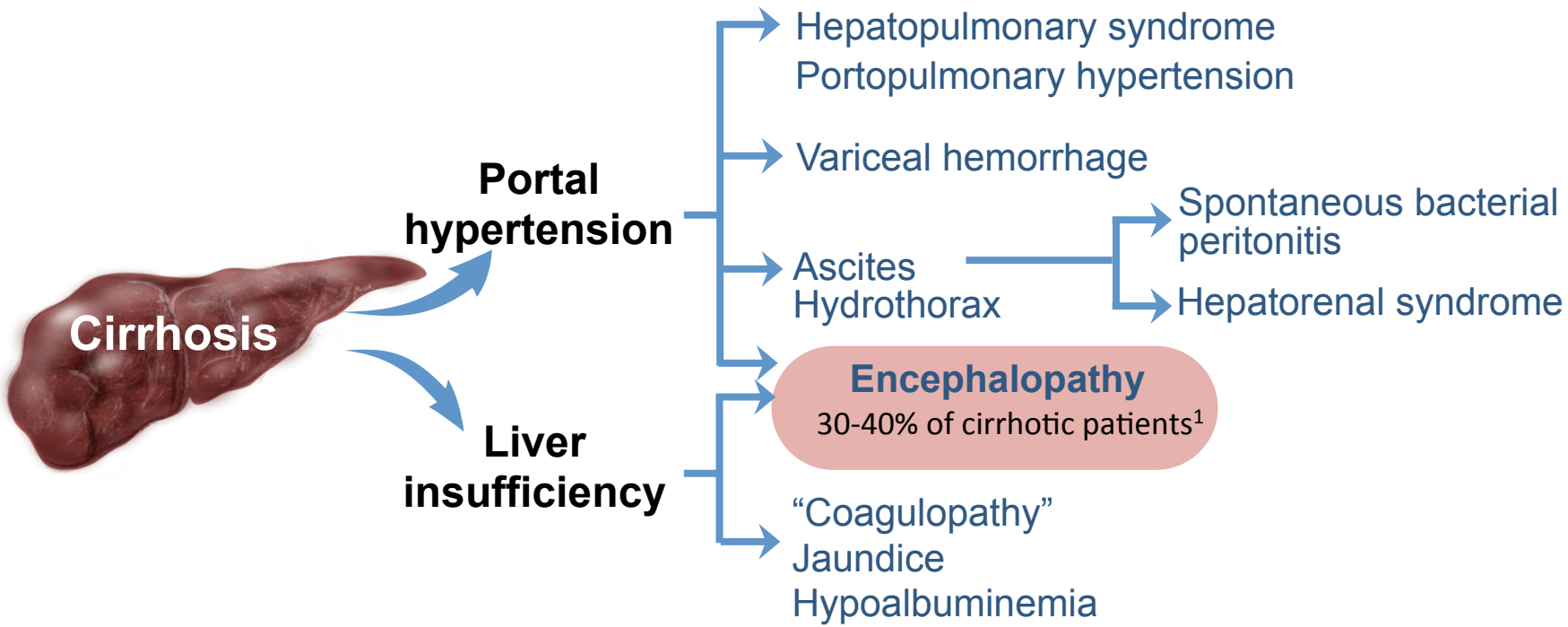
Advances in Hepatic Encephalopathy

K. Rajender Reddy, M.D.

Ruimy Family President's Distinguished Professor in Medicine
Professor of Medicine in Surgery
Director of Hepatology
Medical Director, Liver Transplantation
University of Pennsylvania

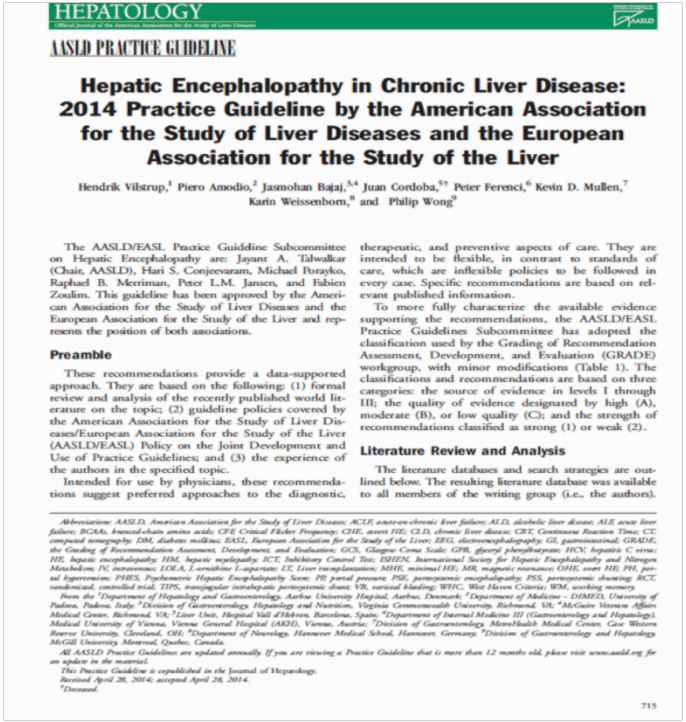
Penn

Complications of Cirrhosis: Distinguish Portal Hypertension from Liver Insufficiency



1. Amodio P et al. *J Hepatol.* 2001;35:37-45.

Definition of Hepatic Encephalopathy



HEPATOLOGY

AASLD PRACTICE GUIDELINE

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver

Hendrik Vilstrup,[1] Piero Amodio,[2] Jasmohan Bajaj,[3,4] Juan Cordoba,[5†] Peter Ferenci,[6] Kevin D. Mullen,[7] Karin Weissenborn,[8] and Philip Wong[9]

The AASLD/EASL Practice Guideline Subcommittee on Hepatic Encephalopathy are: Jayant A. Talwalkar (Chair, AASLD), Hari S. Conjeevaram, Michael Porayko, Raphael B. Merriman, Peter L.M. Jansen, and Fabien Zoulim. This guideline has been approved by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver and represents the position of both associations.

Preamble

These recommendations provide a data-supported approach. They are based on the following: (1) formal review and analysis of the recently published world literature on the topic; (2) guideline policies covered by the American Association for the Study of Liver Diseases/European Association for the Study of the Liver (AASLD/EASL) Policy on the Joint Development and Use of Practice Guidelines; and (3) the experience of the authors in the specified topic.

Intended for use by physicians, these recommendations suggest preferred approaches to the diagnostic, therapeutic, and preventive aspects of care. They are intended to be flexible, in contrast to standards of care, which are inflexible policies to be followed in every case. Specific recommendations are based on relevant published information.

To more fully characterize the available evidence supporting the recommendations, the AASLD/EASL Practice Guidelines Subcommittee has adopted the classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup, with minor modifications (Table 1). The classifications and recommendations are based on three categories: the source of evidence in levels I through III; the quality of evidence designated by high (A), moderate (B), or low quality (C); and the strength of recommendations classified as strong (1) or weak (2).

Literature Review and Analysis

The literature databases and search strategies are outlined below. The resulting literature database was available to all members of the writing group (i.e., the authors).

Abbreviations: AASLD, American Association for the Study of Liver Diseases; ACLF, acute-on-chronic liver failure; ALD, alcoholic liver disease; ALF, acute liver failure; BCAA, branced-chain amino acids; CFF, Critical Flicker Frequency; CHE, covert HE; CLD, chronic liver disease; CRT, Continuous Reaction Time; CT, computed tomography; DM, diabetes mellitus; EASL, European Association for the Study of the Liver; EEG, electroencephalography; GI, gastrointestinal; GRADE, the Grading of Recommendation Assessment, Development, and Evaluation; GCS, Glasgow Coma Scale; GPB, glycerol phenylbutyrate; HCV, hepatitis C virus; HE, hepatic encephalopathy; HM, hepatic myelopathy; ICT, Inhibitory Control Test; ISHEN, International Society for Hepatic Encephalopathy and Nitrogen Metabolism; IV, intravenous; LOLA, L-ornithine L-aspartate; LT, Liver transplantation; MHE, minimal HE; MR, magnetic resonance; OHE, overt HE; PH, portal hypertension; PHES, Psychometric Hepatic Encephalopathy Score; PP, portal pressure; PSE, portosystemic encephalopathy; PSS, portosystemic shunting; RCT, randomized, controlled trial; TIPS, transjugular intrahepatic portosystemic shunt; VB, variceal bleeding; WHC, West Haven Criteria; WM, working memory.

