MÁSTER EN HEPATOLOGÍA

Encefalopatía hepática: nuevas guías de práctica clínica. Trasplante de microbiota fecal.

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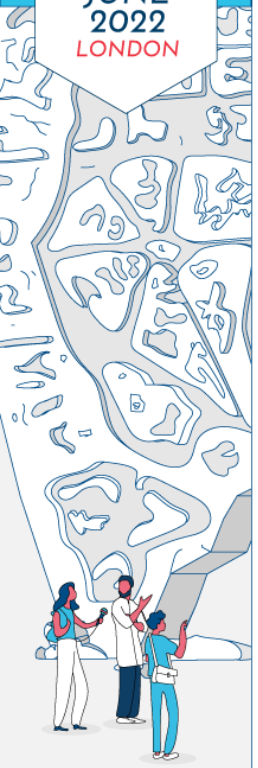

Journal of Hepatology @J... · 1d

🆕 @EASLnews Clinical Practice Guidelines on the management of hepatic encephalopathy, in press ‼️

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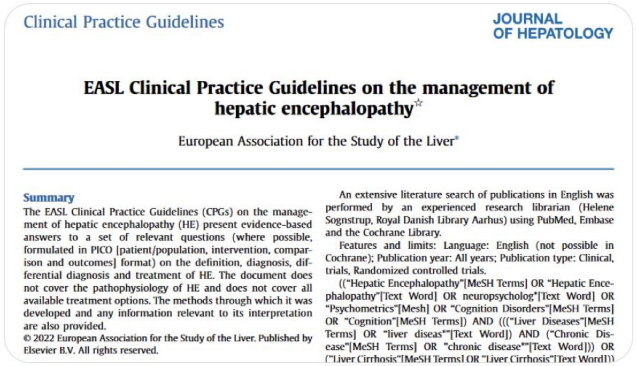

Clinical Practice Guidelines — JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on the management of hepatic encephalopathy☆

European Association for the Study of the Liver*

Summary

The EASL Clinical Practice Guidelines (CPGs) on the management of hepatic encephalopathy (HE) present evidence-based answers to a set of relevant questions (where possible, formulated in PICO [patient/population, intervention, comparison and outcomes] format) on the definition, diagnosis, differential diagnosis and treatment of HE. The document does not cover the pathophysiology of HE and does not cover all available treatment options. The methods through which it was developed and any information relevant to its interpretation are also provided.

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An extensive literature search of publications in English was performed by an experienced research librarian (Helene Sognstrup, Royal Danish Library Aarhus) using PubMed, Embase and the Cochrane Library.

Features and limits: Language: English (not possible in Cochrane); Publication year: All years; Publication type: Clinical, trials, Randomized controlled trials.

(("Hepatic Encephalopathy"[MeSH Terms] OR "Hepatic Encephalopathy"[Text Word] OR neuropsycholog*[Text Word] OR "Psychometrics"[Mesh] OR "Cognition Disorders"[MeSH Terms] OR "Cognition"[MeSH Terms]) AND (("Liver Diseases"[MeSH Terms] OR "liver diseas*"[Text Word]) AND ("Chronic Disease"[MeSH Terms] OR "chronic disease*"[Text Word])) OR ("Liver Cirrhosis"[MeSH Terms] OR "Liver Cirrhosis"[Text Word]))

3 87 166

Thank you to patients, EASL and all hepatologists involved in this exciting project from panelists to Delphi's experts

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☆ Clinical Practice Guideline Panel: Chair: Sara Montagnese; EASL Governing Board representative: Pierre-Emmanuel Rautou; Panel members: Manuel Romero-Gómez, Fin Stolze Larsen, Debbie L. Shawcross, Dominique Thabut, Hendrik Vilstrup, Karin Weissenborn.

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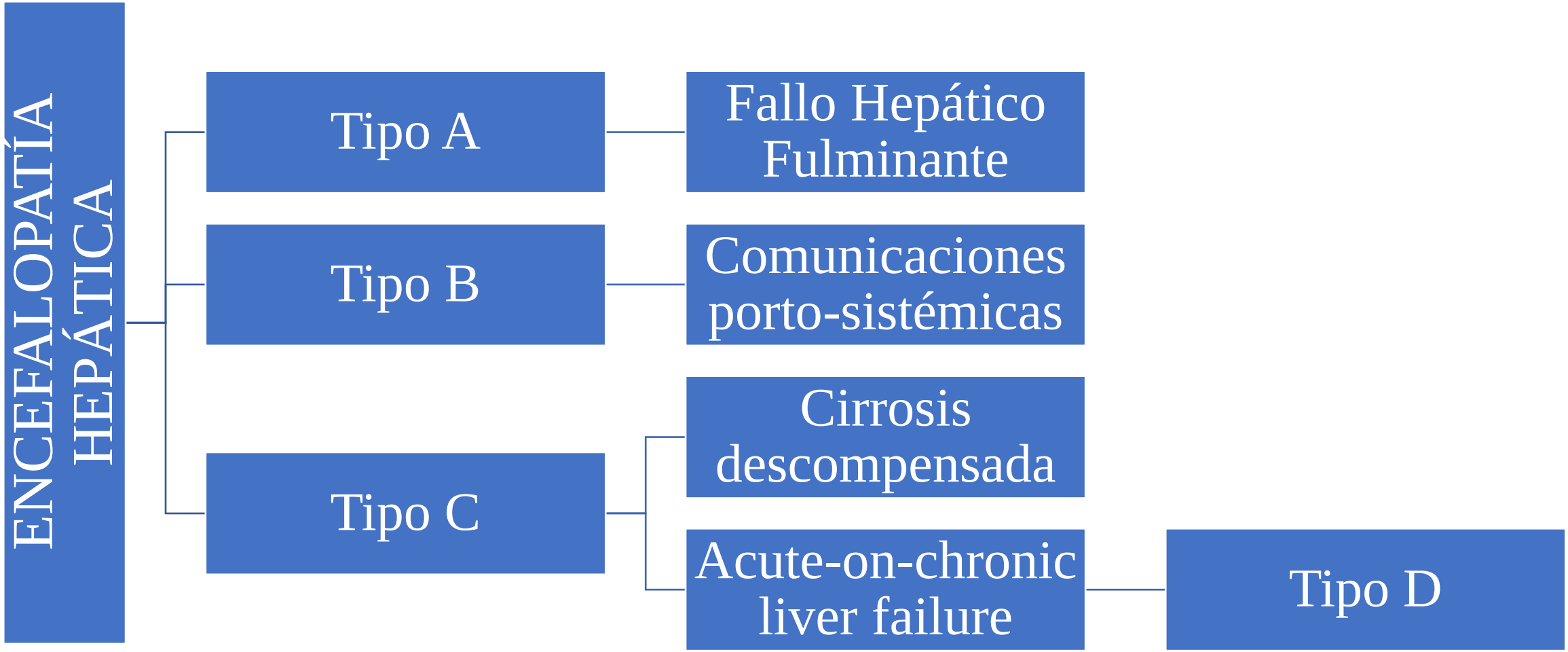
https://doi.org/10.1016/j.jhep.2022.06.001

#1 In patients with HE, can pre-defined classification criteria improve diagnostic accuracy and the effects of treatment?

Recommendation

- HE should be qualified as type A in patients with acute liver failure, type B in those with portosystemic shunt, and type C in those with cirrhosis. Overt HE should be qualified as recurrent if ≥2 bouts occur within 6 months and persistent if the patient does not return to her/his baseline performance between bouts. The severity of mental alterations, any identified precipitants and the presence of portosystemic shunts should also be recorded as these factors impact upon both diagnostic accuracy and treatment **(LoE 5, strong recommendation, 96% consensus).**

Tipos de encefalopatía hepática

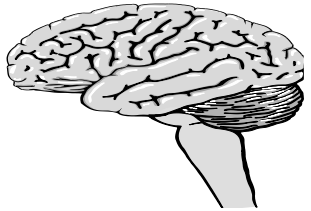


Córdoba et al. J Hepatol 2014

#2 In patients with HE, are the West Haven criteria and Glasgow Coma Scale appropriate for grading?

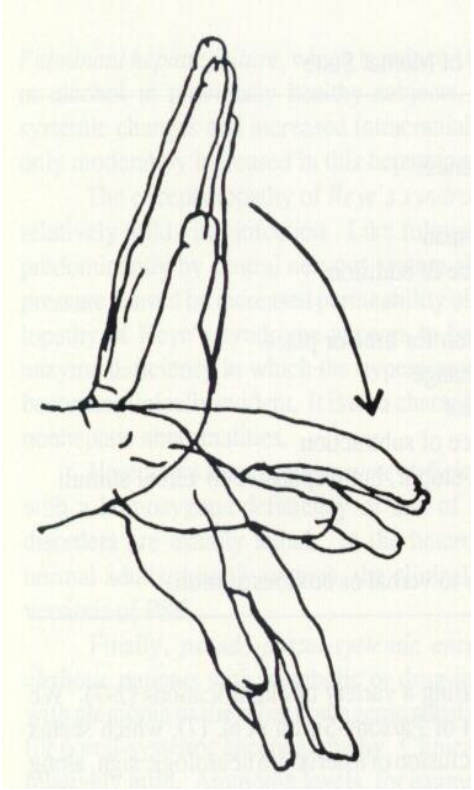
Recommendation

- The West Haven criteria should be used for HE grading when at least temporal disorientation is present (*i.e.* from West Haven grades ≥2). In patients with no or mild neuropsychiatric abnormalities (*i.e.* not meeting the criteria for the diagnosis of HE grades ≥2 based on the West Haven criteria), a neuropsychological/neurophysiological or therapeutic test should be used to diagnose covert HE. In patients with grades III-IV West Haven criteria, the Glasgow coma scale should be added **(LoE 5, strong recommendation, 96% consensus).**



¿Cómo se llama?
¿En que ciudad estamos?
¿Dónde estamos ahora?
¿En que año estamos?
¿En que mes de año estamos?

Extienda las manos, ojos cerrados, separe los dedos



5 aciertos
No flapping

Se descarta Encefalopatía Hepática

≥ 1 fallo o flapping

Encefalopatía Hepática

Valorar

estupor >> somnolencia >> respuesta a estímulos verbales >> confusión >> desorientación grosera >> coma

GLASGOW	COMA SCALE	
Eye opening	Spontaneously	4
	To speech	3
	To pain	2
	none	1
Verbal response	orientated	5
	confused	4
	inappropiate	3
	incomprehensible	2
	none	1
Motor response	Obeys commands	6
	Localises to pain	5
	Withdraw from pain	4
	Flexion to pain	3
	Extension to pain	2
	none	1
SCORE (max)		15

Habilidades motoras finas

Flapping

Desorientación

Coma

#3 How does the term “brain failure” in patients with acute-on-chronic liver failure relate to HE?

- The term “brain failure” was first used in hepatology in 2014 as one of the 6 organ failures defining patients with ACLF.
  - Grade 3/4 Hepatic Encephalopathy
  - Septic Encephalopathy
  - Metabolic Encephalopathy
- It does not exist in standard neurological terminology.
- Acute encephalopathy refers to a pathophysiological process and can translate clinically speaking into sub-delirium, delirium or coma depending on severity.
- The current definition of HE implies that HE is caused by and not only associated with liver failure.
- The terms HE and acute encephalopathy are not interchangeable.
- Acute encephalopathy should be treated according to its underlying cause.


Intensive Care Med (2020) 46:1020–1022
https://doi.org/10.1007/s00134-019-05907-4

WHAT'S NEW IN INTENSIVE CARE

Updated nomenclature of delirium and acute encephalopathy: statement of ten Societies

Arjen J. C. Slooter, Wim M. Otte, John W. Devlin, Rakesh C. Arora, Thomas P. Bleck, Jan Claassen, Matthew S. Duprey, E. Wesley Ely, Peter W. Kaplan, Nicola Latronico, Alessandro Morandi, Karin J. Neufeld, Tarek Sharshar, Alasdair M. J. MacLullich and Robert D. Stevens

Jalan et al. J Hepatol 2014;61:1038-1047
Weiss N et al. J Hepatol 2016;65:1120-1130.
Slooter AJC et al. Intensive Care Med 2020;46:1020-1022

#3 How does the term “brain failure” in patients with acute-on-chronic liver failure relate to HE?

Recommendation

- The term “Brain Failure” should be replaced with the term “acute encephalopathy”, in accordance with international guidelines on delirium. Acute encephalopathy should not be used as a synonym for HE in patients with acute-on-chronic liver failure because while it may be accounted for by HE, there may be alternative or concomitant causes for its development **(LoE 4, strong recommendation, 91% consensus).**

#4 In patients with cirrhosis, do the features and prognosis of HE depend on aetiology of cirrhosis?

The NEW ENGLAND JOURNAL of MEDICINE

Clinical Outcomes in Adults with Nonalcoholic Fatty Liver Disease

MULTICENTER, PROSPECTIVE STUDY

1773 Adults with nonalcoholic fatty liver disease (median follow-up, 4 yr)

	Fibrosis Stage		
	F0 to F2 — No, mild, or moderate fibrosis N=1237	F3 — Bridging fibrosis N=369	F4 — Cirrhosis N=167
Liver-related events		rate per 100 person-yr	
Variceal bleeding	0.00	0.06	0.70
Ascites	0.04	0.52	1.20
Encephalopathy	0.02	0.75	2.39
Hepatocellular carcinoma	0.04	0.34	0.14
Death from any cause	0.32	0.89	1.76

Recommendation

- Patients with HE should not be classified based on the aetiology of their underlying liver disease **(LoE 4, strong recommendation, 93% consensus).**

#5 In patients with suspected HE, can the exclusion or identification of alternative or additional causes of neuropsychiatric impairment improve prognostic accuracy and the results of treatment?

Recommendation

- In patients with suspected HE, alternative or additional causes of neuropsychiatric impairment should be identified to improve prognostic accuracy and the results of treatment **(LoE 4, strong recommendation, 100% consensus).**

#6 Does mild cognitive impairment of an aetiology other than liver dysfunction show features that are different from those of covert HE in patients with cirrhosis?

Considering the features of covert HE – deficits in attention, concentration, visuo-spatial orientation and coordination, motor speed and accuracy, there is an obvious overlap in regard to symptomatology with MCI, but there are also some differences like language and memory are preserved in patients with covert HE while an alteration of motor speed and accuracy is not typical of MCI[32]

Statement

- Features of covert HE and MCI of an aetiology other than liver dysfunction show significant overlap **(LoE 2, 90% consensus).**

Weissenborn K, et al. J Hepatol 2001;34:768-73.

#7 In patients with delirium, is ammonia measurement useful for purposes of diagnosis, differential diagnosis, treatment and prognosis?

Diagnosis

- Blood ammonia levels correlate with the severity of HE.
- Ammonia may remain elevated after clinical HE resolution.
- Plasma ammonia measurement, when measured correctly, should be performed in patients with acute encephalopathy and liver disease and is considered to have a high negative predictive value in relation to a working diagnosis of HE.

