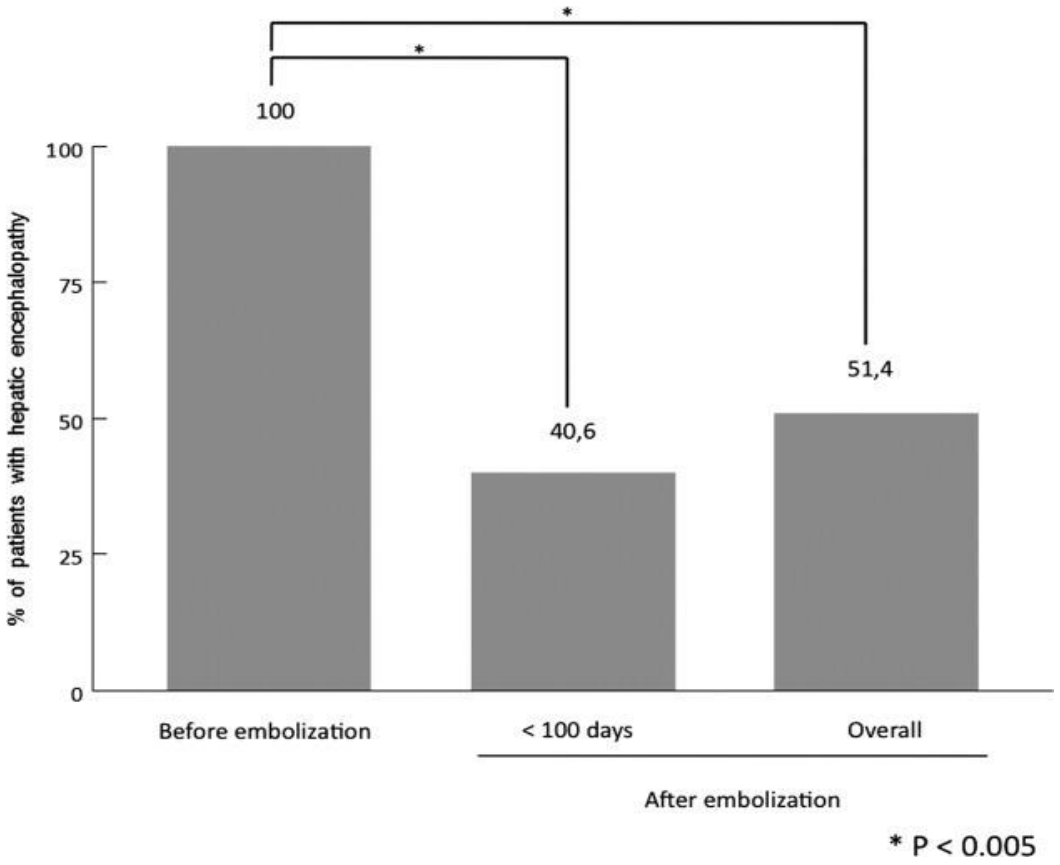


SPSS, spontaneous portosystemic shunts

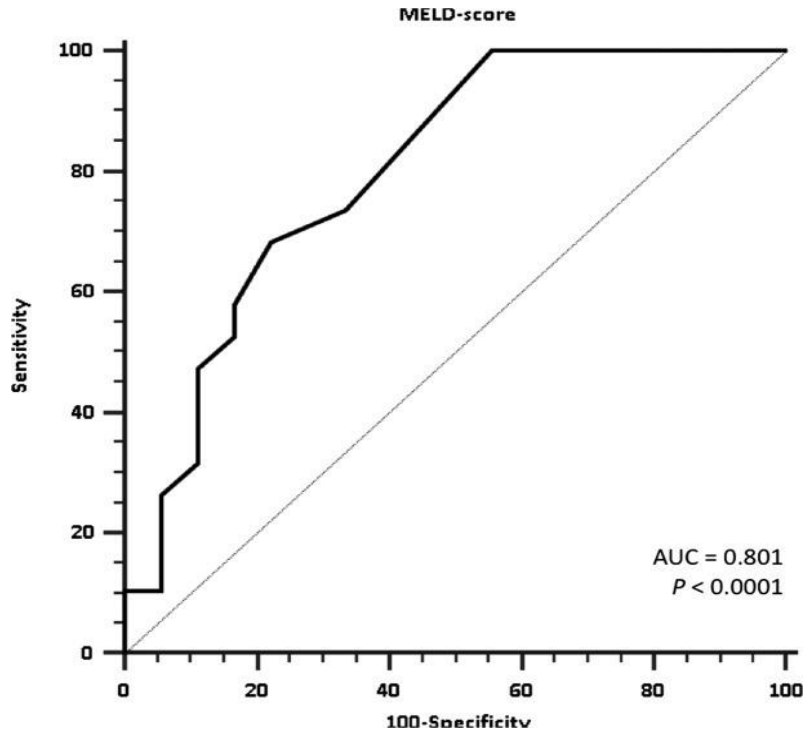
Praktiknjo et al. *J Hepatol* 2020

Embolization of Large Spontaneous Porto-Systemic Shunt (SPSS) for Refractory Hepatic Encephalopathy (HE)