From the [1]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Medicine - DIMED, University of Padova, Padova, Italy; [3]Division of Gastroenterology, Hepatology and Nutrition, Virginia Commonwealth University, Richmond, VA; [4]McGuire Veterans Affairs Medical Center, Richmond, VA; [5]Liver Unit, Hospital Vall d'Hebron, Barcelona, Spain; [6]Department of Internal Medicine III (Gastroenterology and Hepatology), Medical University of Vienna, Vienna General Hospital (AKH), Vienna, Austria; [7]Division of Gastroenterology, MetroHealth Medical Center, Case Western Reserve University, Cleveland, OH; [8]Department of Neurology, Hannover Medical School, Hannover, Germany; [9]Division of Gastroenterology and Hepatology McGill University, Montreal, Quebec, Canada.

All AASLD Practice Guidelines are updated annually. If you are viewing a Practice Guideline that is more than 12 months old, please visit www.aasld.org for an update in the material.

This Practice Guideline is copublished in the Journal of Hepatology.

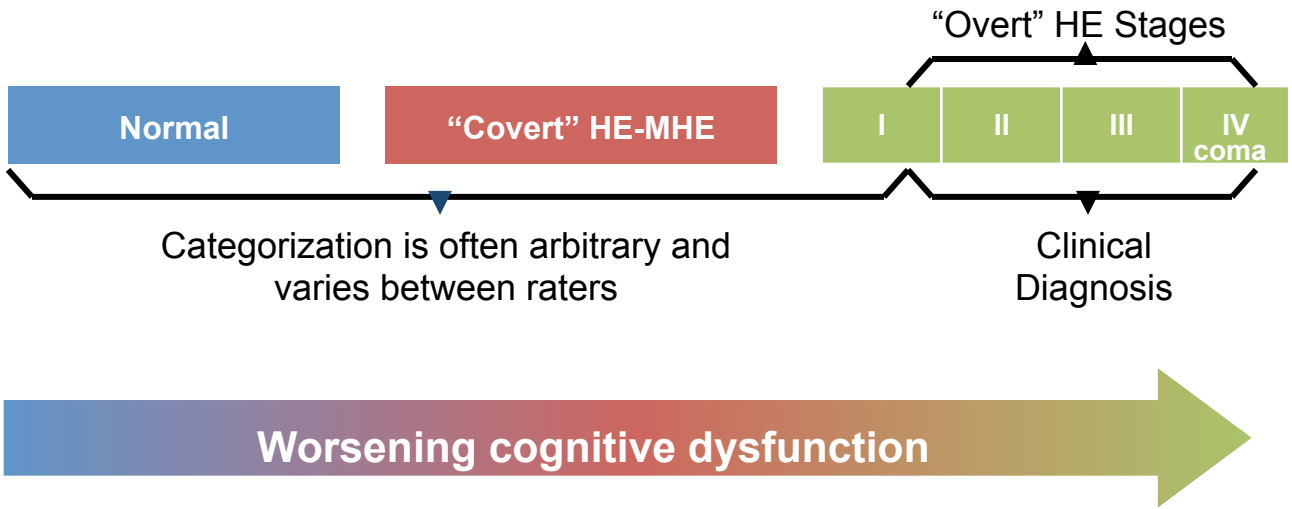
Received April 28, 2014; accepted April 28, 2014.

†Deceased.

Hepatic encephalopathy is a brain dysfunction caused by liver insufficiency and portal systemic shunt; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma

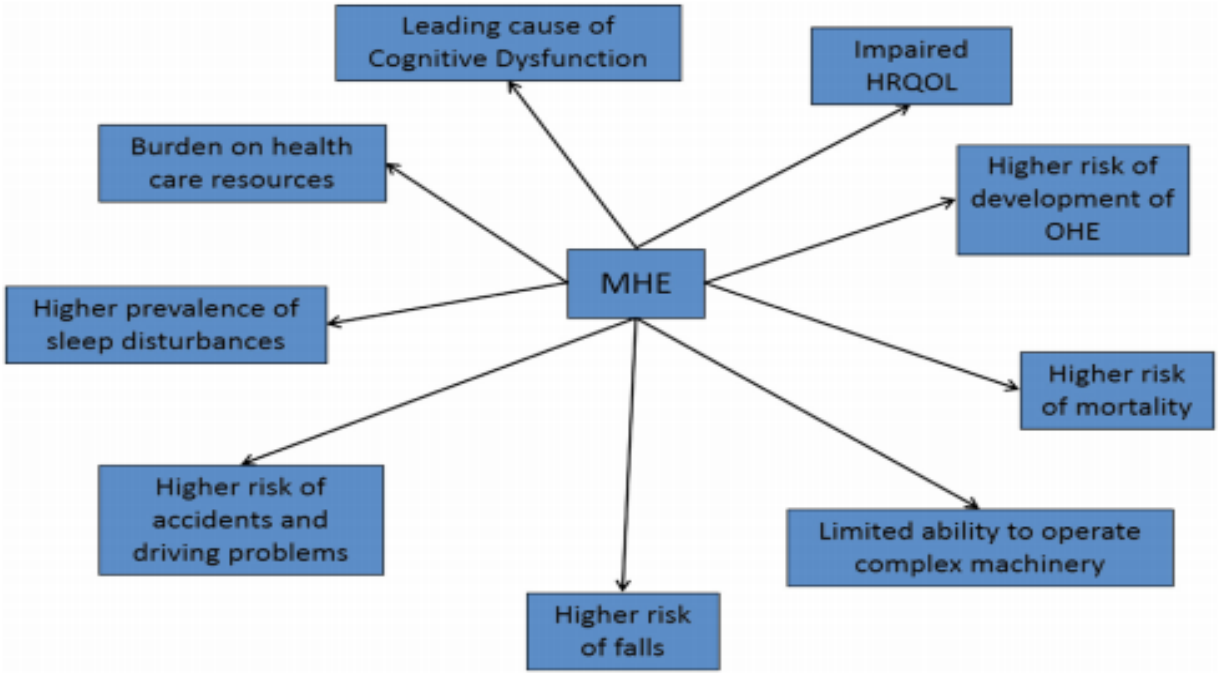
VIlstrup H et al. *Hepatology*. 2014;60(2):714-735.