Treatment.

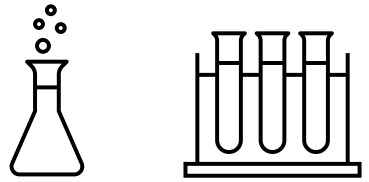
- The role of ammonia measurement in guiding HE treatment and tailoring HE therapy cannot be routinely recommended.

Prognosis.

- Hyperammonemia is associated with raised hospitalizations and decreased transplant-free survival from acute decompensation of cirrhosis [although the prognostic value of ammonia in cirrhosis patients with acute encephalopathy remains unclear].
- Patients with recurrent HE, level of ammonia after recovery was predictive of the onset of new episodes of HE.
- In ACLF suggested a prognostic role of ammonia in patients with overt HE.

Nicolao F et al. J Hepatol 2003;38:441-6; Shalimar et al. Hepatology 2019;70:982-994; Poo et al. Ann Hepatol 2006;5:281-8; Rahimi RS et al. Clin Gastroenterol Hepatol 2021;19:2626-2635.e7; Gundling F et al. Ann Hepatol 2013;12:108-14; Vierling et al. Clin Gastroenterol Hepatol 2016;14:903-906.e1; Haj M et al. Am J Gastroenterol 2020;115:723-728.

Amoniemia



Encefalopatía Hepática en la Enfermedad Hepática Crónica: Guías de Práctica clínica 2014 de la Asociación Americana para el Estudio de las Enfermedades Hepáticas y la Asociación Europea para el Estudio del Hígado.

American Association for the Study of Liver Diseases*,†
European Association for the Study of the Liver*,†

El aumento de amoniaco en sangre por sí solo no supone ningún diagnóstico, estadificación, o valor pronóstico en la EH en pacientes con EHC. Un valor normal requiere reevaluación diagnóstica (**GRADE II-3, A, 1**)

Hepatic encephalopathy: Novel insights into classification, pathophysiology and therapy 2020

Christopher F. Rose[1,*], Piero Amodio[2], Jasmohan S. Bajaj[3], Radha Krishan Dhiman[4], Sara Montagnese[2], Simon D. Taylor-Robinson[5], Hendrik Vilstrup[6], Rajiv Jalan[7,8,*]

EN RESUMEN:

- ✓ Si amonio normal > descartar otras causas de encefalopatía.
- ✓ Confirma la sospecha de encefalopatía hepática: Si amonio alterado desciende paralelo a la mejora clínica.

Amoniemia normal
VPN 0,81

Amoniemia >80 mcmol/L
↓supervivencia tras descompensación aguda, independientemente de la gravedad de la EH

Amoniemia con respuesta al tratamiento
Buenos resultados

#7 In patients with delirium, is ammonia measurement useful for purposes of diagnosis, differential diagnosis, treatment and prognosis?

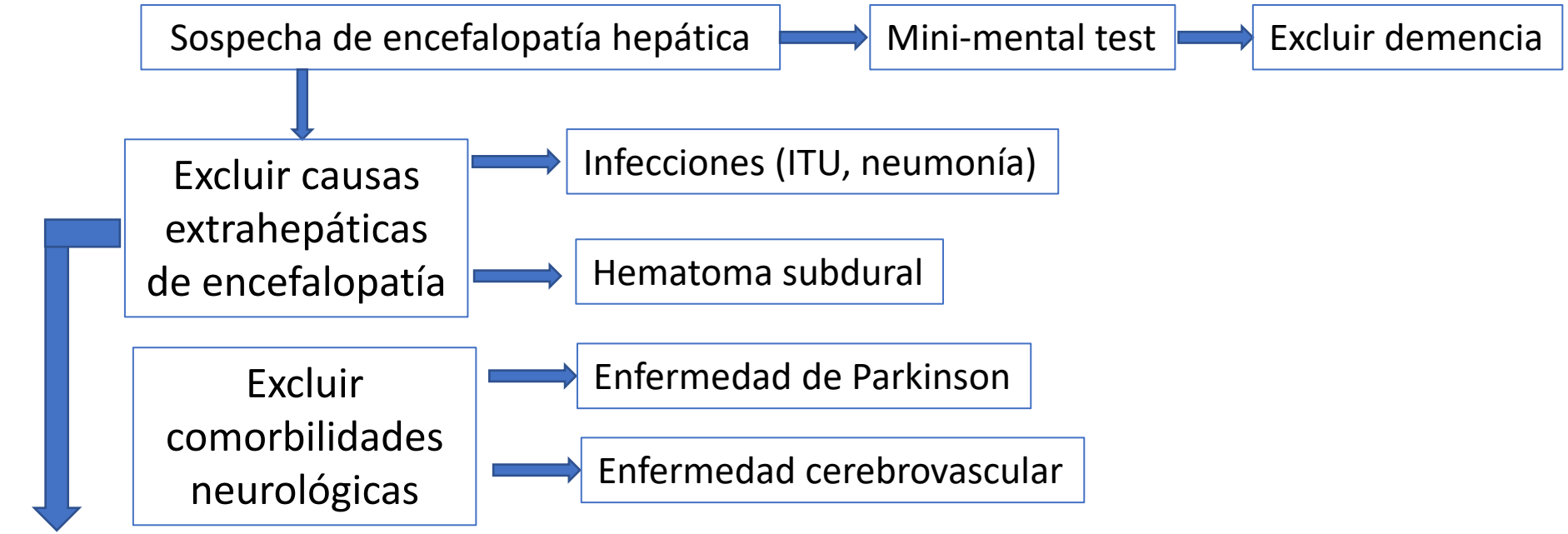
Recommendation

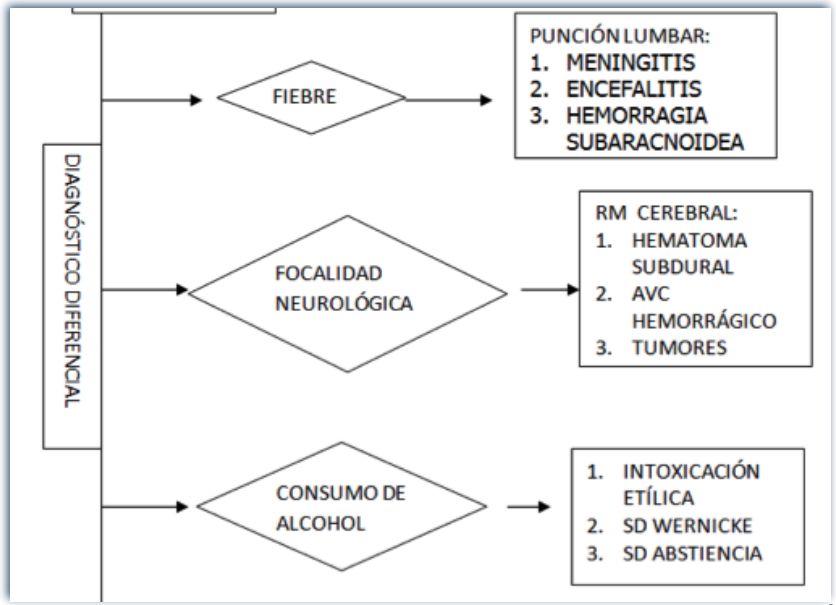
- In patients with delirium/encephalopathy and liver disease, plasma ammonia measurement should be performed, as a normal value brings the diagnosis of HE into question **(LoE 4, strong recommendation, 95% consensus).**

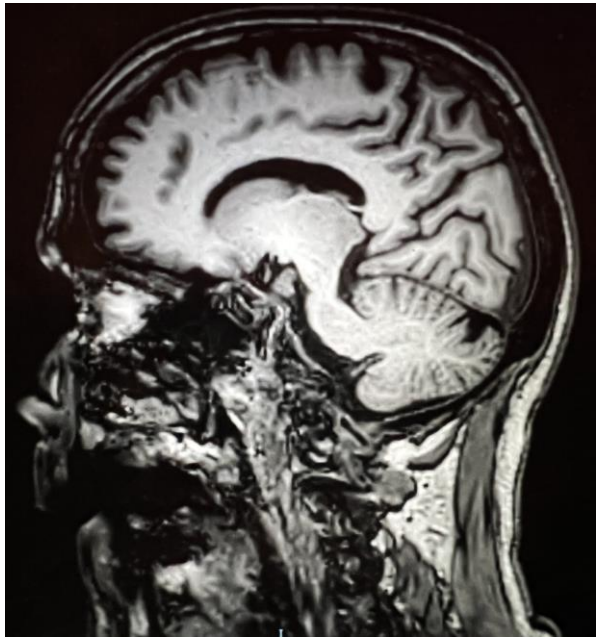
#8 Should patients with cirrhosis and delirium undergo cerebral imaging for purposes of diagnosis, differential diagnosis and treatment?

Recommendation

- In patients with delirium/encephalopathy and liver disease, brain imaging by CT scan or MRI should be performed in case of diagnostic doubts or non-response to treatment **(LoE 5, strong recommendation, 96% consensus).**







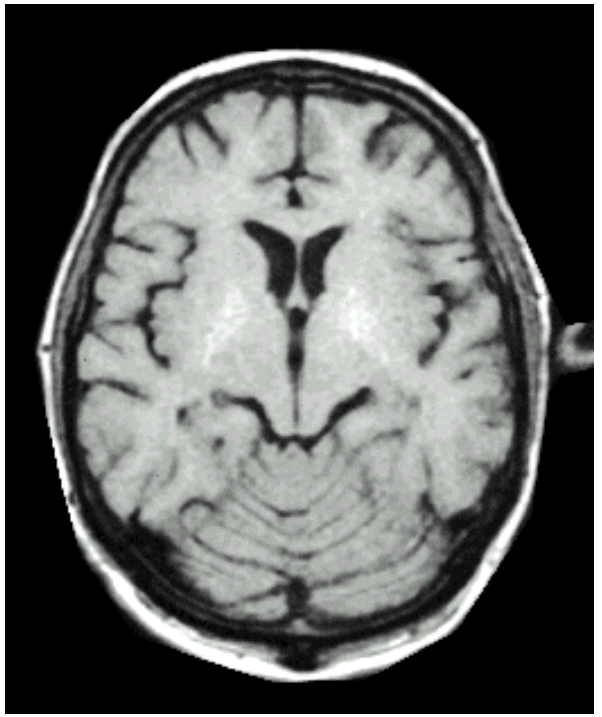


Imagen hiperintensa en T1:

- Prevalence: 52-100%
- Related to liver dysfunction and porto-systemic shunts.
- Manganese deposits
- Parkinson's signs.

Akhtar AJ, Alamy ME, Yoshikawa TT. Extrahepatic conditions and hepatic encephalopathy in elderly patients. Am J Med Sci. 2002;324(1):1-4

#9 In patients with cirrhosis, do any brain imaging methods provide results proving HE?

Statement

- No cerebral imaging proves a diagnosis of HE **(LoE 4, 96% consensus).**

Resonancia magnética en el diagnóstico diferencial

N=1481 pacientes en 31 estudios

RM espectroscópica: aumento de glutamine/glutamato y descenso de mioinositol y colina.

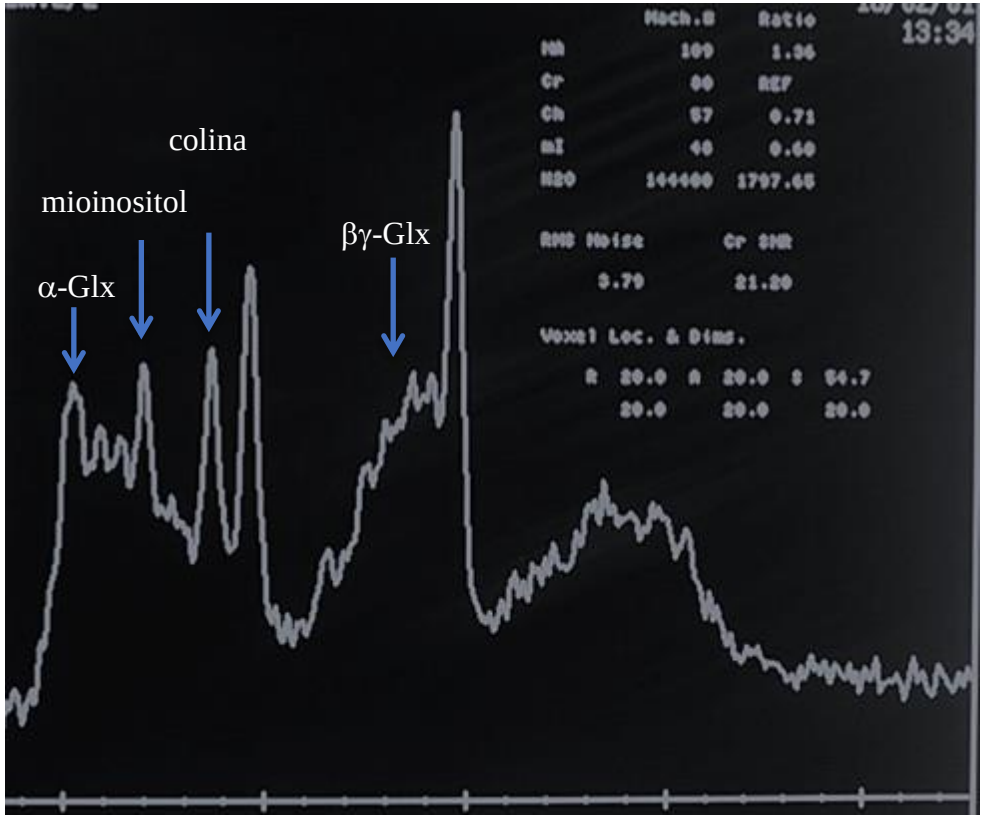


Table 3 Minimal hepatic encephalopathy vs cirrhosis with no hepatic encephalopathy by metabolite and brain region

Metabolite	Region	No. studies	No. patients	SMD	95% CI	*p* Value	I^2 (*p* Value)	Publication bias (*p* value)
Glx	Parietal	8	336	+0.82	+0.49 to +1.15	<0.0001	37.45% ($p = 0.12$)	0.69
	Occipital	6	298	+1.32	−0.95 to +3.59	0.25	98.21% ($p < 0.0001$)	0.0002
	Basal ganglia	7	220	+0.62	+0.10 to +1.14	0.02	65.14% ($p = 0.002$)	0.20
mI	Parietal	9	369	−0.77	−1.19 to −0.34	0.0004	67.48% ($p = 0.004$)	0.25
	Occipital	7	340	−1.02	−2.33 to +0.29	0.13	95.90% ($p < 0.0001$)	0.001
	Basal ganglia	7	241	+0.74	−1.52 to +3.01	0.52	98.27% ($p < 0.0001$)	0.0002
Cho	Parietal	9	372	−0.36	−0.61 to −0.10	0.007	20.00% ($p = 0.20$)	0.70
	Occipital	7	330	−0.04	−0.61 to +0.53	0.89	78.89% ($p = 0.0004$)	0.91
	Basal ganglia	7	197	−0.30	−0.84 to +0.23	0.27	65.36% ($p = 0.01$)	0.71

Abbreviations: Cho = choline-containing compounds; CI = confidence interval; Glx = glutamate + glutamine; MI = myo-inositol; SMD = standard mean difference.