Short- and Long-term efficacy of SPSS-embolization in the occurrence of HE

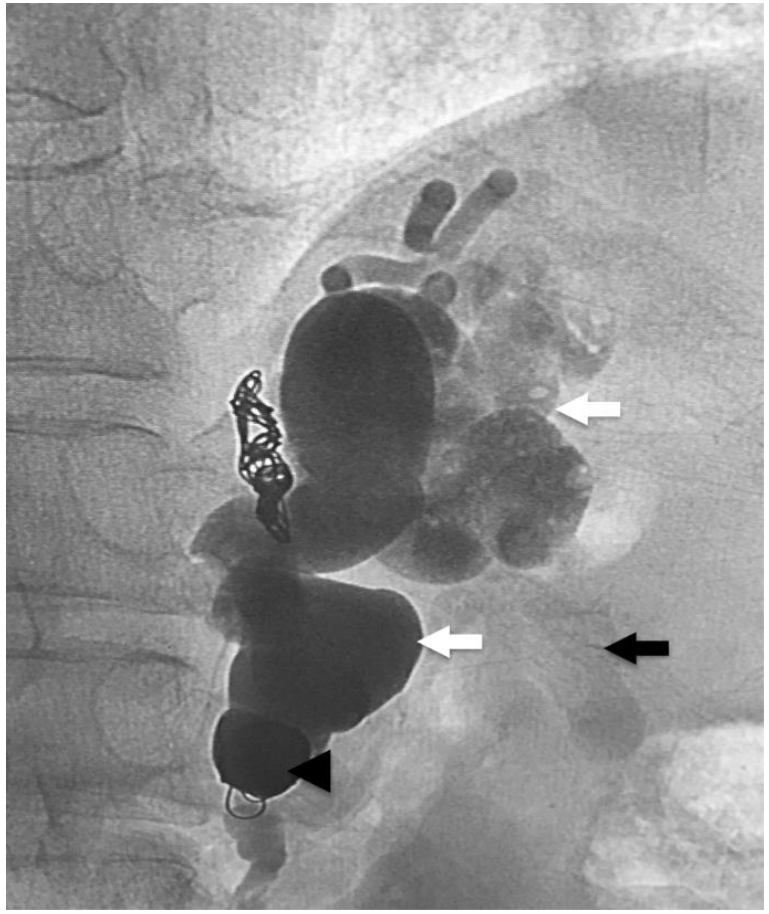


Prediction of HE recurrence. Best cutoff point for the MELD score was 11 with a sensitivity and specificity of 68.4% and 77.6%, respectively.