Characterization of HE Stages



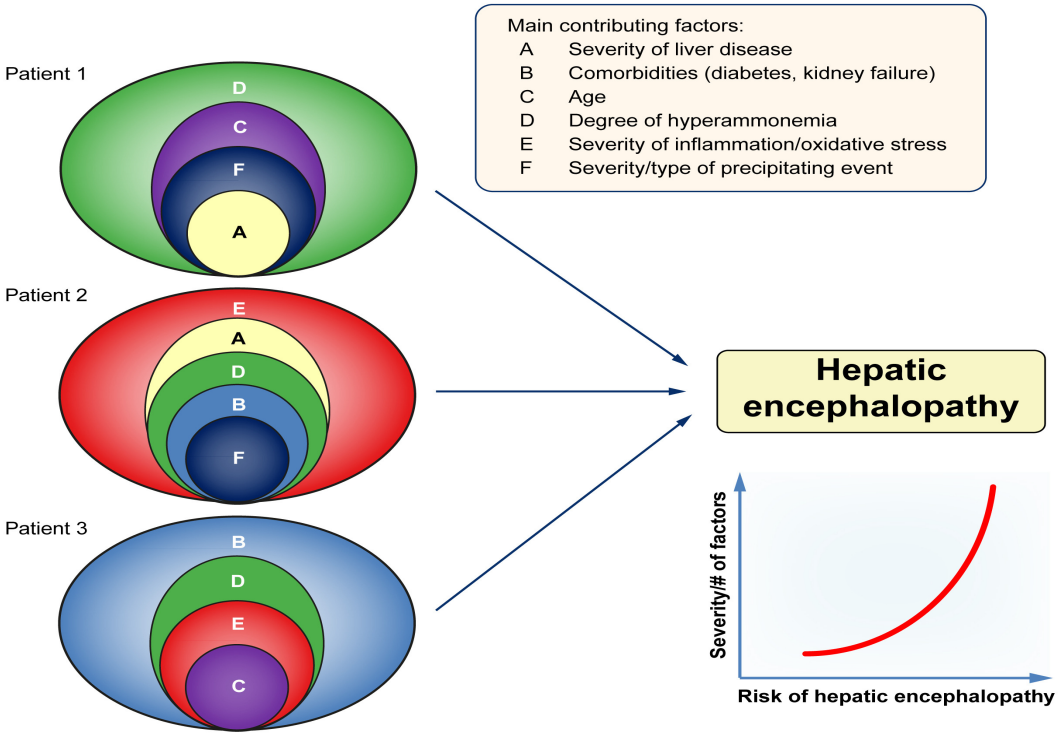
Bajaj JS et al. *Hepatology*. 2009;50:2014-2021.

MHE is Clinically Significant Disorder



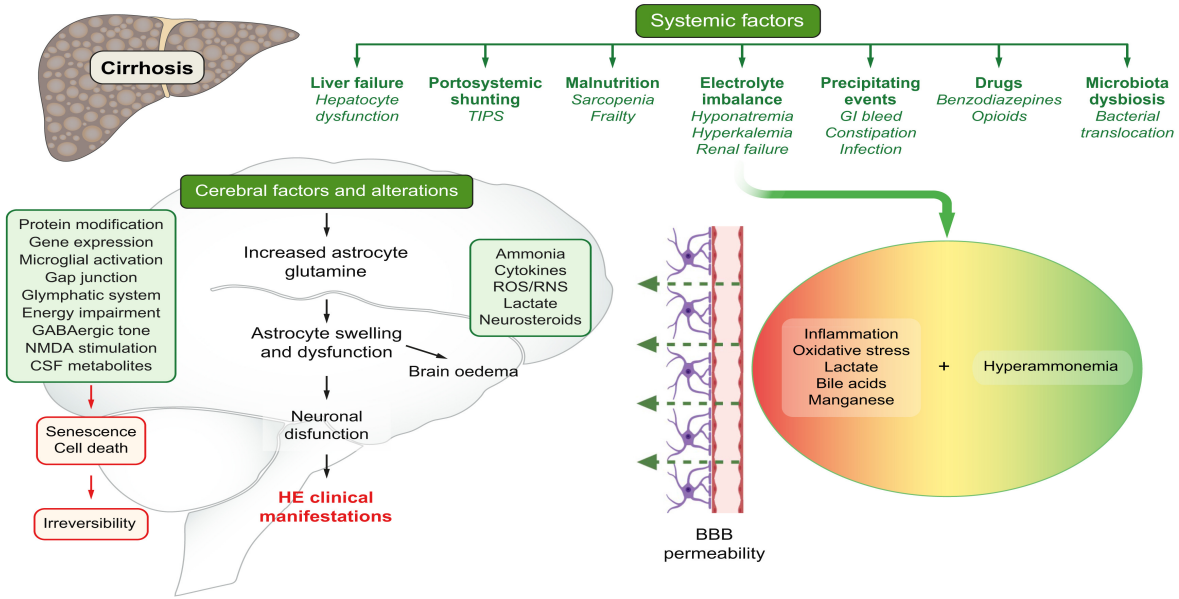
Agrawal S et al. *Journal of Clinical and Experimental Hepatology* 2015;5:S42–S48.

Brain dysfunction increases with cumulative pathogenic factors



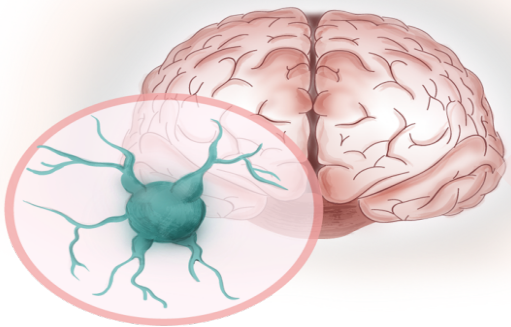
Journal of Hepatology 2020 731526-1547DOI: (10.1016/j.jhep.2020.07.013)

Pathogenesis and pathophysiology of hepatic encephalopathy



Journal of Hepatology 2020 731526-1547DOI: (10.1016/j.jhep.2020.07.013)

Precipitating Factors for HE



Increased ammonia production

GI hemorrhage

Excessive dietary protein

Blood transfusion

Electrolyte imbalance (eg, hypokalemia)

Constipation

Portosystemic shunts

Spontaneous

Iatrogenic (eg, TIPS)

Other

Drugs (eg, opioids, benzodiazepines)

Infections (eg, SBP)

Malignancy (eg, hepatoma)

Vilstrup H et al. *Hepatology*. 2014;60(2):714-735.

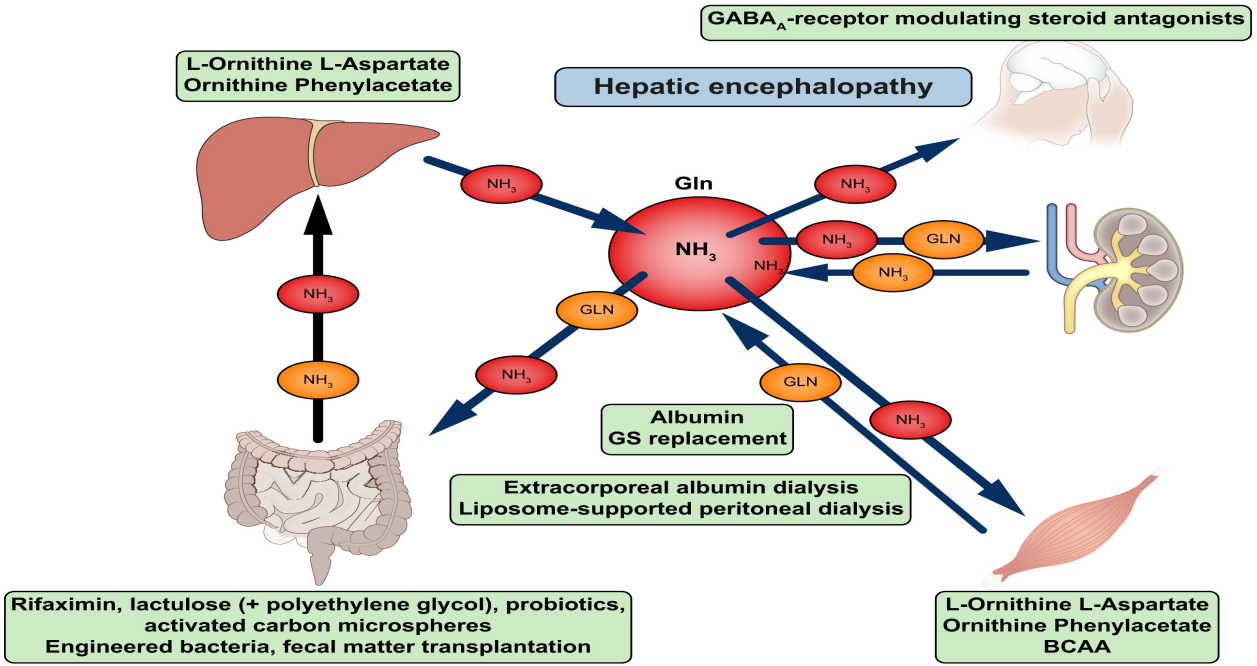
Role of Ammonia Testing in HE

"Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (GRADE II-3, A, 1)"[1]