Table 2 Comparing cirrhosis with no hepatic encephalopathy (NHE), minimal hepatic encephalopathy (MHE), and overt hepatic encephalopathy (OHE) results against controls by metabolite and region

		NHE vs control			MHE vs control			OHE vs control		
Metabolite	Region	SMD	95% CI	*p* Value	SMD	95% CI	*p* Value	SMD	95% CI	*p* Value
Glx	Parietal	+0.53	+0.11 to +0.96	0.01	+1.28	+0.78 to +1.77	<0.0001	+1.89	+1.12 to +2.65	<0.0001
	Occipital	+0.61	−0.27 to +1.48	0.18	+0.95	+0.46 to +1.43	0.0001	+2.11	+1.32 to +2.91	<0.0001
	Basal ganglia	+0.65	+0.18 to +1.12	0.007	+1.32	+0.87 to +1.77	<0.0001	+1.41	+0.81 to +2.01	<0.0001
mI	Parietal	−1.26	−1.72 to −0.79	<0.0001	−2.55	−3.37 to −1.72	<0.0001	−2.92	−4.48 to −1.36	0.0002
	Occipital	−1.36	−1.94 to −0.79	<0.0001	−1.54	−1.98 to −1.10	<0.0001	−4.11	−5.98 to −2.23	<0.0001
	Basal ganglia	−1.23	−1.79 to −0.69	<0.0001	−0.41	−2.65 to +1.83	0.72	−1.73	−2.59 to −0.87	<0.0001
Cho	Parietal	−0.62	−1.05 to −0.20	0.004	−0.84	−1.22 to −0.46	<0.0001	−0.97	−1.72 to −0.22	0.01
	Occipital	−0.46	−0.88 to −0.03	0.04	−0.66	−1.09 to −0.23	0.002	−1.10	−2.07 to −0.13	0.03
	Basal ganglia	−1.26	−2.11 to −0.40	0.004	−1.15	−2.02 to −0.28	0.009	−1.46	−1.81 to −1.11	<0.0001

Abbreviations: Glx = glutamine and glutamate; Cho = choline-containing compounds; CI = confidence interval; mI = myo-inositol; SMD = standard mean difference.

Los cambios en la RMS en los picos de glutamina/glutamato, mioinositol y colina medidos en el lóbulo parietal, correlacionan con la gravedad de la encefalopatía hepática.

Zeng G et al. Neurology 2020;94:e1147

#10. In patients with cirrhosis, should covert HE be screened for in the clinic and/or ward, and how?

Should it be screened?

The diagnosis of covert HE is relevant because the condition occurs in 30-70% of patients with cirrhosis.

Is associated with:

- poor quality of life,
- reduced socio-economic potential,
- increased risk for developing overt HE over time
- impact on cirrhosis progression
- Influence on overall survival

In patients without previous overt HE episodes, covert HE may predict overt HE, while in those with previous overt HE episodes, subsequent overt HE episodes depend more on the severity of liver dysfunction and/or portosystemic shunting.

A genetic risk score combining previous bouts of overt HE, genetic profile and liver dysfunction allowed to calculate risk of HE in the follow-up.

How to screen covert HE?

- The diagnosis is often better based on more than one test, to be chosen depending on available local norms/expertise.
- However, there is no gold standard, and very little data on how to combine and interpret different tests and their outcomes.
- Concordance between tests is low because exploring different pathways.
- Tests can be neuropsychological (paper&pencil or computerized) or neurophysiological.
- Neuropsychological tests are prone to learning effects and affected by both age and educational attainment, thus the availability of pertinent local normality tables is crucial.
- The neuropsychological Animal Naming Test (ANT, i.e. the number of animals listed in 60 seconds, no equipment required) has recently been shown to compare favourably with more established minimal/covert HE measures, and to predict overt HE.

Weissenborn et al. J Hepatol 2001;34:768-73; Gil-Gómez A et al. Am J Gastroenterol 2021;116:1238-1247; Hartmann IJ et al. Am J Gastroenterol 2000;95:2029-34; Schomerus H et al. Metab Brain Dis 2001;16:37-41; Marchesini G et al. Gastroenterology 2001;120:170-8; Bajaj JS et al. Aliment Pharmacol Ther 2011;33:739-47; Romero-Gómez M et al. Am J Gastroenterol 2001;96:2718-23; Patidar KR et al. Am J Gastroenterol 2014;109:1757-63; Flud CR et al. J Clin Exp Hepatol 2019;9:112-116; Kircheis G et al. Gastroenterology 2009;137:1706-15.e1-9; Ampuero et al. J Gastroenterol Hepatol 2018;33:718-725; Ampuero et al. Gastroenterology 2015;149:1483-9; Formentin et al. Liver Int 2021;41:1070-1082; Bajaj JS et al. Clin Gastroenterol Hepatol 2013;11:1511-6; Montagnese et al. Dig Liver Dis 2019;51:190-205; Campagna et al. Hepatology 2017;66:198-208.

#10. In patients with cirrhosis, should covert HE be screened for in the clinic and/or ward, and how?

Recommendation

- In patients with cirrhosis and no history of overt HE, screening for covert HE should be performed with tests for which experience/tools and local norms are available. As the only bedside test available to date, the Animal Naming Test is worthy of further study and validation **(LoE 4, strong recommendation, 83% consensus).**

#11. In patients with cirrhosis, does screening for covert HE allows treatment initiation and overt HE prevention?

- Covert HE is a strong risk factor for overt HE and responds well to anti-HE interventions.
- It is therefore expected, but not yet proven by RCT, that treatment will result in a reduction of overt HE episodes, which would add to the arguments for screening.
- The pathophysiology of any degree of HE is believed to be the same; covert HE is a risk factor for overt HE and, by and large, there is a progression in neuropsychological and neurophysiological abnormalities when moving to overt HE.
- The difference between clinically detectable minor cognitive abnormalities (grade I) and abnormalities that require tests to detect (minimal) is often difficult to establish.
- This may speak in favour of considering both conditions as one entity (covert HE), also for purposes of treatment initiation.
- There is evidence of beneficial effects of anti-HE strategies on neuropsychological and neurophysiological performance in several studies and a some network metanalyses. However, there are no robust data to confirm that treatment of covert HE also results in a reduction of overt HE risk.
- In a situation where covert HE is suspected, treatment with non-absorbable disaccharides (and/or rifaximin) could be initiated and, if beneficial, also used as confirmation of the diagnosis (*ex juvantibus*).

Mittal et al. Eur J Gastroenterol Hepatol 2011;23:725-32; Egberts et al. Gastroenterology 1985;88:887-95; Morgan et al. J Hepatol 1989;8:208-17; Malaguarnera et al. Dig Dis Sci 2008;53:3018-25; Malaguarnera et al. Dig Dis Sci 2007;52:3259-65;Pratap Mouli V et al. Hepatol Res 2015;45:880-9; Sidhu et al. Liver Int 2016;36:378-85; Li et al. Medicine (United States) 2018;97(17); Xia et al. J Int Med Res 2018;46:3596-604; Goh et al. Cochrane Database Syst Rev. 2018;5(5):Cd012410; Dhiman et al. Clin Gastroenterol Hepatol. 2020 Apr;18(4):800-812.e25; Gluud et al. Cochrane Database Syst Rev. 2016;2016(5):Cd003044; Zacharias et al. Cochrane Database Syst Rev. 2019;6(6):Cd012334.

#11. In patients with cirrhosis, does screening for covert HE allows treatment initiation and overt HE prevention?

Recommendation

- Patients with covert HE should be treated with non-absorbable disaccharides **(LoE 3, strong recommendation, 92% consensus).**

#12 In patients with liver failure and HE, are liver-support systems of proven benefit for HE?

Statement

- In patients with liver failure and overt HE, albumin dialysis ameliorates HE and can be considered. The impact on prognosis is, however, uncertain and further study is warranted **(LoE 2, 77% consensus).**

#13 In patients with overt HE, does the prevention of further decompensation/worsening of the underlying liver disease improve prognosis?

Recommendation

- In patients with HE, all measures to control progression of the underlying liver disease should be undertaken **(LoE 4, strong recommendation, 100% consensus).**

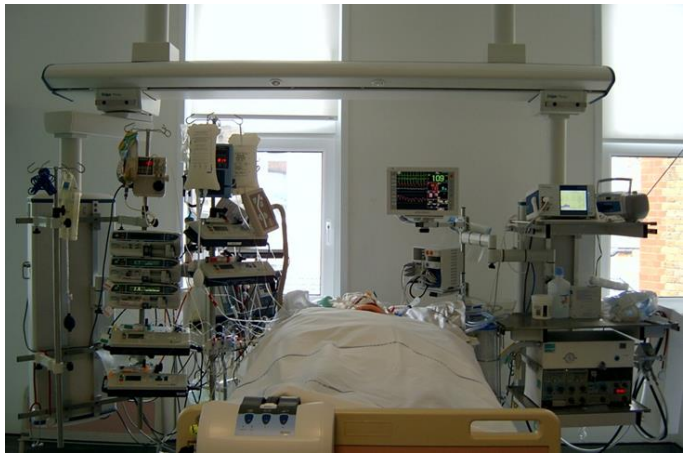
#14 In patients with overt HE, do the identification, prevention, and management of precipitating events, if any, improve treatment outcomes and prognosis?

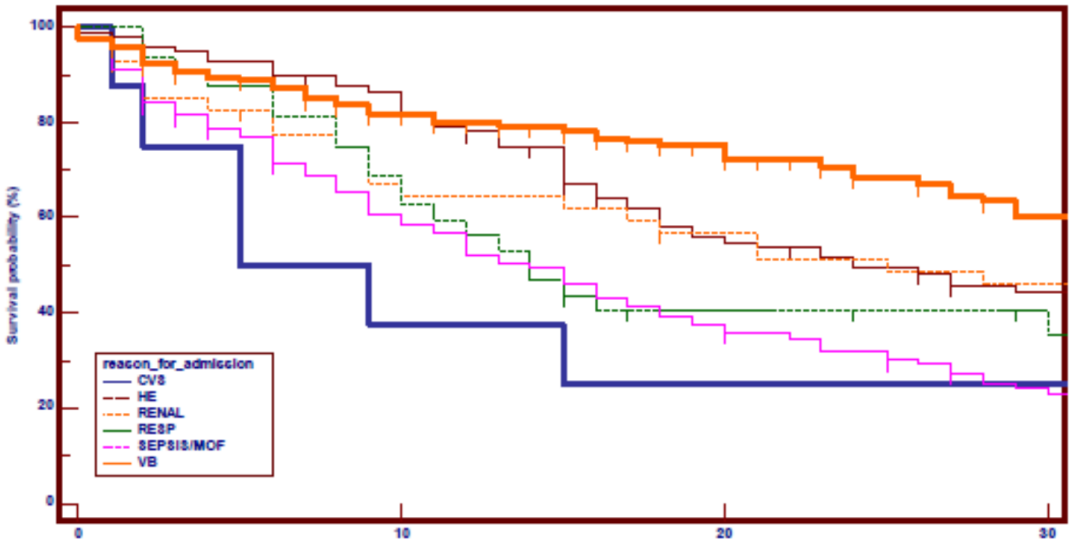
Recommendation

- In patients with HE, precipitating factors should be sought and managed **(LoE 2, strong recommendation, 100% consensus).**

#15 In patients with overt HE, which criteria should be used to guide admission to an intensive care unit (ICU) to improve outcome?

- In patients with HE grade 3-4 and a Glasgow Coma Score <7, respiratory function is endangered as the patient is unable to protect their airway. In such cases management in the ICU is recommended.
- Relatively old studies showed a reluctance towards admitting such patients to the ICU.
- However, several prognostic scores *i.e* MELD, APACHE II (Acute Physiology & Chronic Health Evaluation) and the CLIF-C organ failure are now available and can help identify patients with an unacceptably high predicted mortality, in whom ICU care may not be warranted due to futility.





Wehler M, Kokoska J, Reulbach U, Hahn EG, Strauss R. Short-term prognosis in critically ill patients with cirrhosis assessed by prognostic scoring systems. Hepatology 2001;34:255–261.

Shellman RG, Fulkerson WJ, DeLong E, Piantadosi CA. Prognosis of patients with cirrhosis and chronic liver disease admitted to the medical intensive care unit. Crit Care Med 1988;16:671–678.

Shawcross D et al. J Hepatol. 2012 May;56(5):1054-62

Paciente con encefalopatía hepática crónica recurrente

1. Comprobar diagnóstico de certeza
2. Comprobar adherencia al tratamiento
3. Comprobar respuesta terapéutica (amonio)
4. Descartar comunicaciones porto-sistémica
5. Reevaluar función hepática (MELD).