Laleman W et al. *Hepatol* 2013

Retrograde Transvenous Obliteration for the Treatment of Hepatic Encephalopathy



A radiographic image of CARTO procedure demonstrating
- Black arrowhead ~ coil occlusion of efferent (draining) gastrorenal shunt
- White arrow ~ gelfoam filled gastrorenal shunt (white arrow)
- Black arrow ~ gelfoam filled gastric varices

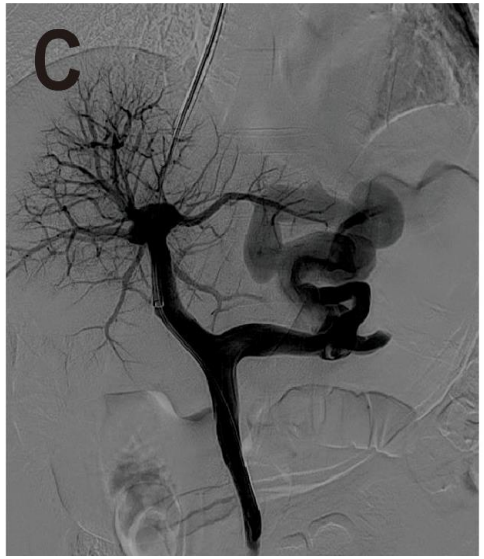
The patient's West Haven score improved from 4 to 1 in 2 days post-CARTO and the ammonia level decreased from 257 to 46 µg/dL

Potential Side Effects
- worsening of portal hypertension
- formation of additional shunts

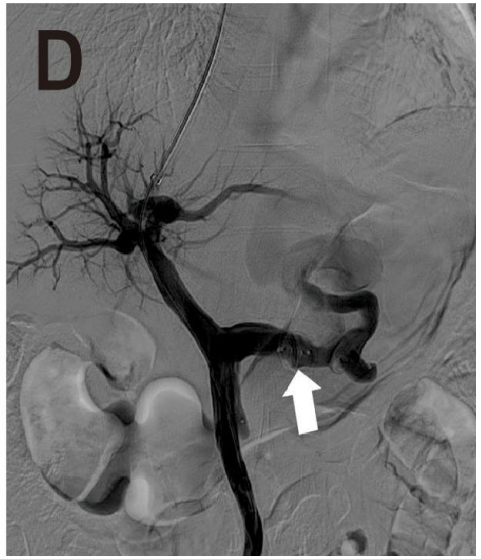
Lee EW, Lee AE, Saab S, Kee ST. *Dig Dis Sci*. 2020

Venography before and after Selective Embolization of the Splenic Vein

SMV venography before SESV



SMV venography after SESV



SV, splenic vein; SESV, selective embolization of the splenic vein

Zhang L, et al. *Dig Liv Dis Sci*. 2023

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Utility of TIPS in Patients with Chronic Liver Disease

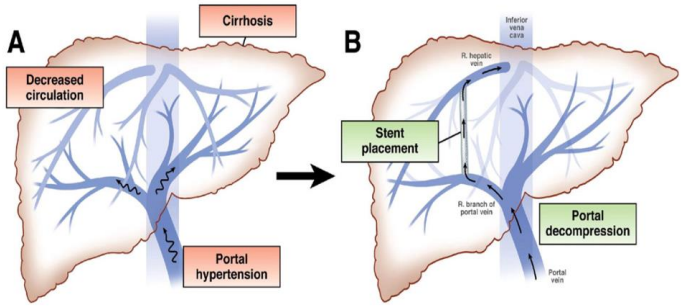


Table 2. Indications for transjugular intrahepatic portosystemic shunt placement

	AASLD (2009)	EASL (2018)	ACR-SIR-SPR (2017)[a]
Resistant cirrhotic ascites	I	I	✓
Secondary prevention of variceal hemorrhage	I	I	✓
Uncontrollable variceal hemorrhage ("rescue" therapy)	II-3	I	✓
Recurrent hepatic hydrothorax	II-3	II-2	✓
Portal hypertensive gastropathy, in those for whom beta-blockers fail	II-3	II-3	✓
Budd-Chiari syndrome, in those who fail to improve with anticoagulation	II-3	Not addressed	✓
Hepatorenal syndrome	Further research needed	II-2 for type 2, further research needed	✓
Hepatopulmonary syndrome	Not recommended	Further research needed	✓
Decompression of portosystemic collaterals prior to abdominal surgical procedures	Not addressed	Not addressed	✓

AASLD, American Association for the Study of Liver Diseases; ACR, American College of Radiology; EASL, European Association for the Study of the Liver; SIR, Society of Interventional Radiology; SPR, Society for Pediatric Radiology.
[a]ACR-SIR-SPR guidelines do not report levels of evidence.
From AASLD (ref. [1]), EASL (ref. [2]), and ACR-SIR-SPR (ref. [3]).