Ammonia level>200 µmol/L is predictive of poor outcome in acute liver failure[2]

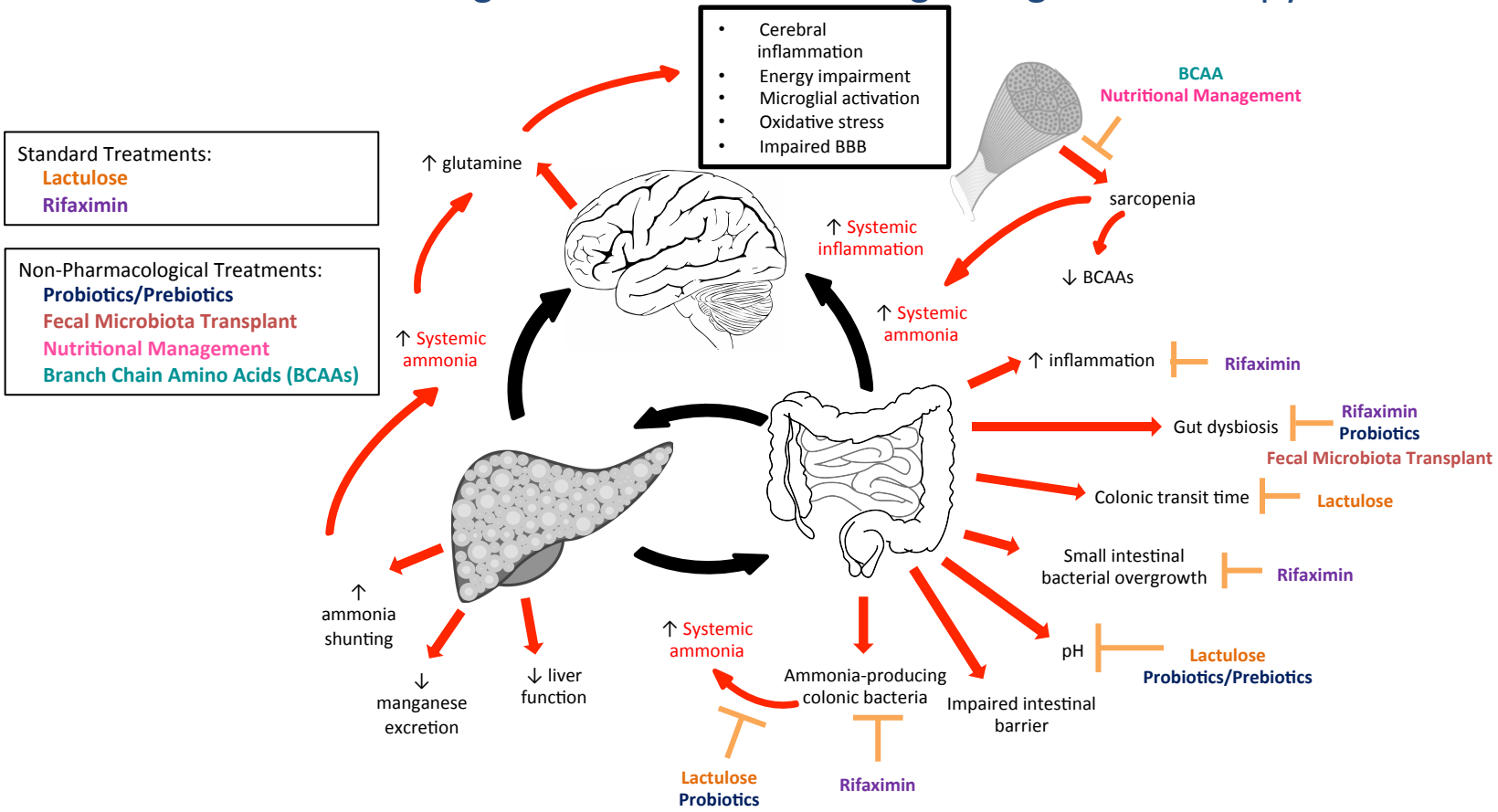
1. Vilstrup H et al. *Hepatology*. 2014;60(2):714-735; 2. Bernal W et al. *Hepatology*. 2007;46(6):1844-1852.

Therapeutic targets for hepatic encephalopathy



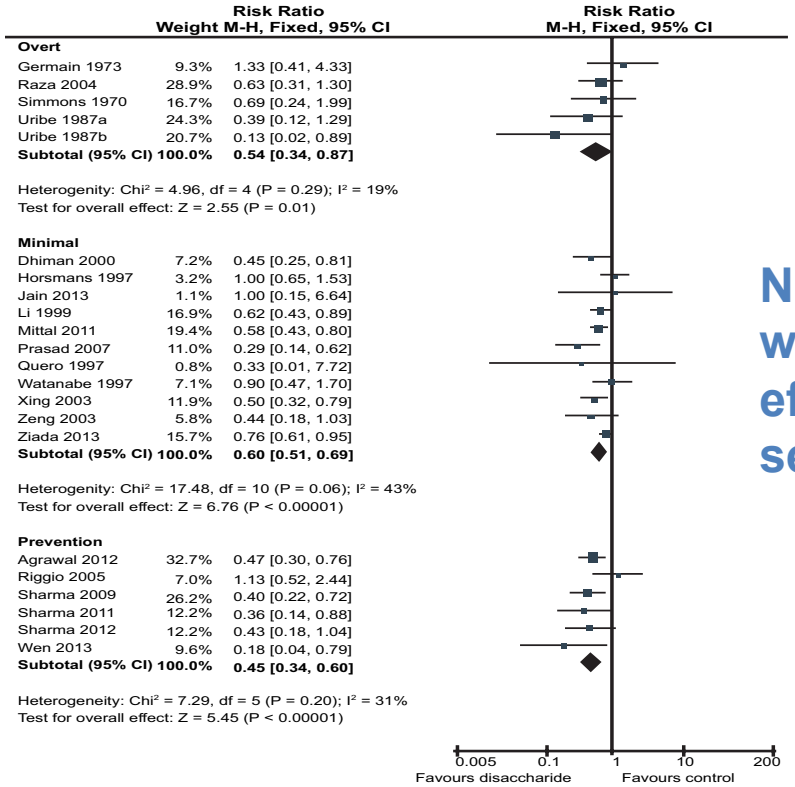
Journal of Hepatology 2020 731526-1547DOI: (10.1016/j.jhep.2020.07.013)

Pharmacologic and Non-Pharmacologic Targets of Therapy



Weir V and Reddy R, Clin Liver Disease 2020;24:243-61

Meta-Analysis of Lactulose for HE



Non-absorbable disaccharides were associated with beneficial effects on HE, mortality, and serious adverse events

Gludd LL et al. *Cochrane Database Syst Rev*. 2016;4:CD003044.

Practical Considerations for Use of Lactulose in HE

Dosage/Administration

- Administered orally, by mouth or through a nasogastric tube or via retention enemas[1,2]
- Initiated at 25 mL every 1-2 hours to achieve ≥2 soft of loose stools per day[2]

Safety

Key side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence[1,3]

1. Mullen KD, et al. *Semin Liver Dis*. 2007;27(Suppl 2):32-47; 2. Vilstrup H et al. *Hepatology*. 2014;60(2):714-735;
3. Patidar KR, Bajaj JS. *Clin Gastroenterol Hepatol*. 2015;12(12):2048-2061.