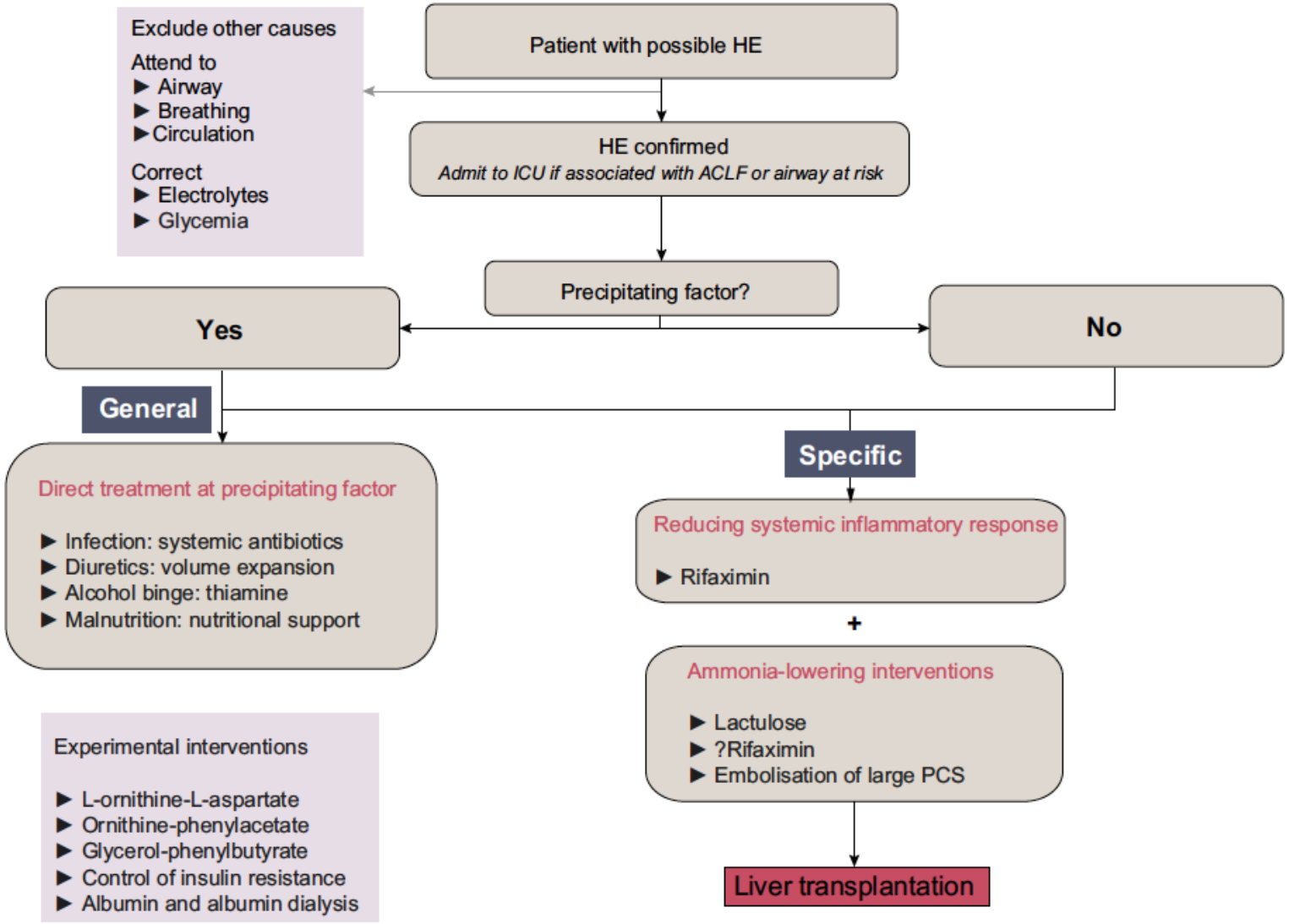


Fig. 4. An algorithm for the management of hepatic encephalopathy in a hospitalized cirrhotic patient.

Romero-Gómez et al. J Hepatol 2015

#29 In patients with cirrhosis and covert HE, is it useful to institute treatment for the purposes of differential diagnosis and to reduce the likelihood of developing overt HE?

Recommendation

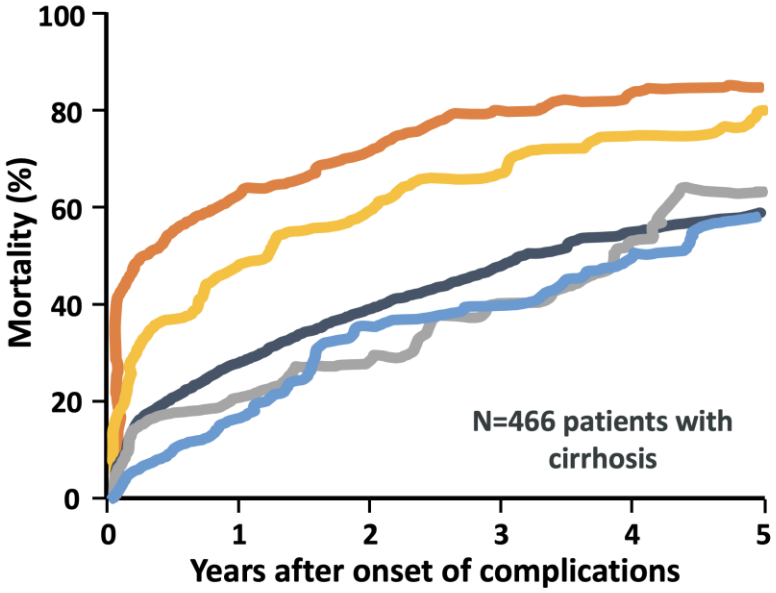
- In patients with covert HE, anti-HE treatment should be considered for the purposes of differential diagnosis and to prevent overt HE **(LoE 5, strong recommendation, 89% consensus).**

#15 In patients with overt HE, which criteria should be used to guide admission to an intensive care unit (ICU) to improve outcome?

Recommendation

- Patients with overt HE grade 3 and 4 are at risk of aspiration and should be treated in the ICU. No single marker can identify patients who will benefit from ICU admission, and referral relies on clinical judgement **(LoE 4, strong recommendation, 96% consensus).**

#16 In patients with overt HE, which criteria should be used to guide referral to a liver transplantation centre?



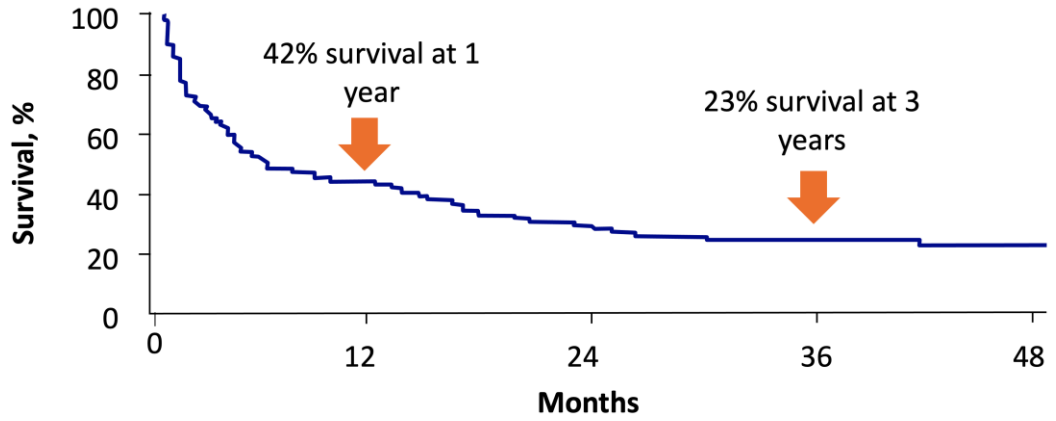
Complication of cirrhosis:

- Hepatic encephalopathy
- Ascites + variceal bleeding
- Ascites alone
- Variceal bleeding alone
- No complications

One-year mortality was 17% among patients with no initial complications and 64% following HE

Recommendation

- Patients with recurrent or persistent HE should be considered for liver transplantation and a first episode of overt HE should prompt referral to a transplant centre for evaluation **(LoE 5, strong recommendation, 85% consensus).**



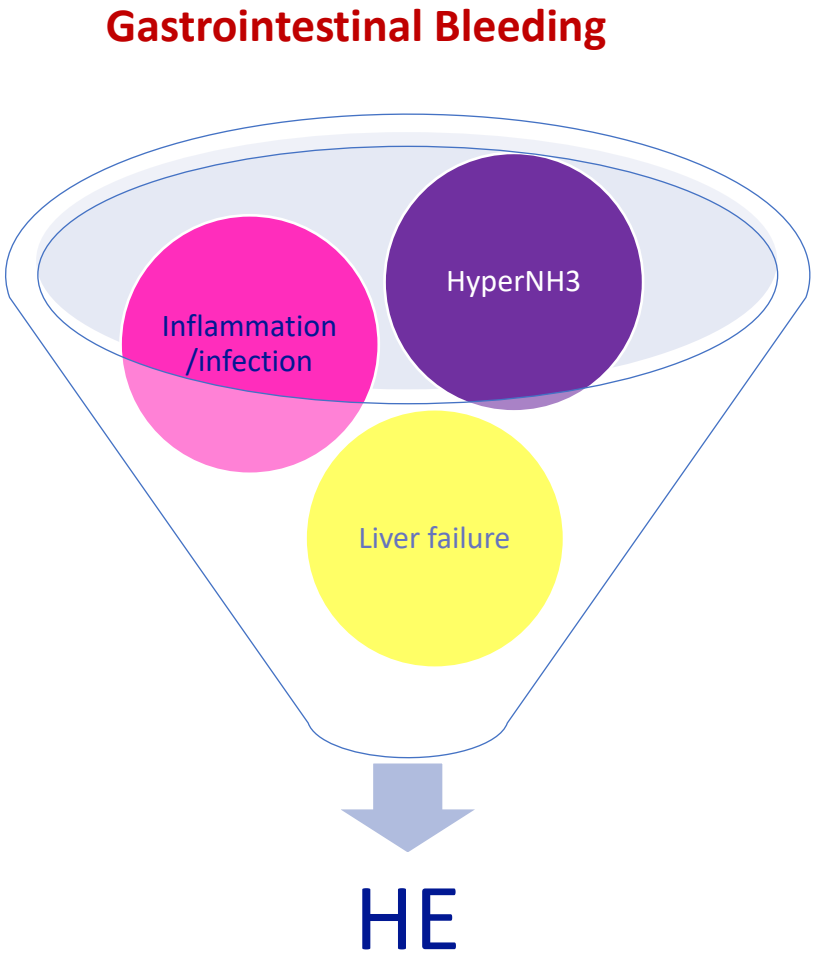
Bustamante et al. J Hepatol. 1999;30:890-895; Jepsen P, et al. Hepatology 2010 51:1675–82; Artru F, et al. J Hepatol 2017; 67: 708-15; Sundaram V, et al. Gastroenterology 2019; 156: 1381-1391; Thuluvath PJ, et al. J Hepatol 2018; 69: 1047-56.

#17 In patients who have had a first episode of overt HE, should secondary prophylaxis be initiated to prevent further episodes?

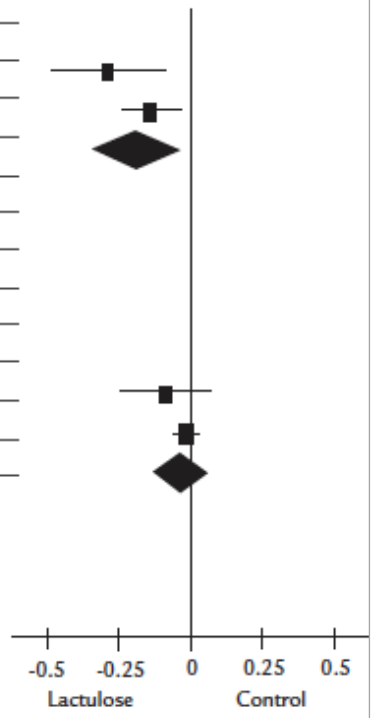
Recommendations

- Lactulose is recommended as secondary prophylaxis following a first episode of overt HE, and should be titrated to obtain 2-3 bowel movements per day **(LoE 1, strong recommendation, 96% consensus).**
- Rifaximin as an adjunct to lactulose is recommended as secondary prophylaxis following ≥1 additional episodes of overt HE within 6 months of the first one **(LoE 2, strong recommendation, 92% consensus).**

#18: Should prophylaxis of HE be used in an acute bleeding episode in patients with cirrhosis?



Study	Lactulose		Control			Difference in risk	Difference in risk
	n	Total	n	Total	Weight	M-H, Random, 95CI	M-H, Random, 95CI
Incidence of hepatic encephalopathy							
Sharma P, 2001	5	35	15	35	20.1%	-0.29 [-0.49, -0.08]	
Wen J, 2013	2	65	11	65	26.9%	-0.14 [-0.24, -0.04]	
Total (95CI)		**100**		**100**	**47.1%**	**-0.19 [-0.33, -0.04]**	
Total of events	**7**		**26**				
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 1.89$; $df = 1$ ($p = 0.17$); $I^2 = 47\%$							
Overall effect test: $Z = 2.53$ ($p = 0.01$)							
Mortality							
Sharma P, 2001	3	35	6	35	23.3%	-0.09 [-0.24, 0.07]	
Wen J, 2013	0	65	1	65	29.7%	-0.02 [-0.06, 0.03]	
Total (95CI)		**100**		**100**	**52.9%**	**-0.03 [-0.12, 0.06]**	
Total of events	**3**		**7**				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.68$; $df = 1$ ($p = 0.20$); $I^2 = 40\%$							
Overall effect test: $Z = 0.71$ ($p = 0.48$)							



Factors associated with HE (MV)

- Child-Pugh, Lactulose Tx

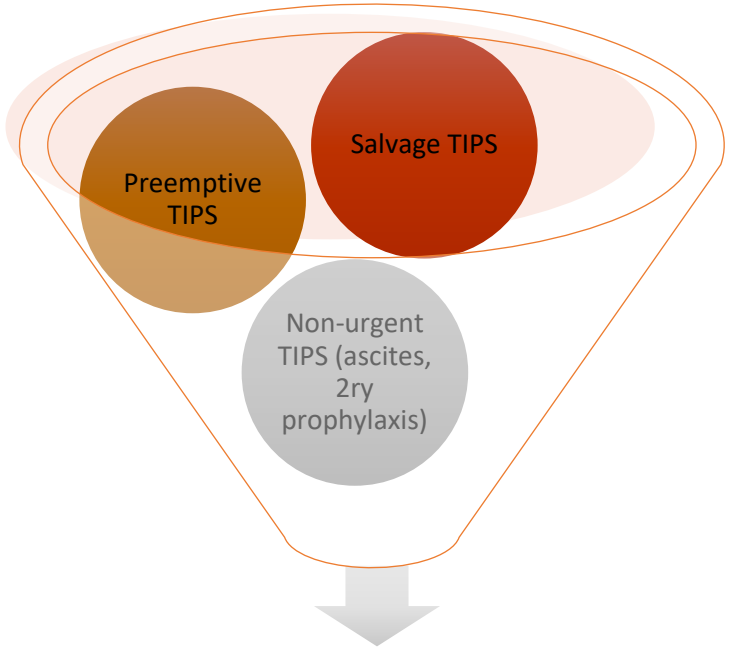
Bessman AN et al., Gastroenterology 1963; Sharma P et al., JGH 2011; Wen J et al., Digestion 2013; Aires FT et al., Rev Ass Med Bras 2016

#18: Should prophylaxis of HE be used in an acute bleeding episode in patients with cirrhosis?

Recommendation

- In patients presenting with gastrointestinal bleeding, rapid removal of blood from the gastrointestinal tract (lactulose or mannitol by naso-gastric tube or lactulose enemas) can be used to prevent HE **(LoE 1, strong recommendation, 85% consensus).**

#19: Should prophylaxis of HE be used before TIPS placement procedure in patients with cirrhosis?