Table 3. Relative and absolute contraindications to transjugular intrahepatic portosystemic shunt placement

Contraindications	
Relative	**Absolute**
Advanced age	Severe or poorly controlled HE
Remote history of HE	Severe liver failure
Elevated MELD	Heart failure or severe cardiac valvular insufficiency
Elevated right or left heart pressures	Marked pulmonary arterial hypertension
Moderate portopulmonary hypertension	Severe portopulmonary hypertension
Extensive primary or metastatic hepatic malignancy	Unrelieved biliary obstruction
Severe uncorrectable coagulopathy	Active systemic infection or sepsis
Severe uncorrectable thrombocytopenia	

HE, hepatic encephalopathy; MELD, Model for end-stage liver disease.

Saab S. et al. *Am J Gastroenterol 2020;* Gonzalez JG. AASLD Liver Fellow Network. https://www.aasld.org/liver-fellow-network . Accessed 9/2/23

Predictors of Post-TIPS Hepatic Encephalopathy

Predictors of Post-TIPS Hepatic Encephalopathy
Occurs in up to 50% of patients after TIPS

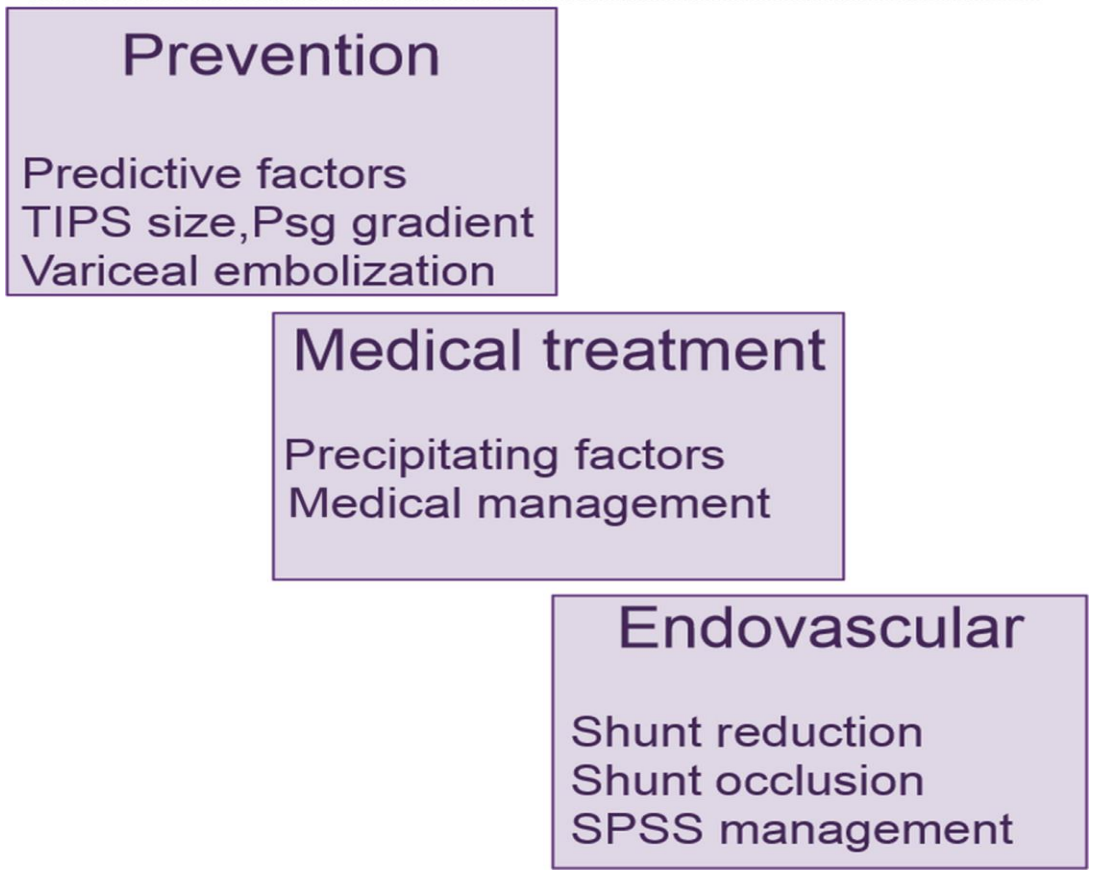
Mechanism of Post-TIPS Hepatic Encephalopathy
First pass hepatic clearance
Increase splanchnic blood flow
Upregulation of intestinal glutaminase