Rifaximin

Description

- Minimally absorbed (<0.4%) oral antibiotic[1,2]
- Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria[2]

Indication

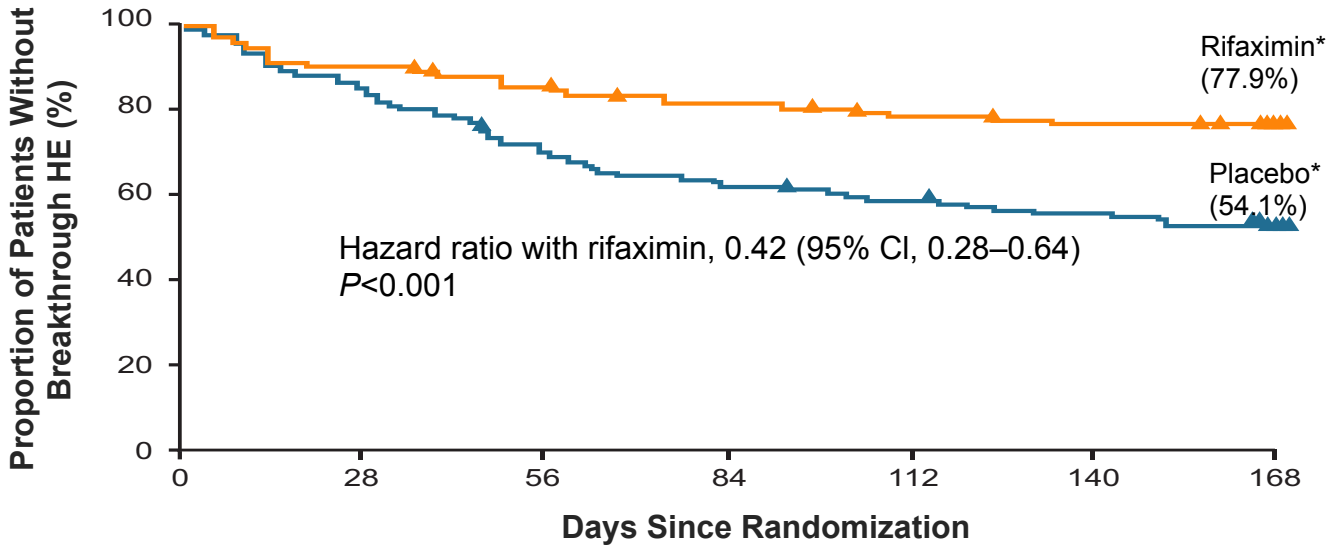
- 550 mg BID for reduction in risk of OHE in patients ≥18 years of age[2]

Safety

- No clinical drug interactions reported[2]
- No dosing adjustment required in patients with liver disease or renal insufficiency[2]

1. Sharma P, Sharma BC. *J Clin Exper Hepatol*. 2015;5:S82-S87; 2. Daily Med. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=53ba0e35-546f-6a7c-e054-00144ff8d46c. Accessed March 27, 2018.

Rifaximin Randomized, Controlled Trial: Time to First Breakthrough HE Episode Primary Endpoint



*Rifaximin 550 mg or placebo twice daily. 91% of patients in both arms received concomitant lactulose.

Bass NM et al. *N Engl J Med*. 2010;362:1071-1081.

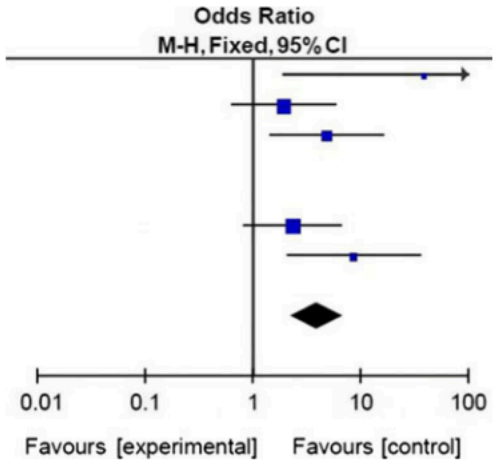
Probiotics

Improvement in minimal hepatic encephalopathy comparing probiotics and no treatment/placebo

Source	Probiotic		No treatment/placebo		Weight (%)	Risk Ratio, (95% CI)
Bajaj 2008	12	17	0	8	1.5%	38.64 [1.88, 794.36]
Liu 2004	10	20	12	35	33.0%	1.92 [0.63, 5.88]
Mittal 2011	14	40	4	40	19.7%	4.85 [1.43, 16.42]
Pereg 2011	0	18	0	18		Not estimable
Sanji 2011	0	21	0	22		Not estimable
Sharma 2014	16	32	9	30	35.1%	2.33 [0.82, 6.63]
Ziada 2013	14	26	3	25	10.7%	8.56 [2.04, 35.81]
Total (95% CI)		174		178	100.0%	3.91 [2.25, 6.80]
Total events	66		28			

Heterogeneity: $I^2 = 33\%$

Test for overall effect: Z = 4.84 (P < 0.00001)



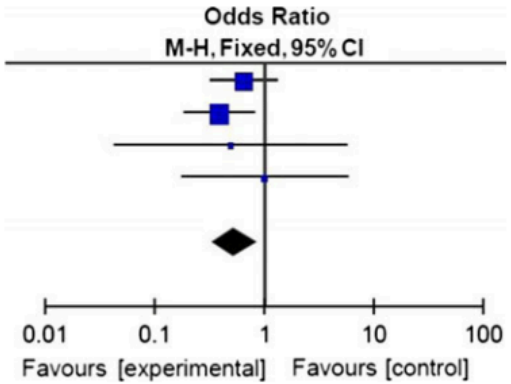
Saab et al Liver Int. 2016

Hospitalization comparing probiotics and no treatment/placebo

Source	Probiotic		No treatment/placebo		Weight (%)	Risk Ratio, (95% CI)
Agrawal 2012	21	64	28	65	41.1%	0.65 [0.32, 1.32]
Dhiman 2014	16	66	29	64	49.1%	0.39 [0.18, 0.82]
Mittal 2011	1	40	2	40	4.3%	0.49 [0.04, 5.60]
Pereg 2011	3	18	3	18	5.5%	1.00 [0.17, 5.77]
Total (95% CI)		188		187	100.0%	0.53 [0.33, 0.86]
Total events	41		62			

Heterogeneity: $I^2 = 0\%$

Test for overall effect: Z = 2.57 (P = 0.01)



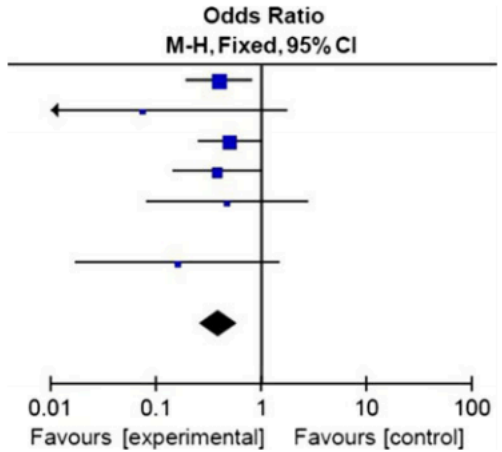
Saab et al Liver Int. 2016

Improvement on progression or worsening hepatic encephalopathy comparing probiotics and no treatment/placebo

Source	Probiotic		No treatment/placebo		Weight (%)	Risk Ratio, (95% CI)
Agrawal 2012	22	64	37	65	33.6%	0.40 [0.19, 0.81]
Bajaj 2008	0	17	2	8	4.5%	0.07 [0.00, 1.76]
Dhiman 2014	23	66	33	64	30.5%	0.50 [0.25, 1.02]
Lunia 2014	7	86	14	74	19.3%	0.38 [0.14, 1.00]
Mittal 2011	2	40	4	40	5.3%	0.47 [0.08, 2.75]
Pereg 2011	0	18	0	18		Not estimable
Ziada 2013	1	26	5	25	6.8%	0.16 [0.02, 1.48]
Total (95% CI)		317		294	100.0%	0.40 [0.26, 0.60]
Total events	55		95			