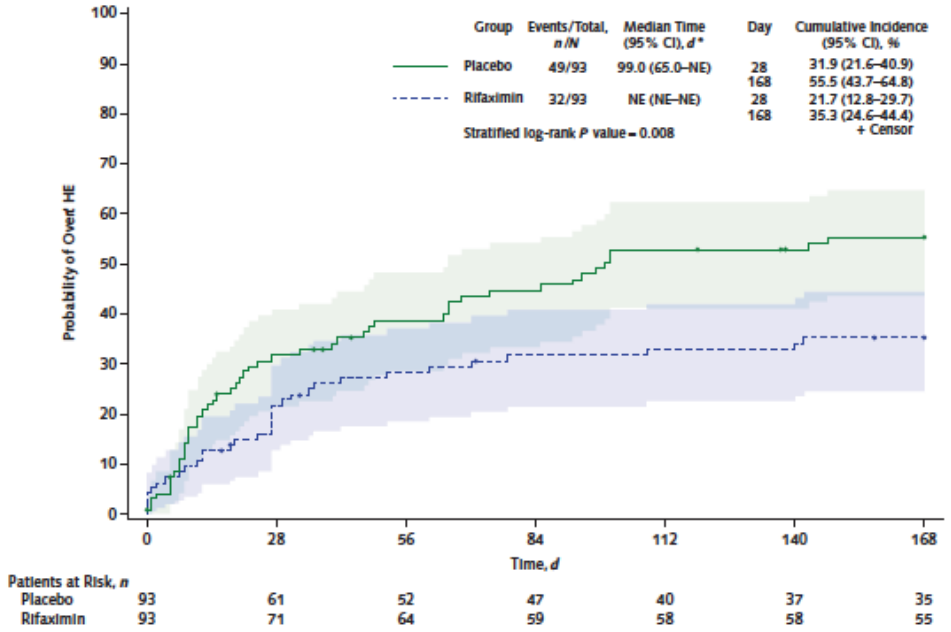


HE: 35-50% (mortality doubled)

- Reduction of TIPS diameter ?
- HE prophylaxis

Riggio O et al., Dig Dig Sc 1996; Zuo L et al., JVIR 2019
Riggio O et al., J Hepatol 2010; Wang Q et al., J Hepatol 2017;
Schepis F et al., CGH 2018

- RCT: 186 pts randomized
- RFX vs placebo
- PE: Occurrence of HE



Riggio O et al., J Hepatol 2005; Bureau C et al., Gastroenterology 2019

#19: Should prophylaxis of HE be used before TIPS placement procedure in patients with cirrhosis?

Recommendation

- In patients with cirrhosis and previous episodes of overt HE, rifaximin can be considered for prophylaxis of HE prior to non-urgent TIPS placement. Non-absorbable disaccharides, as a stand-alone or in combination, are worthy of further study in this context **(LoE 2, strong recommendation, 82% consensus).**

#20 When should prophylactic therapy for HE be discontinued in patients with cirrhosis?

Recommendation

- In patients with a history of overt HE with improvement of liver function and nutritional status and in whom precipitant factors have been controlled, discontinuation of anti-HE therapy should be considered on an individual basis **(LoE 5, weak recommendation, 77% consensus).**

#21 In patients with HE, is zinc supplementation a treatment option to improve mental status?

Recommendation

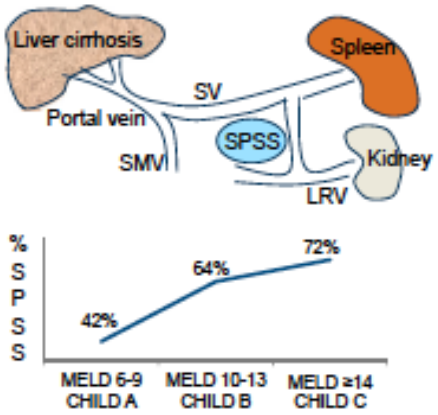
- In patients with HE, routine zinc supplementation is not recommended **(LoE 2, strong recommendation, 95% consensus).**

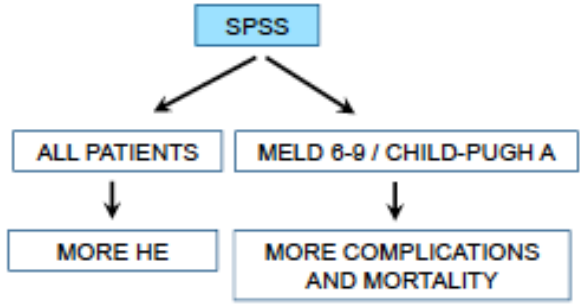
#22 In patients with HE is vitamin/micronutrient supplementation a treatment option to improve mental status?

Recommendation

- In patients with HE, demonstrated or suspected vitamin/micronutrient deficiencies should be treated, as they can compound HE **(LoE 4, weak recommendation, 88% consensus).**

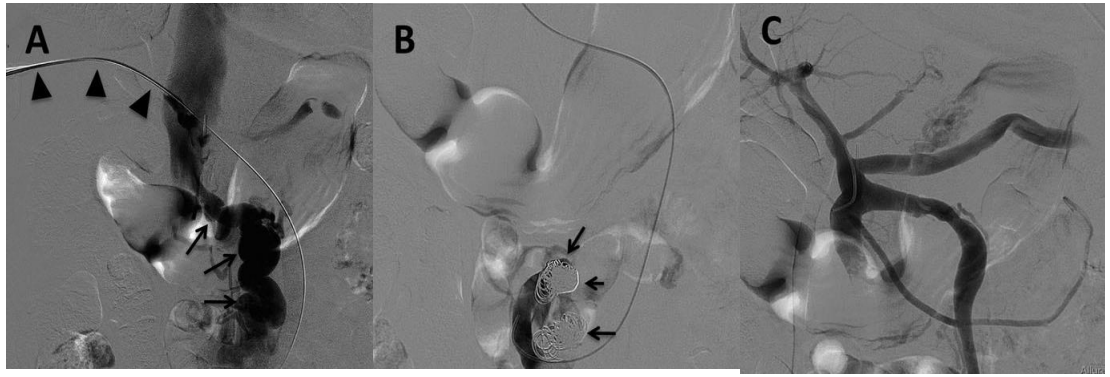
#23: In patients with recurrent/persistent HE, is the identification and, where possible, the obliteration of portal-systemic shunts a treatment option to improve outcome?





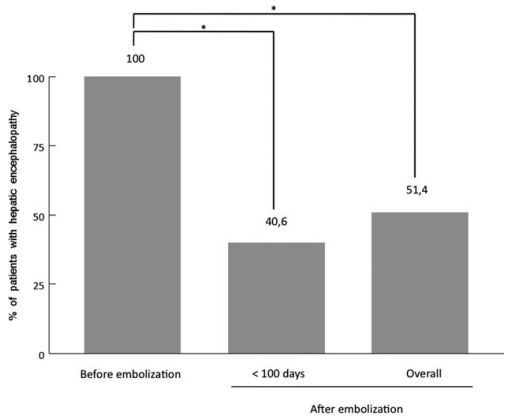
Gastroenterology

- 60% of spontaneous PSS
- HE in 48% of L-PSS

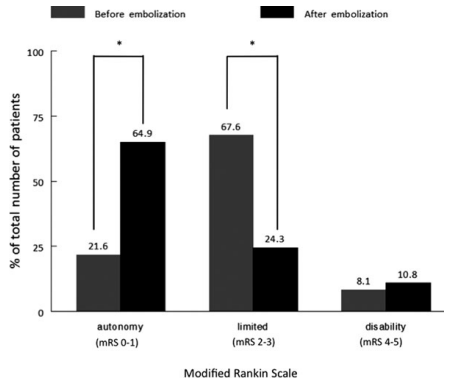


Embolization of portocaval shunt

- European retrospective study
- Inclusion of 37 pts with refractory HE
- L-PSS embolisation



Occurrence of HE * P < 0.005



Degree of disability

- 50% free of HE at 2-year
- Safe of MELD<11

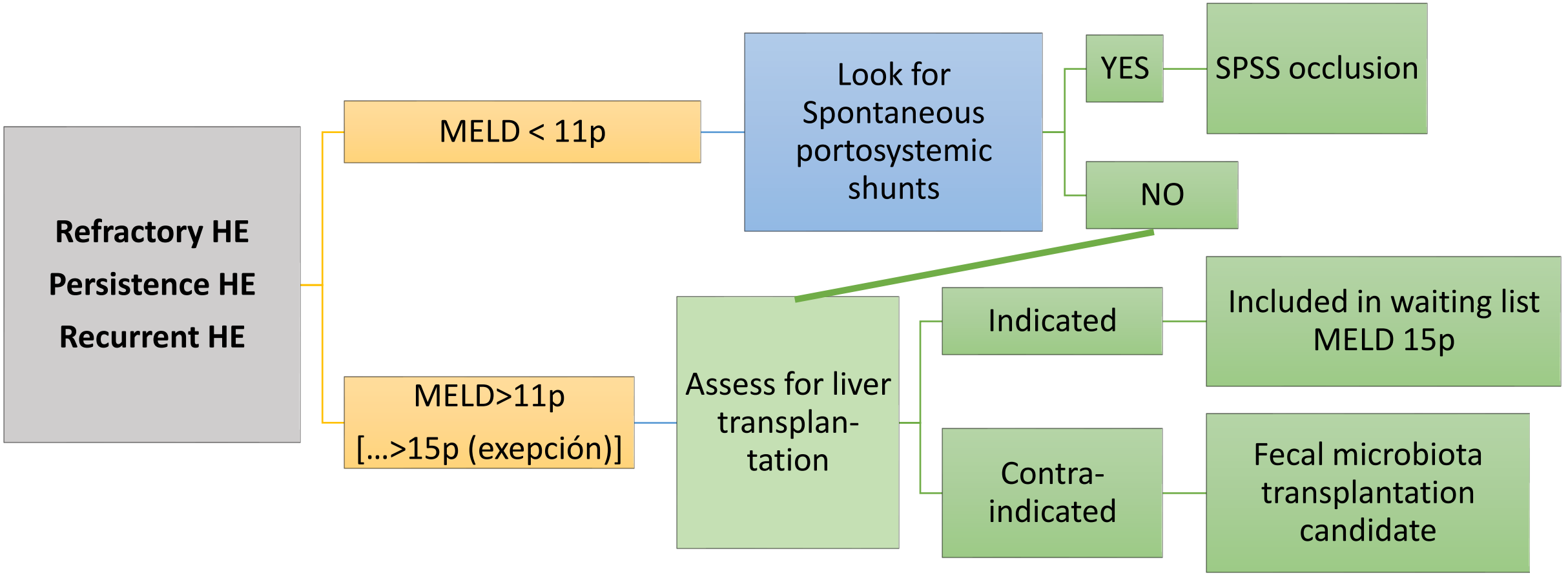
Simon-Talero M et al., Gastroenterology 2018; Praktiknjo M et al., J Hepatol 2022
Laleman W et al., J Hepatol 2013; Philips CA, IJG 2017; Lee EW, AJG 2018

#23: In patients with recurrent/persistent HE, is the identification and, where possible, the obliteration of portal-systemic shunts a treatment option to improve outcome?

Recommendation

- Obliteration of accessible portal-systemic shunts in patients with cirrhosis with recurrent or persistent HE (despite adequate medical treatment) can be considered in stable patients with a MELD score <11 **(LoE 4, weak recommendation, 100% consensus).**

Management of recurrent/persistent HE



#31 In patients with cirrhosis who are considered for TIPS, which neurologic workup should take place to assess risk of post-TIPS HE?

Recommendation

- In patients scheduled for non-urgent TIPS, the presence and/or history of overt and covert HE should be thoroughly assessed. One single episode of HE is not an absolute contraindication, especially if precipitated by bleeding **(LoE 5, strong recommendation, 89% consensus).**

#24 In patients with recurrent/persistent HE, is the replacement of animal with vegetable and dairy protein a treatment option to improve outcome?

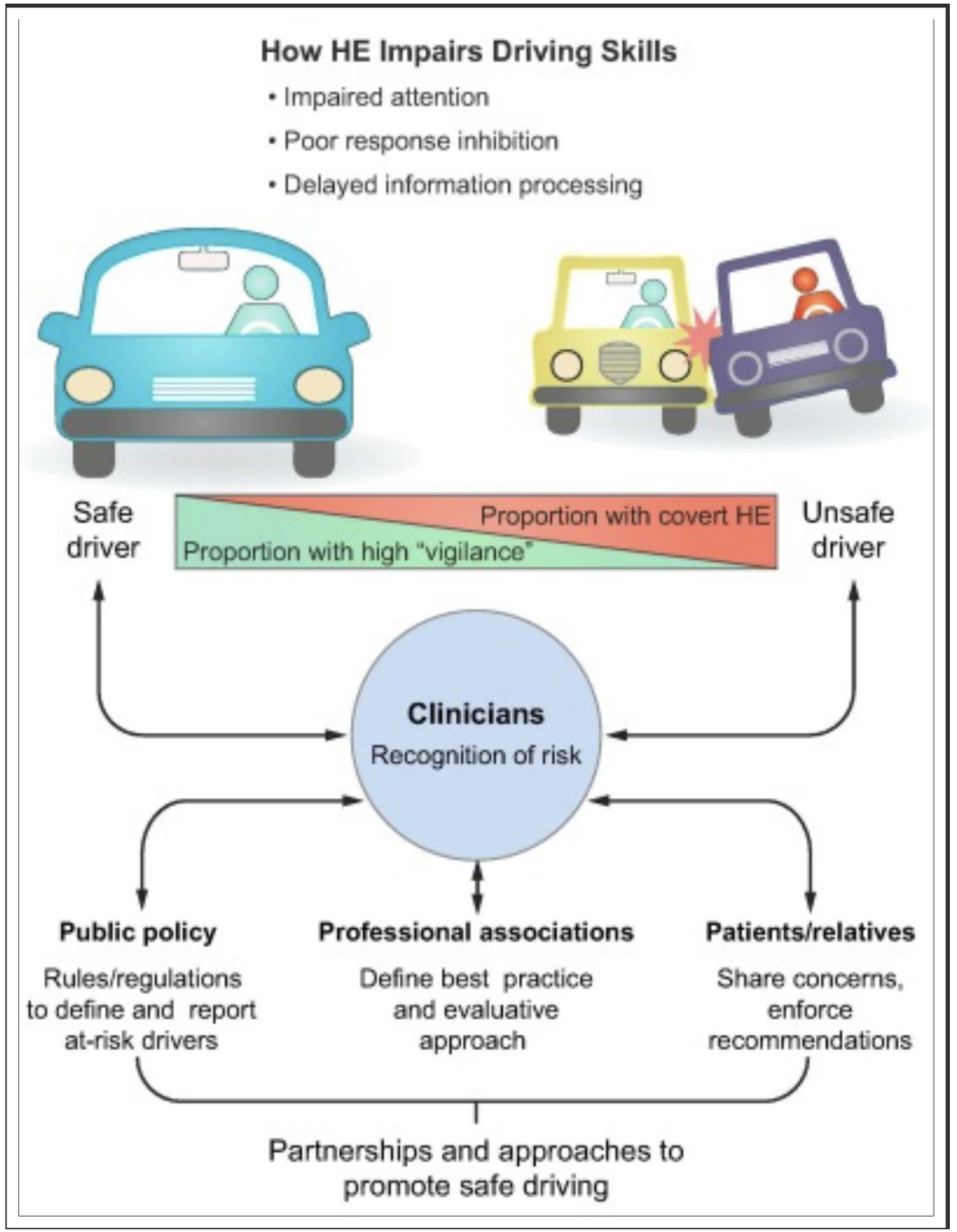
Recommendation

- In patients with recurrent/persistent HE, replacement of animal protein with vegetable and dairy protein can be considered, provided that overall protein intake is not compromised and that patient's tolerance is considered **(LoE 4, weak recommendation, 83% consensus).**

#30 Should patients with a history of, or with, overt HE be provided with advice in relation to driving for the purposes of their own and public safety?