Technical Factors
- Diameter of the TIPS

Host Factors
- poorly treated HE
- Advanced age (>65)
- Sarcopenia
- Liver insufficiency (MELD >22, CP > 10)
- Renal insufficiency
- Hyponatremia
- Hypoalbuminemia
- Presence of shunting

Bai M et al. *J Gastroenterol Hepatol 2011;* Saab S. et al. *Am J Gastroenterol* 2020; Gonzalez JG. AASLD Liver Fellow Network. https://www.aasld.org/liver-fellow-network . Accessed 9/2/23

Management of Post-TIPS Hepatic Encephalopathy

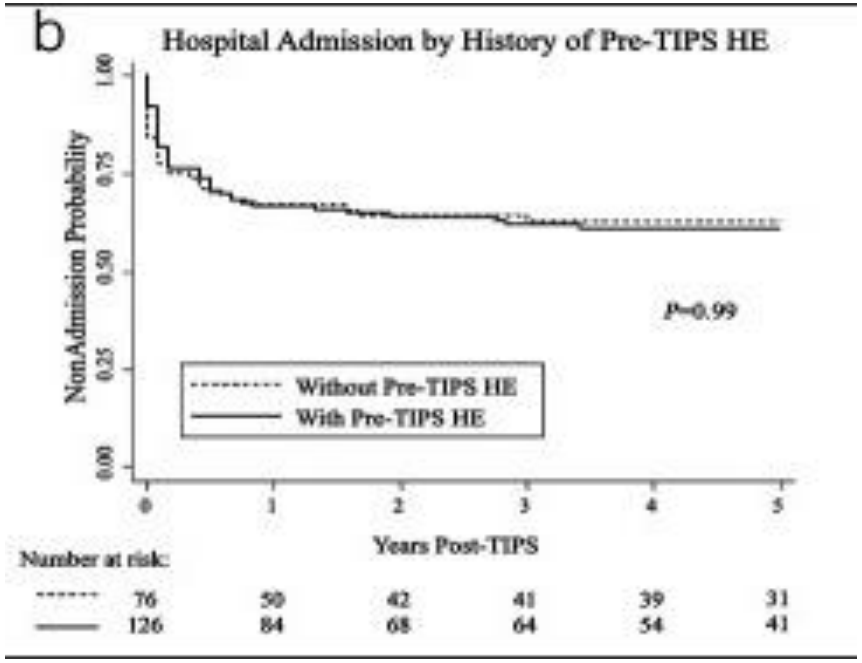


- Lactulose and/or rifaximin used to treat and prevent recurrence of hepatic encephalopathy (HE)
- AASLD and EASL **do not** recommend primary pharmacologic HE prophylaxis with lactulose or rifaximin