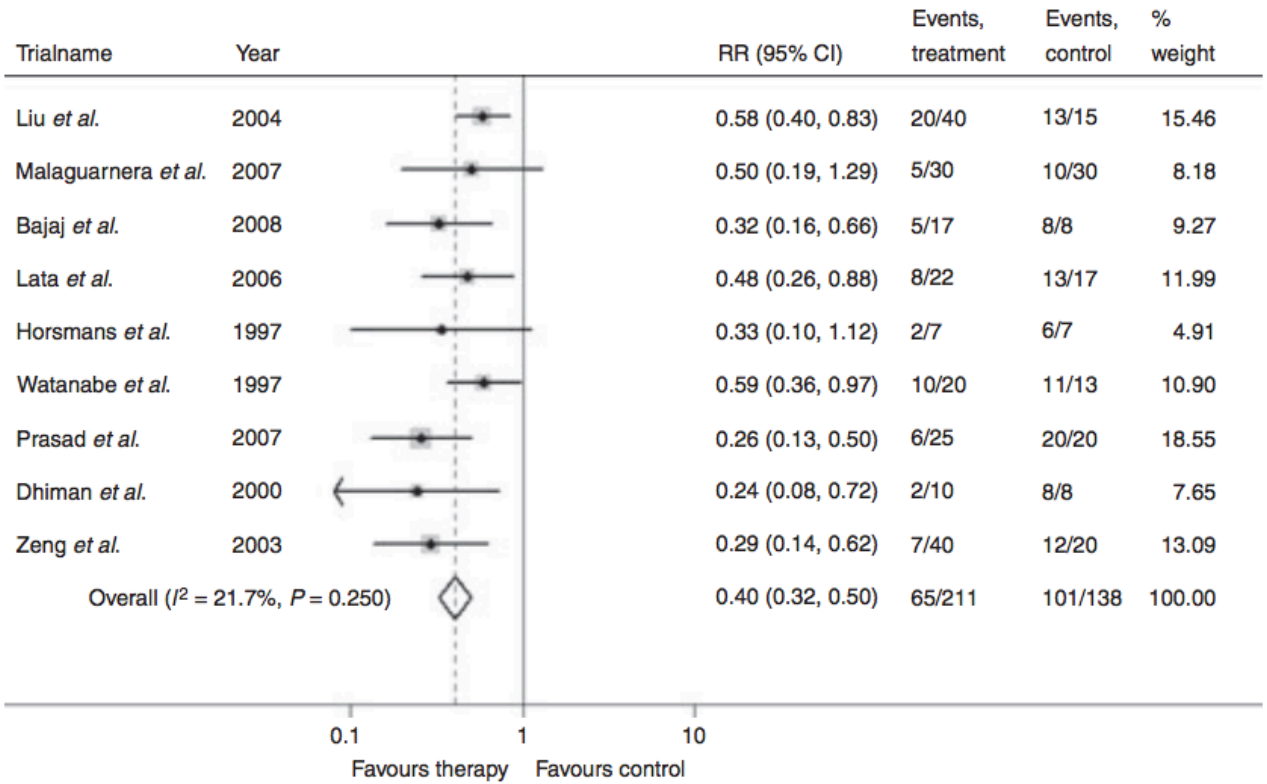
Heterogeneity: $I^2 = 0\%$

Test for overall effect: Z = 4.33 (P < 0.0001)



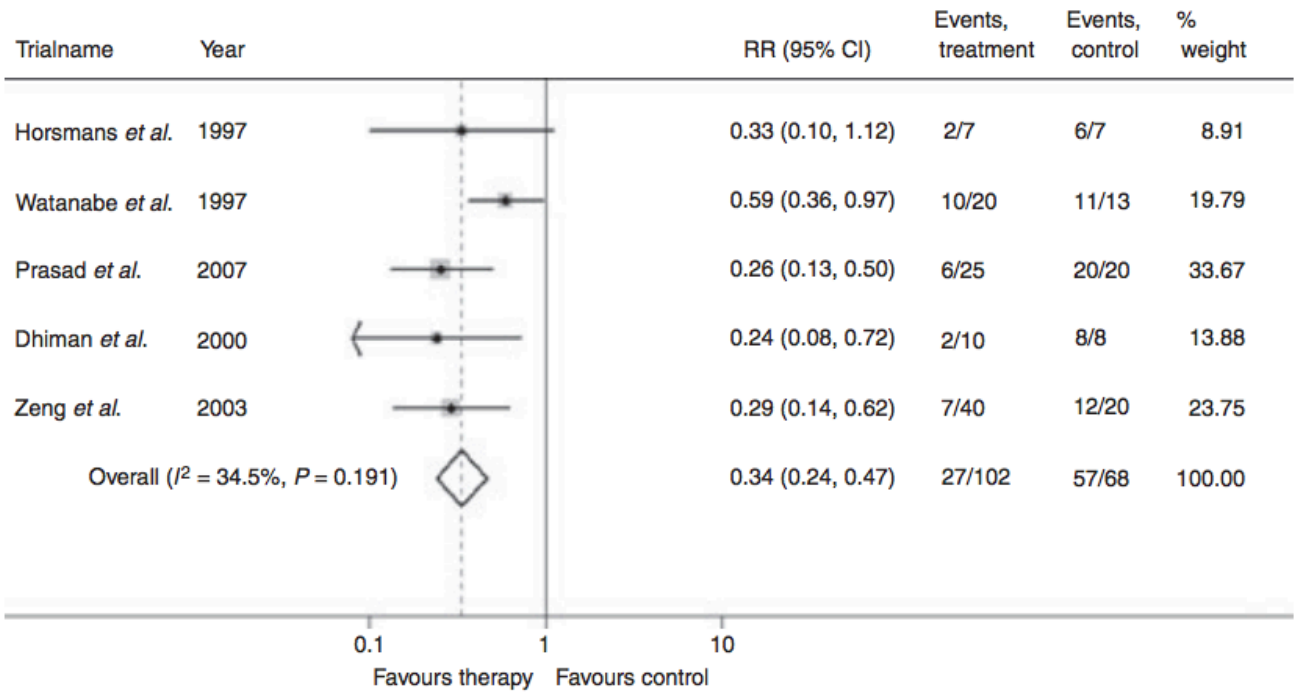
Saab et al Liver Int. 2016

Number of patients without improvement of MHE in trials with prebiotics, probiotics and synbiotics compared with control