Recommendation

- Patients who have had an episode of overt HE should be provided with information on the risks associated with driving and on the appropriateness of formal driving assessment with the relevant authorities **(LoE 5, strong recommendation, 100% consensus).**



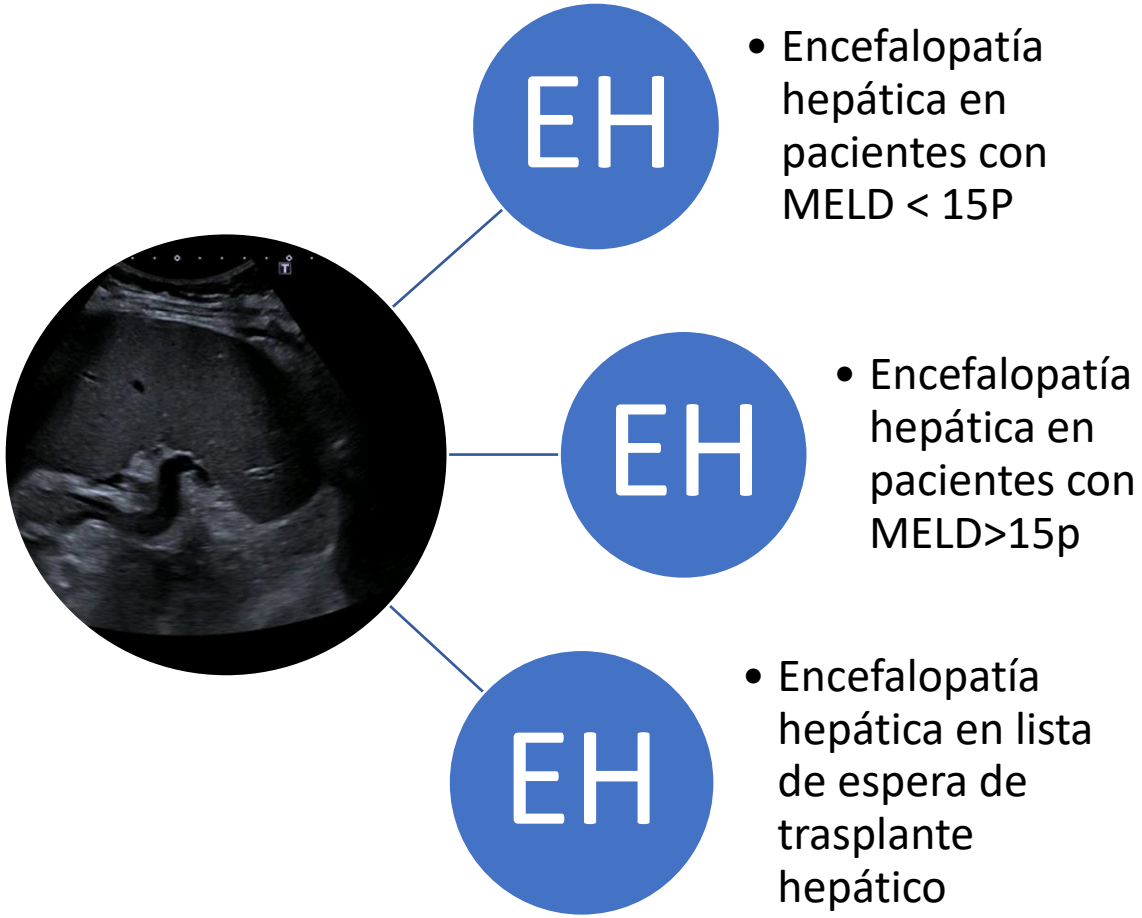
Tapper E, Romero-Gómez M, Bajaj J. J Hepatol 2019;70:590

#25 In patients with recurrent/persistent HE, is liver transplantation a treatment option to improve outcome?

Recommendation

- Patients with end-stage liver disease and recurrent or persistent HE not responding to other treatments should be assessed for liver transplantation **(LoE 4, strong recommendation, 100% consensus).**

Encefalopatía hepática en el trasplante hepático



- Encefalopatía hepática en pacientes con MELD < 15P
- Encefalopatía hepática en pacientes con MELD>15p
- Encefalopatía hepática en lista de espera de trasplante hepático

A. La encefalopatía hepática no está incluida en el MELD de manera directa ni indirecta.

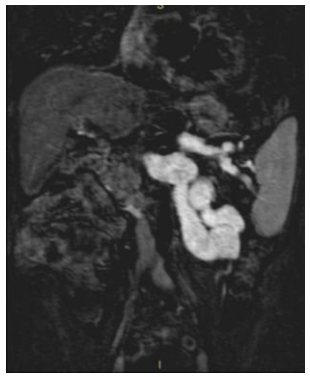
B. La encefalopatía hepática grave no siempre correlaciona con el nivel de disfunción hepática.

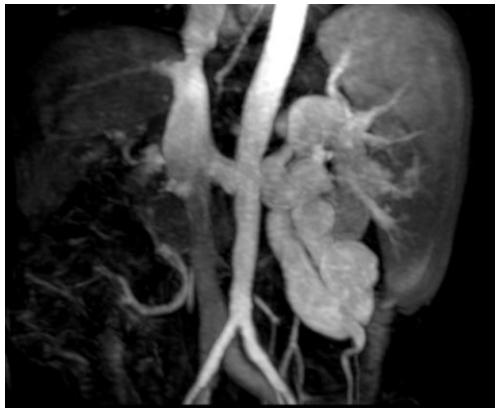
C. El diagnóstico diferencial puede ser controvertido en pacientes con comorbilidades neurológicas.

D. La encefalopatía hepática crónica/recurrente es un criterio de excepción para la indicación de trasplante hepático

Excepciones al MELD en la indicación de trasplante hepático

Complicaciones de la cirrosis	Otras patologías del hígado
Ascitis refractaria	**Budd-Chiari**
Hemorragia digestiva recurrrente	**Polineuropatía amiloidótica familiar**
Encefalopatía crónica o recurrente	**Fibrosis quística**
Síndrome hepatopulmonar	**Telangiectasia hemorrágica hereditaria**
Hipertensión portopulmonar	
Prurito resistente a tratamiento	Hígado poliquístico
Malignidad	Oxaluria primaria
Colangiocarcinoma	Colangitis recurrente
Carcinoma Hepatocelular	Enfermedades metabólicas hepáticas
Tumores de hígado poco frecuentes (**hemangioendotelioma epitelioide**)	





If outside referral and is a new patient, obtain records to confirm clinical grade 2 or higher OHE

History of cirrhosis and OHE and potential LT candidate

Document OHE details:
- 1st OHE admission date, reason for precipitation
- Number of OHE episodes over last 6 months (recurrent OHE) and reasons for precipitation
- Confirm adherence to medications
- Confirm resolution of precipitant(s)
- Assess for shunts: Determine if shunt(s) are embolizable or not and if HE course improved after that

Confirmed recurrent OHE despite adherence and absence of embolizable shunt
Or continuing episodes despite embolization
Patient without dementia on detailed neurocognitive evaluation

- Appeal to national LT board for consideration for additional MELD points for listing
- Consider living donor transplant

- Assess for covert HE
- Detailed neurocognitive evaluation (especially if dementia differential diagnosis)
- Assess for HRQOL, frailty, and sarcopenia to determine impact

FIG. 3. Proposed algorithm for prioritizing patients with HE for listing.

#26 In patients with hepatic myelopathy, is liver transplantation a treatment option to improve outcome?

Recommendation

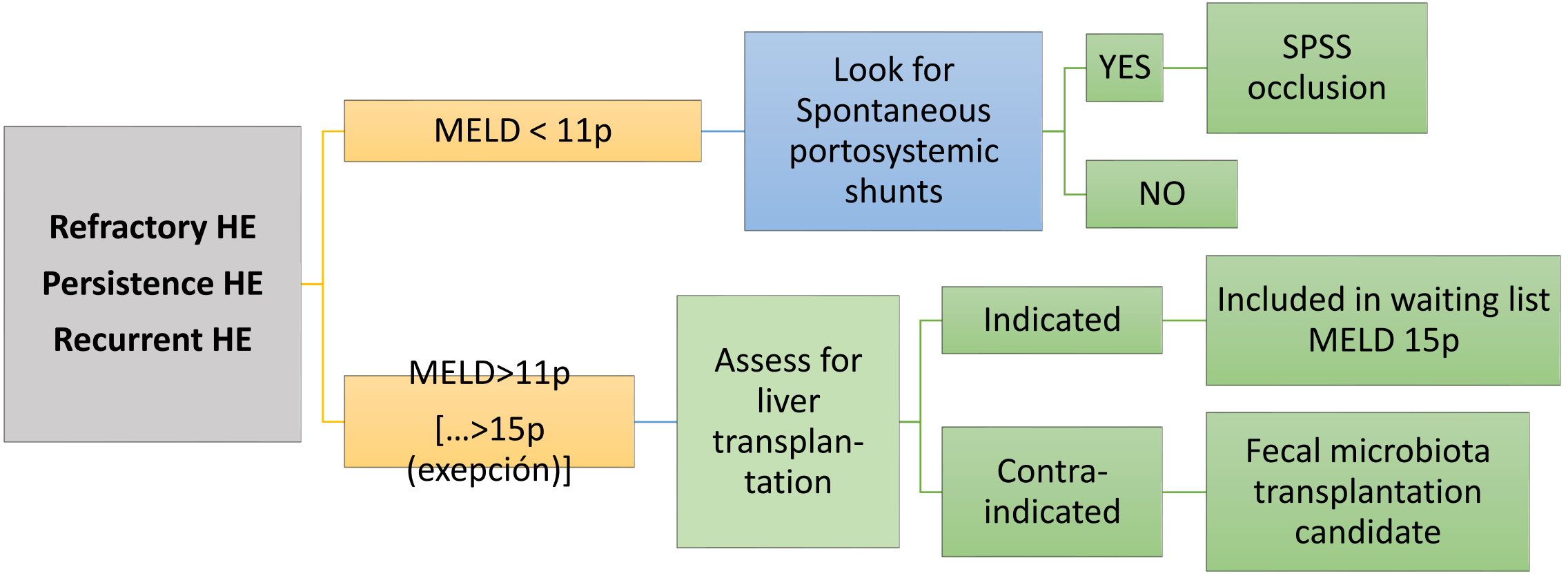
- In patients with hepatic myelopathy, liver transplantation should be considered as soon as possible since there is no other therapeutic option **(LoE 4, strong recommendation, 94% consensus).**

#27. In patients with cirrhosis-related Parkinsonism, are dopaminergic drugs a treatment option to improve outcome?

Recommendation

- In patients with cirrhosis-related Parkinsonism, dopaminergic treatment should be tested **(LoE 2, strong recommendation, 95% consensus).**

#28 In patients with recurrent/persistent HE, is fecal microbiota transplantation a treatment option to improve outcome?



Fecal microbiota transplantation in HE

- ✓ Chronic liver disease is associated with alterations in gut microbial function and composition, which can propagate the disease process in the presence of altered systemic and local immune changes.
- ✓ Two small RCT demonstrated safety and potential benefit in HE, which was also associated with reduction in antibiotic resistance genes.
- ✓ Changes in human gut-liver axis can be transmitted to germ-free mice post-FMT.

FMT in HE	
Risk/Benefit	**Not stablished**
Duration and dose of therapy	No dose-ranging studies
Likelihood of long-lasting therapy or cure	Maybe from a limited perspective i.e. cognitive function but liver transplant still needed
Route of therapy tried and efficacy	**Enema, colonoscopy and capsules have all been tried**
Pre-procedure antibiotics	One trial used it, but rest did not
Antibiotics withheld post-FMT	**Two trials did not hold rifaximin**, 3rd did not include people on rifaximin
Possibility of harm	Extended spectrum beta-lactamases (ESBL) bacteremia was reported

Bajaj J. IBIS 14 January 2021

Gut microbiota and hepatic encephalopathy

Bacterial Family	Saliva			Stool		
	Controls (%)	No-HE (%)	HE (%)	Controls (%)	No-HE (%)	HE (%)
Clostridiales XIV‡	7.8	5.6	2.7*	9.2	6.6	4.5*
Lachnospiraceae‡	20.2	15.0	9.5*	27.0	21.3	16.0*
Ruminococcaceae‡	7.0	4.9	3.7*	13.4	8.7	7.4*
Fusobacteriaceae	0.0	1.6	1.6†	0.0	0.0	1.0
Prevotellaceae	4.2	7.3	7.4†	5.4	5.3	5.0
Enterococcaceae	0.0	2.5	3.1†	0.0	0.0	1.0
Enterobacteriaceae	2.2	5.5	5.8†	0.0	3.0	3.1†
Erysipelotrichaceae	3.5	1.2	1.3†	5.3	1.9	0.6*
Bacteroidaceae	3.4	3.8	4.6	19.9	24.5	24.9
Streptococcacae	33.0	29.1	33.3	2.4	4.4	1.9

Family_Genus, % abundance	Control Mucosa (n = 17)	HE Mucosa (n = 19)	P Value
Burkholderiaceae_Burkholderia	0.0	0.2	0.001
Incertae Sedis XIV_Blautia	8.6	3.0	0.006
Incertae Sedis XIV_other	1.6	0.4	0.01
Lachnospiraceae_Roseburia	2.1	0.4	0.009
Lachnospiraceae_other	20.3	9.1	0.005
Ruminococcaceae_Faecalibacterium	3.5	1.6	0.02
Ruminococcaceae_Subdoligranulum	1.1	0.2	0.002
Streptomycetaceae_Streptomyces	0.0	1.9	0.001

Family_Genus, % abundance	HE Mucosa (n = 17)	No-HE Mucosa (n = 19)	P Value
Lachnospiraceae_Roseburia	0.5	2.5	0.002
Veillonellaceae_Veillonella	0.7	0	0.001
Burkholderiaceae_other	0.8	0	0.001
Veillonellaceae_Megasphaera	2.4	0	0.001
Streptomycetaceae_Streptomyces	2.7	0	0.001
Fusobacteriaceae_other	3.5	0	0.001
Bifidobacteriaceae_Bifidobacterium	3.8	0	0.001
Enterococcaceae_Enterococcus	7.7	0	0.001