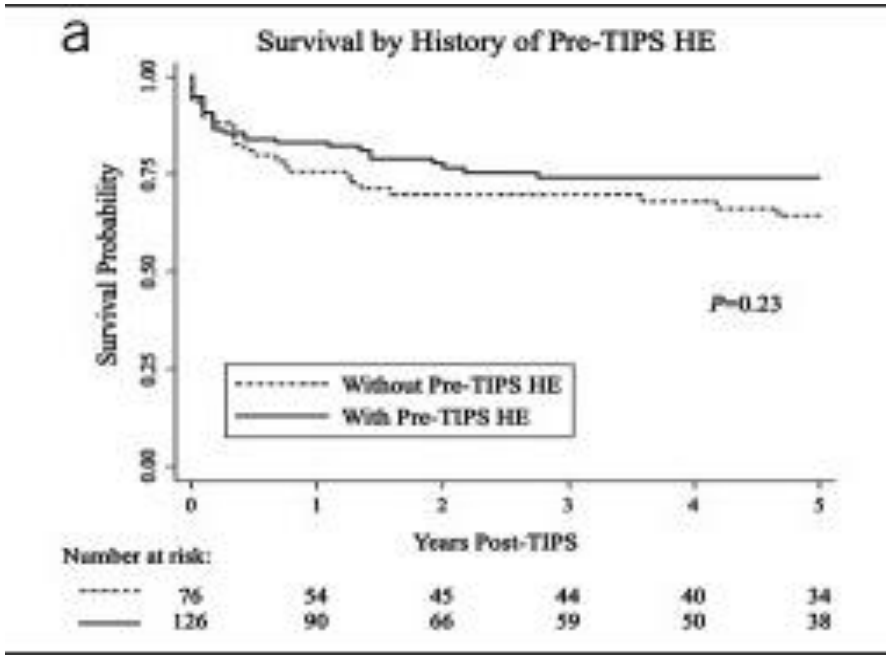
Pereira K C et al. *Liver International* 2015; Vilstrup H et al. *Hepatology*. 2014; EASL *J Hepatol* 2022

Pre-TIPS Hepatic Encephalopathy Not Absolute Contraindication for TIPS

Five-year hospital admission for HE after TIPS placement in patients with and without pre-TIPS HE



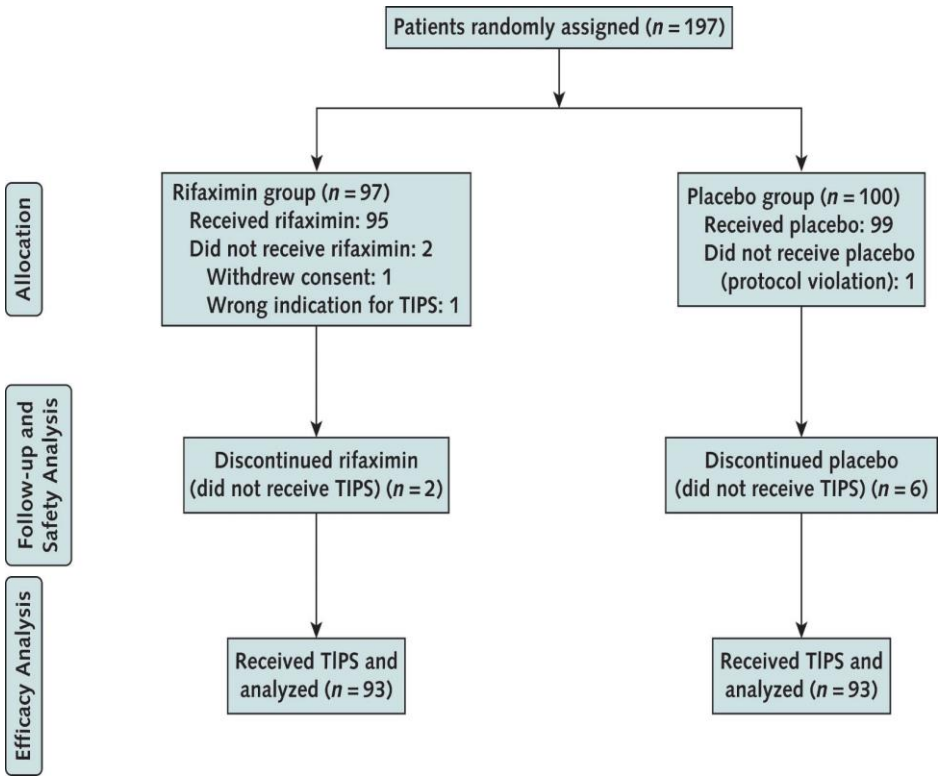
Five-year survival after TIPS placement in patients with and without pre-TIPS HE