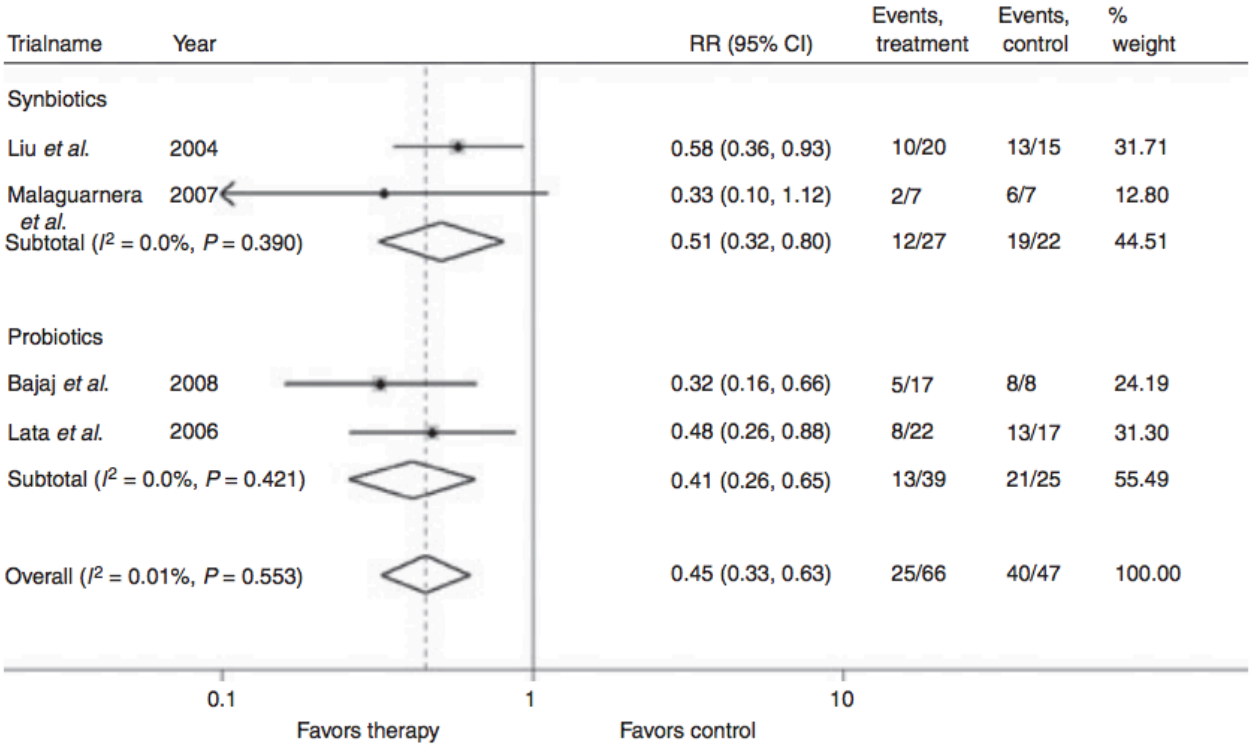
Shukla et al Aliment Pharmacol. 2011

Number of patients without improvement of MHE in trials with Lactulose compared with control



Shukla et al Aliment Pharmacol. 2011

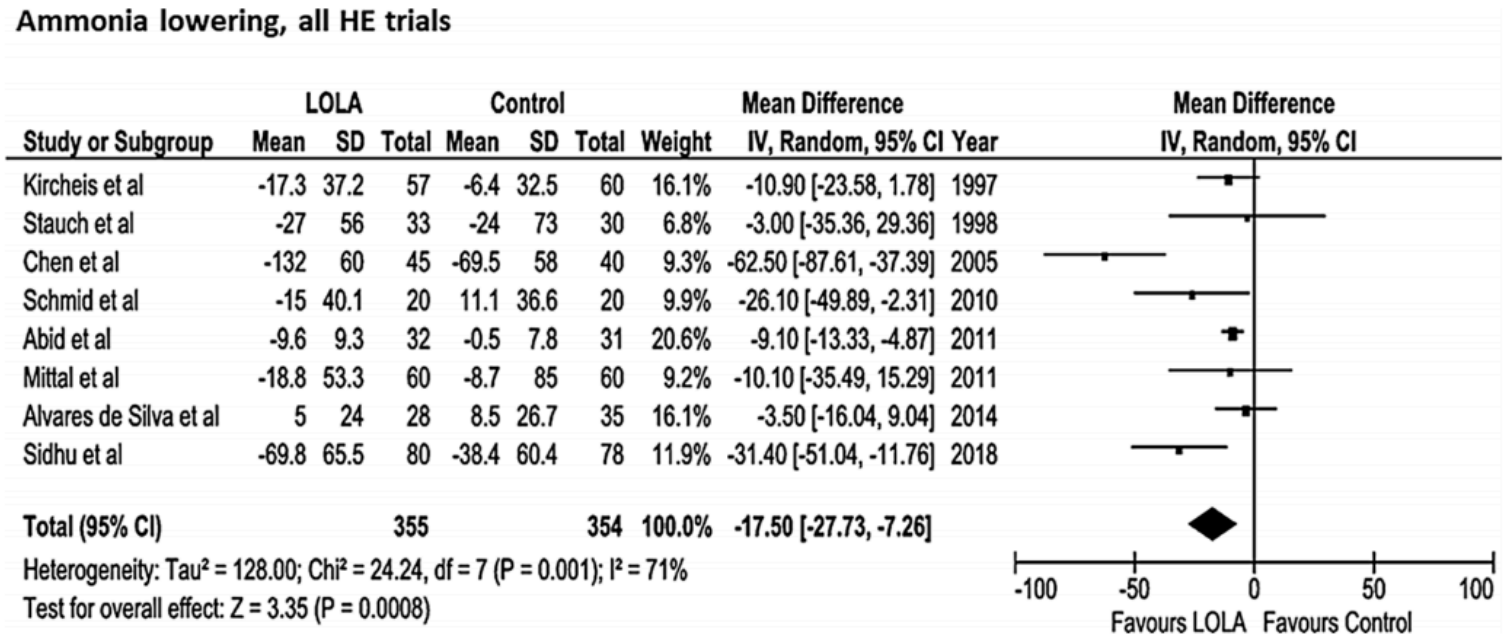
Number of patients without improvement of MHE in trials with synbiotics and probiotics compared with control



Shukla et al Aliment Pharmacol. 2011

L-Ornithine L-Aspartate (LOLA)

LOLA-ammonia lowering, all HE trials



Butterworth &McPhail Drugs 2019

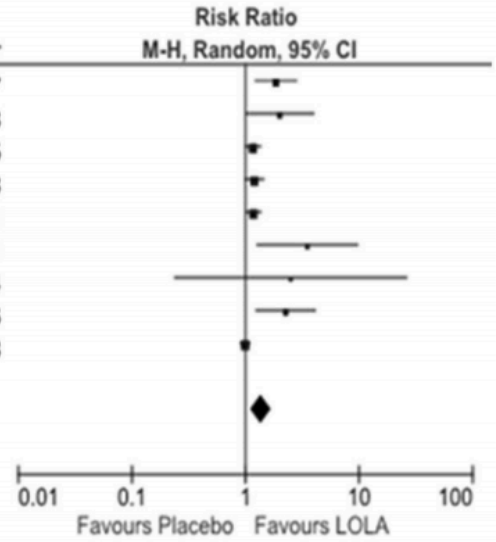
LOLA-Improvement of mental state, HE

a All HE trials, either formulation

Study	LOLA Events	LOLA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kircheis et al	37	63	20	63	11.2%	1.85 [1.22, 2.81]	1997
Stauch et al	17	34	8	32	6.5%	2.00 [1.01, 3.98]	1998
Chen et al	43	45	33	40	17.4%	1.16 [0.99, 1.35]	2005
Ahmad et al	37	40	31	40	16.7%	1.19 [0.99, 1.44]	2008
Abid et al	55	60	47	60	17.5%	1.17 [1.00, 1.36]	2011
Mittal et al	14	40	4	40	3.6%	3.50 [1.26, 9.72]	2011
Alvares de Silva et al	2	28	1	35	0.8%	2.50 [0.24, 26.17]	2014
Sharma et al	21	31	9	30	7.7%	2.26 [1.24, 4.11]	2016
Sidhu et al	76	83	73	79	18.6%	0.99 [0.90, 1.09]	2018
Total (95% CI)		**424**		**419**	**100.0%**	**1.36 [1.10, 1.69]**	
Total events	302		226				

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 48.38$, $df = 8$ ($P < 0.00001$); $I^2 = 83\%$

Test for overall effect: $Z = 2.82$ ($P = 0.005$)