⬇ autochtonous taxa (Lachonospiraceae Ruminococcaceae, *Blautia*)

⬆ Alcaligenaceae, Porphyromonadaceae Veillonellaceae & potentially pathogenic taxa (Enterobacteriaceae)

Bajaj JS et al J Hepatol 2014; 60: 940-47

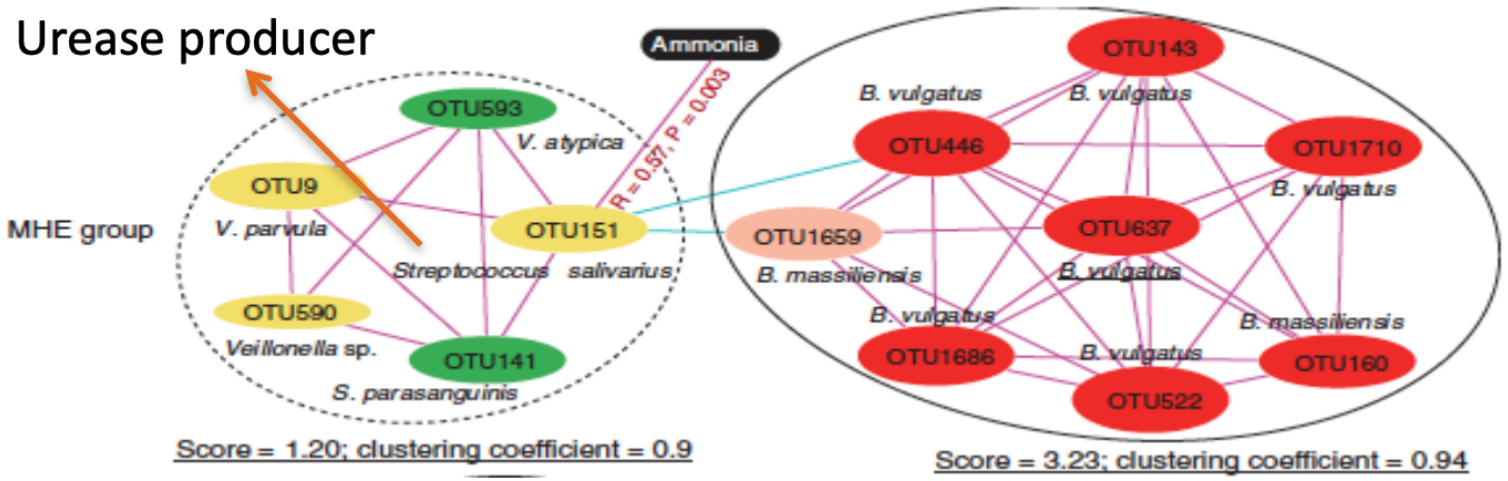
Bajaj JS et al. Am J Physiol Gastrointest Liver Physiol 2012

Large-Scale Survey of Gut Microbiota Associated With MHE Via 16S rRNA-Based Pyrosequencing

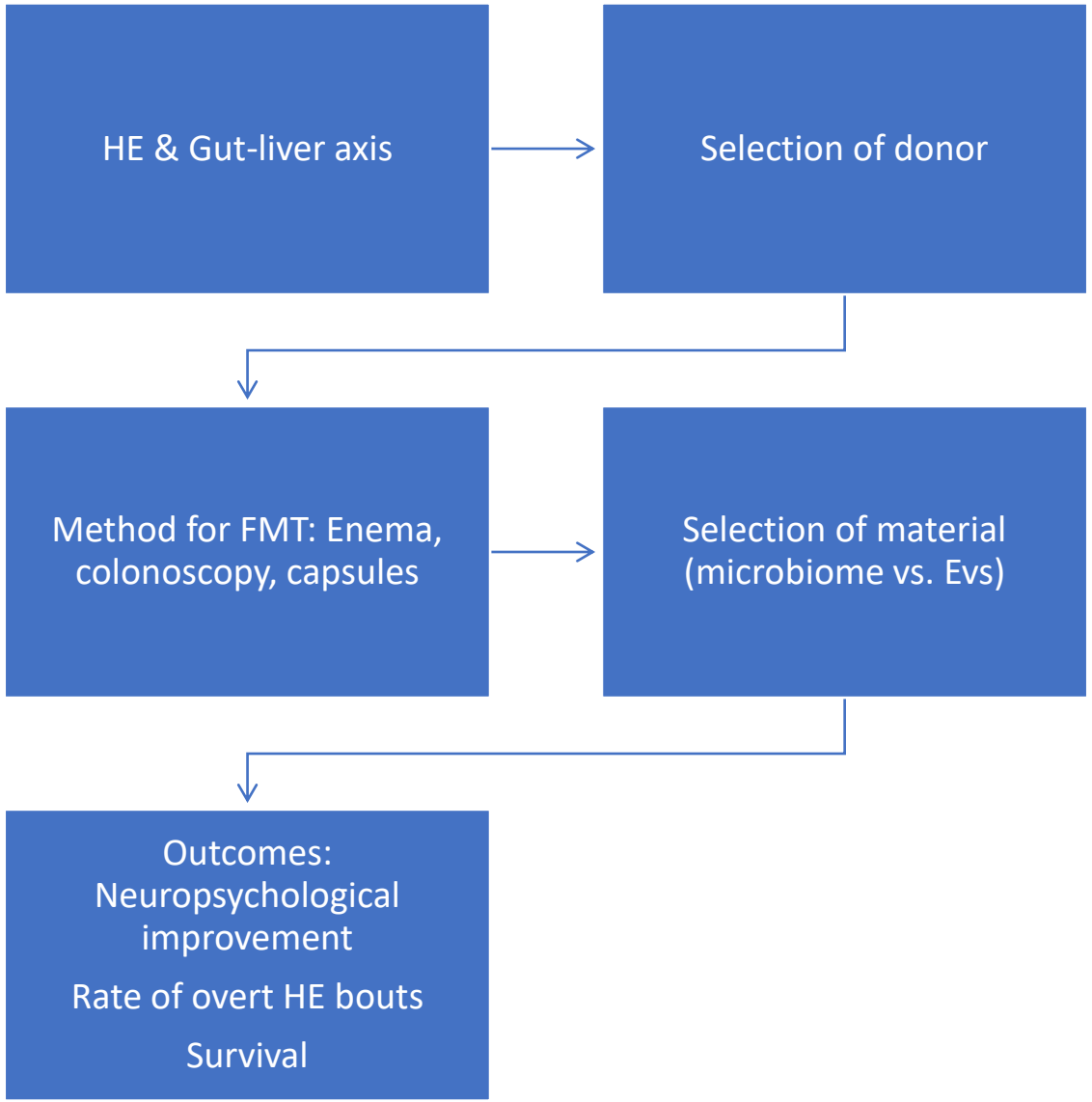
Am J Gastroenterol 2013; 108:1601–1611

Zhigang Zhang, PhD[1,3], Huiqin Zhai, BD[2,3], Jiawei Geng, BD[2,3], Rui Yu, BD[1], Haiqing Ren, MD[1], Hong Fan, BD[2] and Peng Shi, PhD[1]

- Increase in Streptococcaceae and Veillonellaceae
- The abundance of *S. salivarius* was significantly higher in cirrhotic patients with MHE (P = 0.030)
- The change in the amount of *S. salivarius* was positively correlated with ammonia accumulation (R = 0.58, P = 0.003)



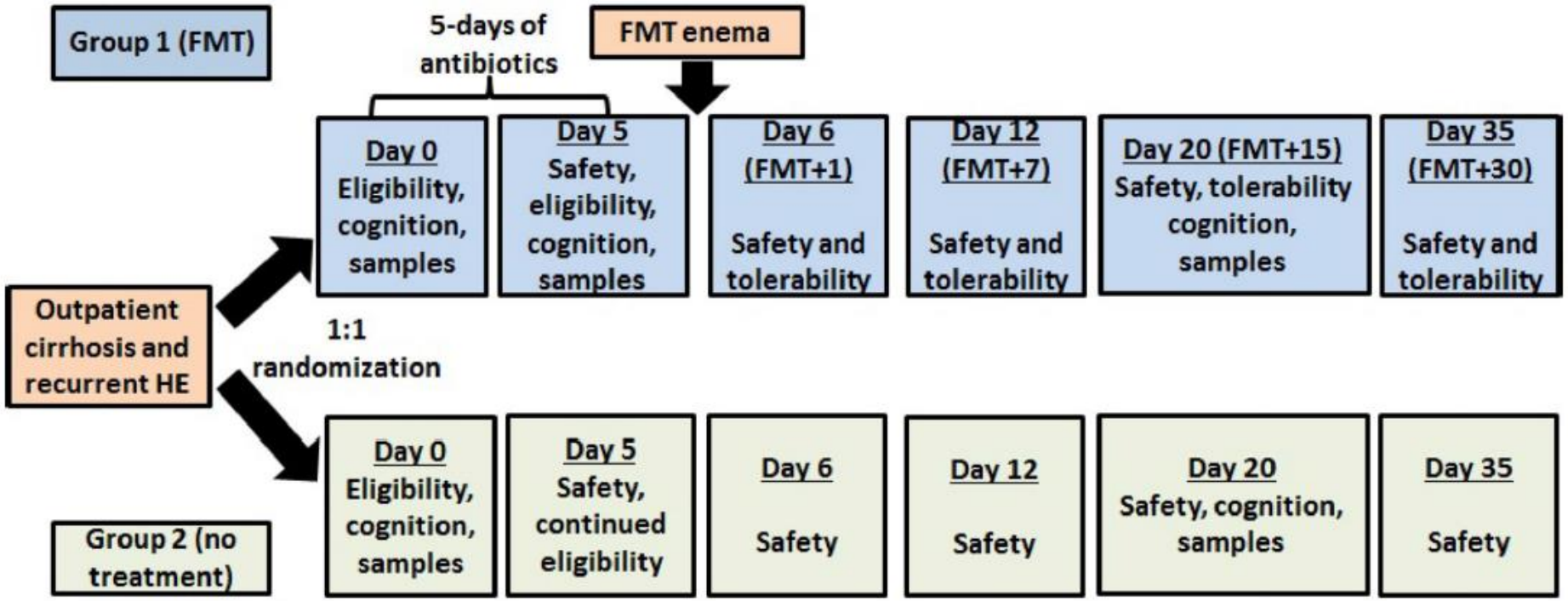
FMT in HE


HE & Gut-liver axis
Selection of donor
Method for FMT: Enema, colonoscopy, capsules
Selection of material (microbiome vs. Evs)
Outcomes:
Neuropsychological improvement
Rate of overt HE bouts
Survival

HEPATOLOGY
HEPATOLOGY, VOL. 00, NO. 00, 2017
RAPID COMMUNICATION

Fecal Microbiota Transplant From a Rational Stool Donor Improves Hepatic Encephalopathy: A Randomized Clinical Trial

Jasmohan S. Bajaj,[1] Zain Kassam,[2,5] Andrew Fagan,[1] Edith A. Gavis,[1] Eric Liu,[3] L. Jane Cox,[4] Raffi Kheradman,[3] Douglas Heuman,[1] Jessica Wang,[3] Thomas Gurry,[5] Roger Williams,[4] Masoumeh Sikaroodi,[3] Michael Fuchs,[1] Eric Alm,[5] Binu John,[1] Leroy R. Thacker,[1] Antonio Riva,[4] Mark Smith,[2] Simon D. Taylor-Robinson,[6] and Patrick M Gillevet[3]



- 20 patients with cirrhosis and recurrent HE;
- SOC vs FMT (after 5 days of antibiotics) + SOC;
- **FMT administered via enema.**

Primary outcomes: FMT-related serious adverse events (SAEs) at day 150 (death, hospitalizations, ER visits or trasmissible infections)

Secondary outcomes: cognitive function at day 20 (PHES, Encephalapp), cirrhosis severity (MELD score, albumin), changes in liver function and WBC count, development of all AEs, changes in microbiota composition and function.

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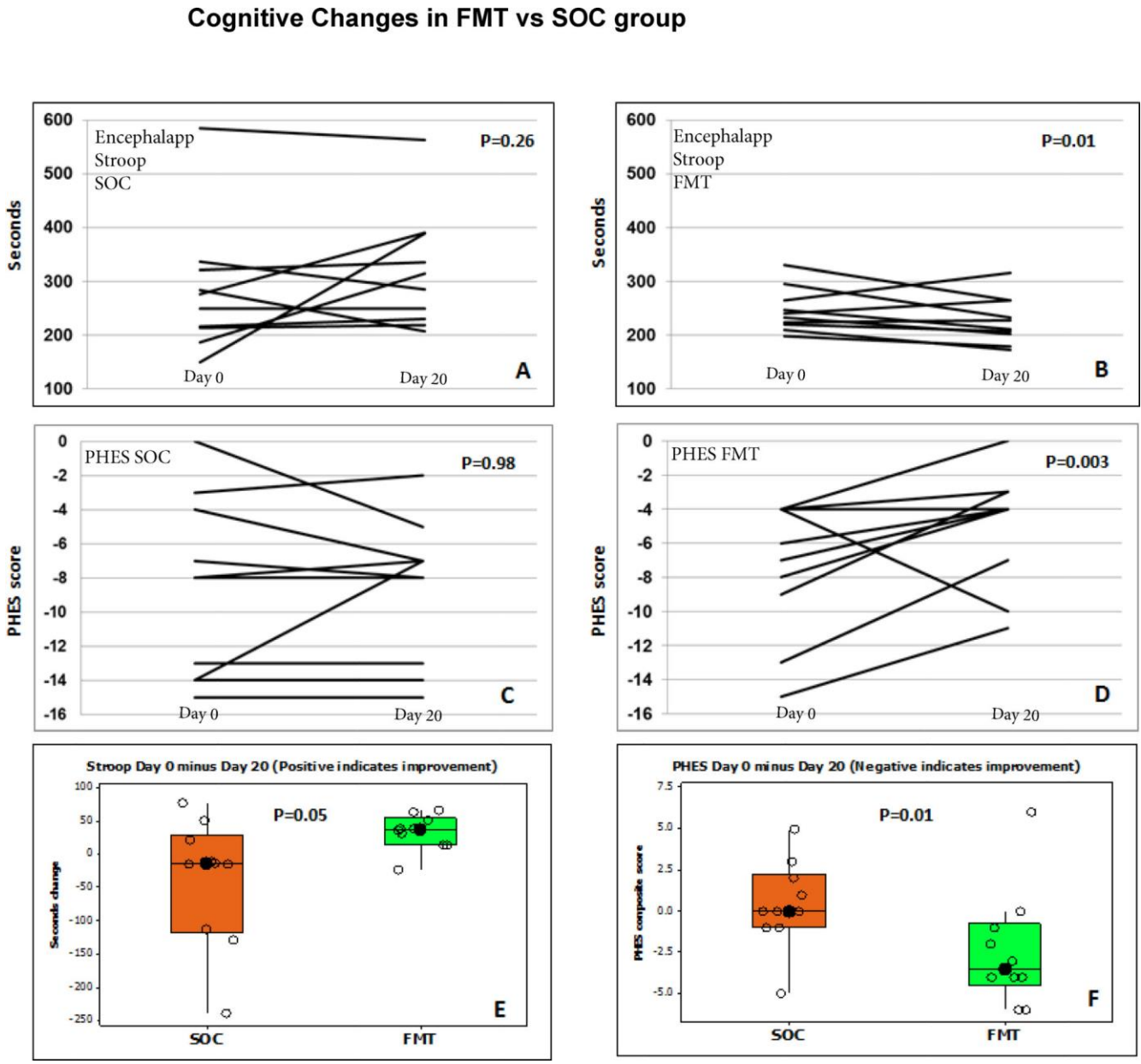
PRIMARY OUTCOME (SAFETY):
SAEs significantly lower tan control group at 150 days. No changes in MELD, WBC count, AST, ALT, albumin or hemoglobin were seen in either arm.