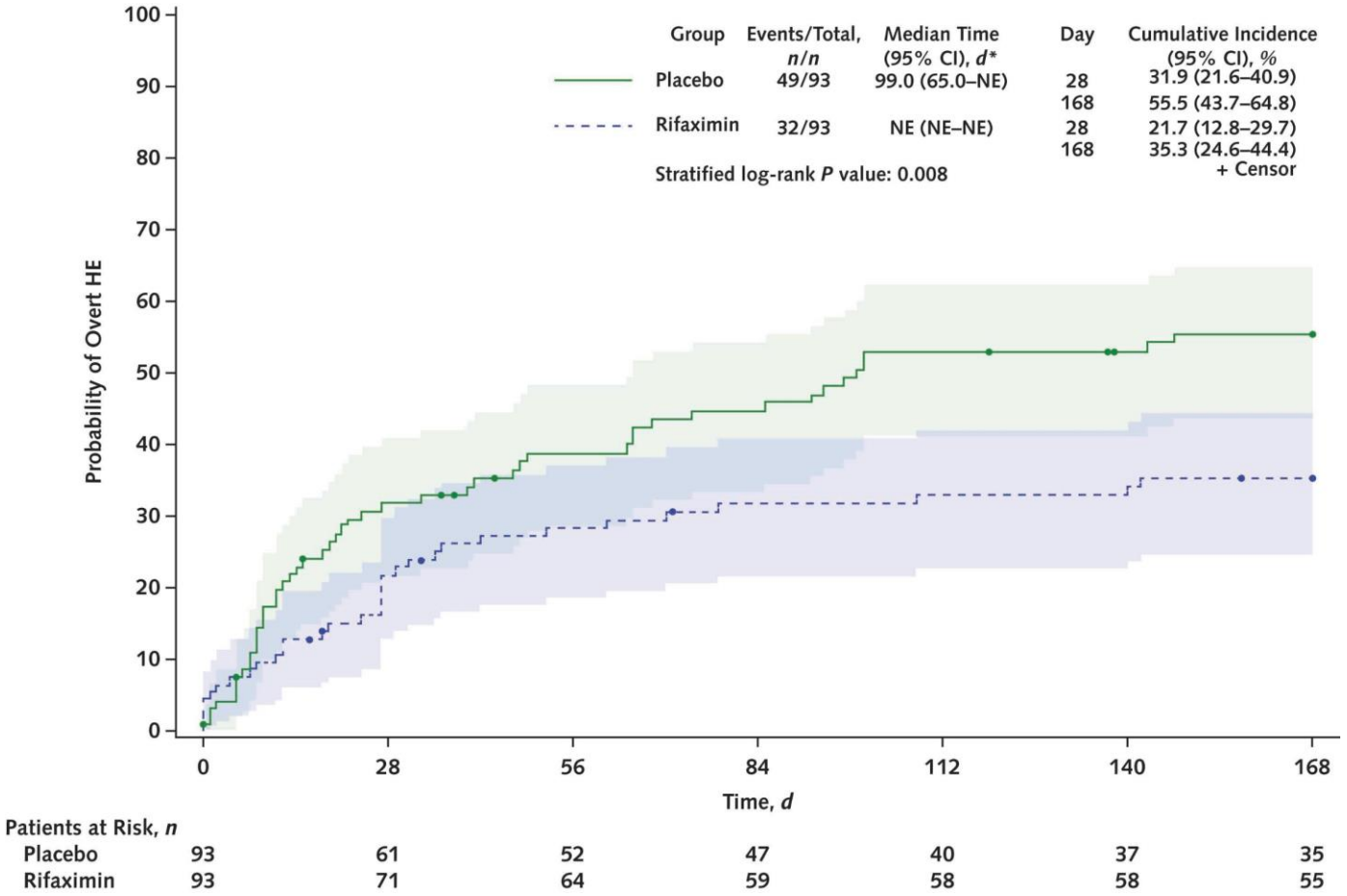


HE, hepatic encephalopathy; ICU, intensive care unit; TIPS, transjugular intrahepatic portosystemic shunt.

Saab S et al. *Clin Transl Gastroenterol* 2021

Pre-TIPS Use of Rifaxamin may Reduce Risk of Post-TIPS Hepatic Encephalopathy





Bureau C et al. *Ann Intern Med* 2021

Conclusions

- Hepatic encephalopathy (HE) is an important complication of cirrhosis, and should not be considered a benign problem
- Early recognition and treatment of HE essential for improved patient related outcomes
- Shunting is an important cause of HE
- Although refractory HE is uncommon, a systematic approach will lead to best outcomes.