SECONDARY OUTCOMES (EFFICACY)
There was a significant improvement in PHES total score (P=0.003) and EncephalApp Stroop (P=0.01) in the FMT group compared to baseline, but none in prevalues and postvalues among the SOC arm (PHES, P=0.98; EncephalApp, P 5 0.26). No HE episode vs 6/10 in SOC.

SHORT-TERM MICROBIAL COMPOSITION
In the SOC arm, no significant changes in microbiota composition or diversity were seen. ülncrease microbial Alpha diversity and relative abundance of beneficial
taxa (Lactobacillaceae and Bifidobacteriaceae) was seen post-FMT.



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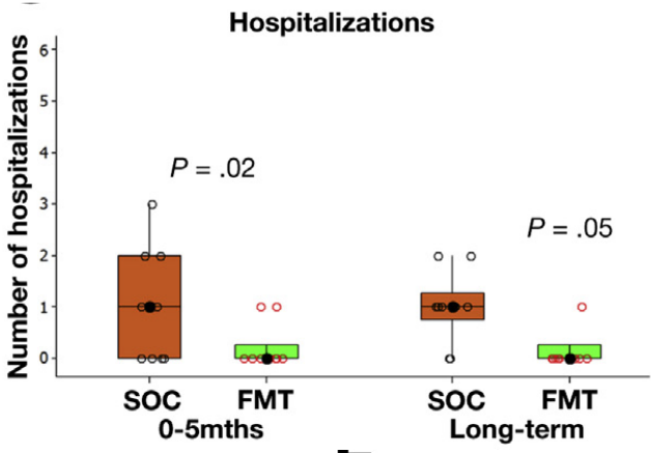
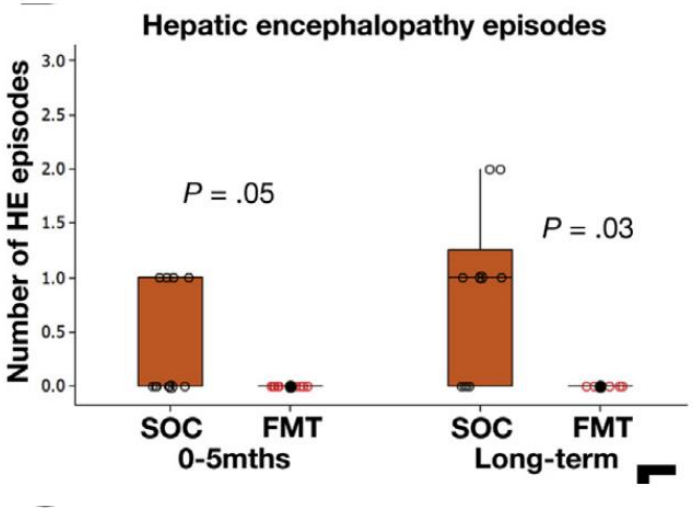
Long-term Outcomes (12-15 months) of Fecal Microbiota Transplantation in Patients With Cirrhosis: hospitalizations, HE events, cognitive function, microbial composition

LONG-TERM OUTCOMES:

In the SOC arm, there was a total of 10 hospitalization (HE 4, infection 2, ascites 2) compared to 1 in the FMT arm (ascites1) (p=0.05). In the SOC arm, there was a total of 8 HE events compared to 0 in the FMT arm (p=0.03). Cognitive function, which had improved in the FMT arm at Day 20 post-FMT, remained significantly better in the FMT arm compared to SOC.





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Long-term Outcomes of Fecal Microbiota Transplantation in Patients With Cirrhosis

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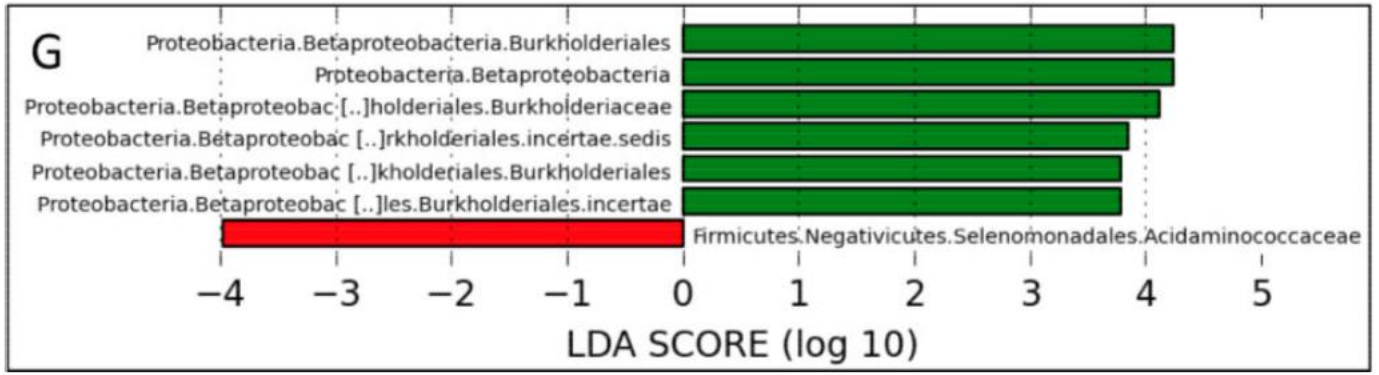
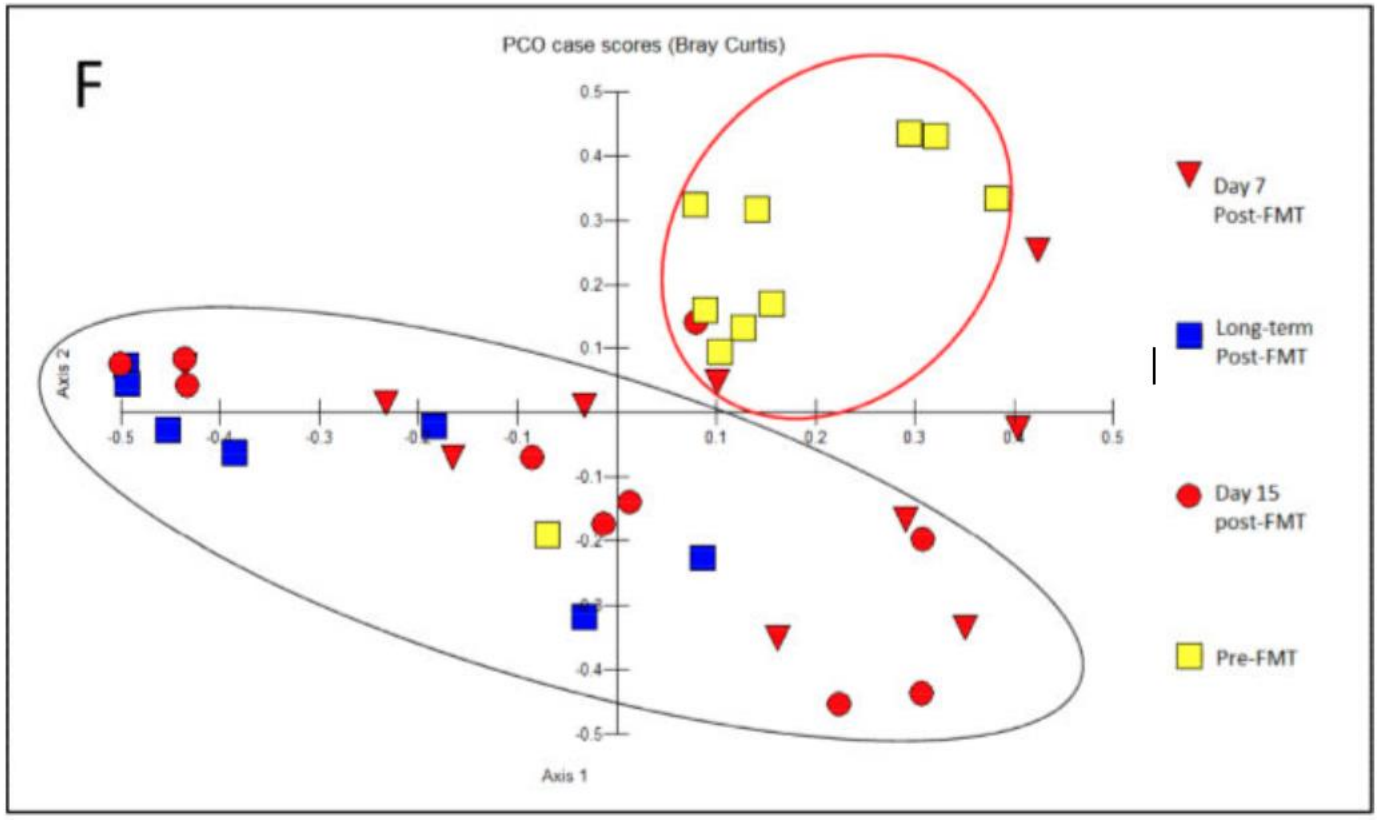
LONG-TERM MICROBIOAL COMPOSITION
Increase in relative abundance of Burkholderiaceae and decreased Acidaminoccocaceae in the FMT arm. Microbiota were similar post-FMT regardless of short or long-term follow up compared to pre-FMT microbial composition (relative clustering between the post-FMT group microbiota (black oval) compared to pre-FMT (red oval)).





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A Systematic Review of the Efficacy and Safety of Fecal Microbiota Transplantation in the Treatment of Hepatic Encephalopathy

Author/Year	Type of Donor	Method of FMT Administration	Exposure to Antibiotics Prior to FMT	Cognitive Performance Before FMT	Cognitive After FMT	Number of AEs	Number of SAEs
Bajaj et al., 2021 [18]	Single donor	Enema	None	PHES: -5.5 (-10.00-0.0)*; EncephalApp: 197.8 (164.7-222.1)*	PHES: -2.5 (-9.25-1.00)*; EncephalApp: 187.5 (167.8-213.3)*	Not reported	0 [0.25]*
Bajaj et al., 2019 [24]	Single donor enriched in *Lachnospiraceae* and *Ruminococcaceae*	Capsule	None (all subjects were on rifaximin)	PHES: -6.8 ± 6.3**; EncephalApp: 277.8 ± 123.5	PHES: -5.7 ± 5.4; EncephalApp: 226.7 ± 56.1	Constipation (n = 2); diarrhea (n = 1); bloating (n = 1)	1 (0,0-1)[¥] : a case of hepatic encephalopathy that was found to be unrelated to FMT
Bajaj et al., 2019 [6]	Single donor	Enema	Ciprofloxacin 500 mg PO BID, Amoxicillin 500 mg PO TID, Metronidazole 500 mg PO TID for 5 days	PHES: -6.5 (-9.9, -3.9)[£]; EncephalApp: 237.2 (218.1, 271.9)[£]	PHES: -5.9 (-7.9, -3.9) [£]; EncephalApp: 222.2 (203.1, 232.9)[£]	Not reported	Ascites (n = 1)
Mehta et al., 2018 [25]	Patient-identified	Colonoscopy	All patients were given broad-spectrum antibiotics for 5 days	Not utilized[ǥ]	Not utilized[ǥ]	Recurrence of hepatic encephalopathy (n = 2)[&]	Death due to sepsis from bronchopneumonia(n = 1)[&]; hepatic encephalopathy (n = 1)[&]; SBP (n = 2)[&]

N=127 cirrhotic patients received FMT.
Hepatic encephalopathy was evaluated by cognitive tests, such as the Psychometric Hepatic Encephalopathy Score (PHES) and EncephalApp Stroop test.
FMT was associated with an improvement in the cognitive performance, and decreased hospitalizations and overt HE rate.
Low rate of adverse events.
FMT showed therapeutic potential to treat hepatic encephalopathy based on safety and efficacy.

Serious Adverse Events	Frequency
Death	2
Hepatic encephalopathy	3*
Spontaneous bacterial peritonitis	2
Ascites	1
Crohn's disease flare	1
Fecal urgency	1
Acute kidney injury	1
Portal hypertensive bleed	1
E. coli bacteremia	1

Tun KM et al. Cureus 2022;14:e25537

#28 In patients with recurrent/persistent HE, is fecal microbiota transplantation a treatment option to improve outcome?

Recommendation

- In patients with recurrent/persistent HE, FMT is not routinely recommended as a treatment option but its validation in large randomised placebo-controlled trials powered for clinical outcomes is warranted **(LoE 2, weak recommendation, 93% consensus).**

Consensus CPG EASL HE

Recommendation	Consensus	Recommendation	Consensus
#1	**96%**	#17a	**96%**
#2	**96%**	#17b	**92%**
#3	**91%**	#18	**85%**
#4	**93%**	#19	**82%**
#5	**100%**	#20	**77%**
#6	**90%**	#21	**95%**
#7	**95%**	#22	**88%**
#8	**96%**	#23	**100%**
#9	**96%**	#24	**83%**
#10	**83%**	#25	**100%**
#11	**92%**	#26	**94%**
#12	**77%**	#27	**95%**
#13	**100%**	#28	**93%**
#14	**100%**	#29	**89%**
#15	**96%**	#30	**100%**
#16	**85%**	#31	**89%**

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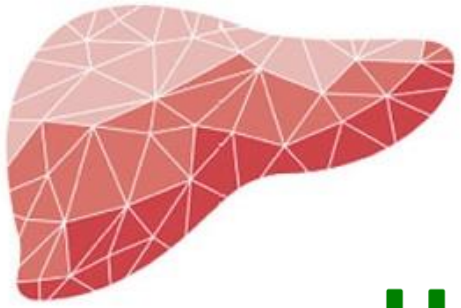

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