Butterworth &McPhail Drugs 2019

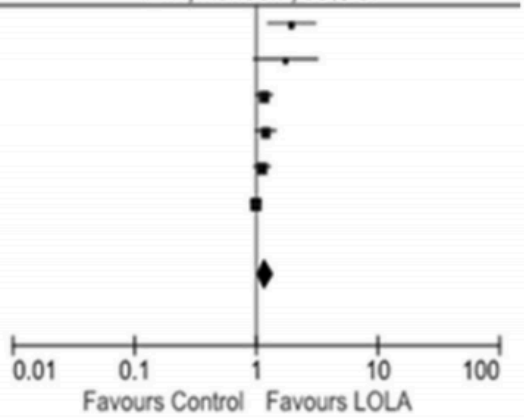
LOLA-Improvement of mental state, OHE

b OHE, either formulation

Study	Control Events	Control Total	LOLA Events	LOLA Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kircheis et al	28	37	14	36	8.4%	1.95 [1.24, 3.05]	1997
Stauch et al	16	23	8	20	5.5%	1.74 [0.95, 3.17]	1998
Chen et al	43	45	33	40	21.1%	1.16 [0.99, 1.35]	2005
Ahmad et al	37	40	31	40	19.3%	1.19 [0.99, 1.44]	2008
Abid et al	49	54	44	54	21.3%	1.11 [0.96, 1.30]	2011
Sidhu et al	76	83	73	79	24.4%	0.99 [0.90, 1.09]	2018
Total (95% CI)		**282**		**269**	**100.0%**	**1.19 [1.01, 1.39]**	
Total events	249		203				

Heterogeneity: Tau² = 0.02; Chi² = 20.10, df = 5 (P = 0.001); I² = 75%

Test for overall effect: Z = 2.14 (P = 0.03)



Butterworth &McPhail Drugs 2019

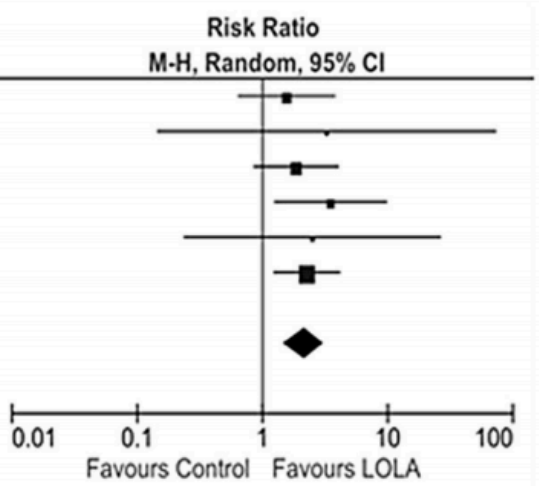
LOLA-Improvement of mental state, MHE

a MHE, either formulation

Study	LOLA Events	LOLA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kircheis et al	9	26	6	27	18.3%	1.56 [0.65, 3.76]	1997
Stauch et al	1	11	0	12	1.5%	3.25 [0.15, 72.36]	1998
Abid et al	6	6	3	6	24.1%	1.86 [0.86, 4.01]	2011
Mittal et al	14	40	4	40	13.7%	3.50 [1.26, 9.72]	2011
Alvares de Silva et al	2	28	1	35	2.6%	2.50 [0.24, 26.17]	2014
Sharma et al	21	31	9	30	39.8%	2.26 [1.24, 4.11]	2016
Total (95% CI)		**142**		**150**	**100.0%**	**2.15 [1.48, 3.14]**	
Total events	53		23				

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.70$, df = 5 (P = 0.89); $I^2 = 0\%$

Test for overall effect: Z = 3.98 (P < 0.0001)



Butterworth &McPhail Drugs 2019

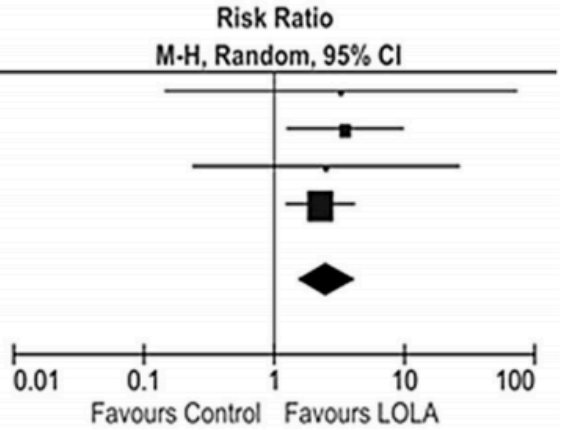
LOLA-Improvement of mental state, MHE

b MHE, oral formulation

Study	LOLA Events	LOLA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Stauch et al	1	11	0	12	2.6%	3.25 [0.15, 72.36]	1998
Mittal et al	14	40	4	40	23.7%	3.50 [1.26, 9.72]	2011
Alvares de Silva et al	2	28	1	35	4.5%	2.50 [0.24, 26.17]	2014
Sharma et al	21	31	9	30	69.2%	2.26 [1.24, 4.11]	2016
Total (95% CI)		**110**		**117**	**100.0%**	**2.54 [1.54, 4.18]**	
Total events	38		14				

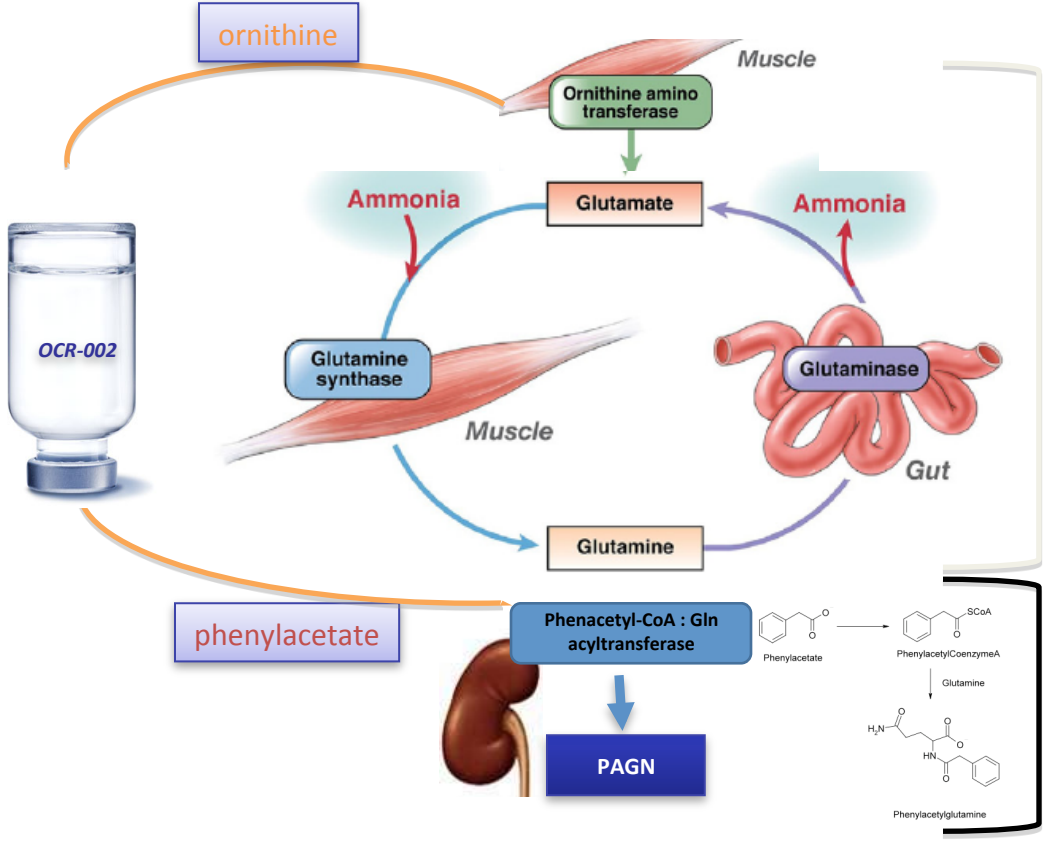
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.58$, df = 3 (P = 0.90); $I^2 = 0\%$

Test for overall effect: Z = 3.67 (P = 0.0002)



Butterworth &McPhail Drugs 2019

OCR-002 (Ornithine Phenylacetate) Uses Physiological Pathway to Eliminate Nitrogen

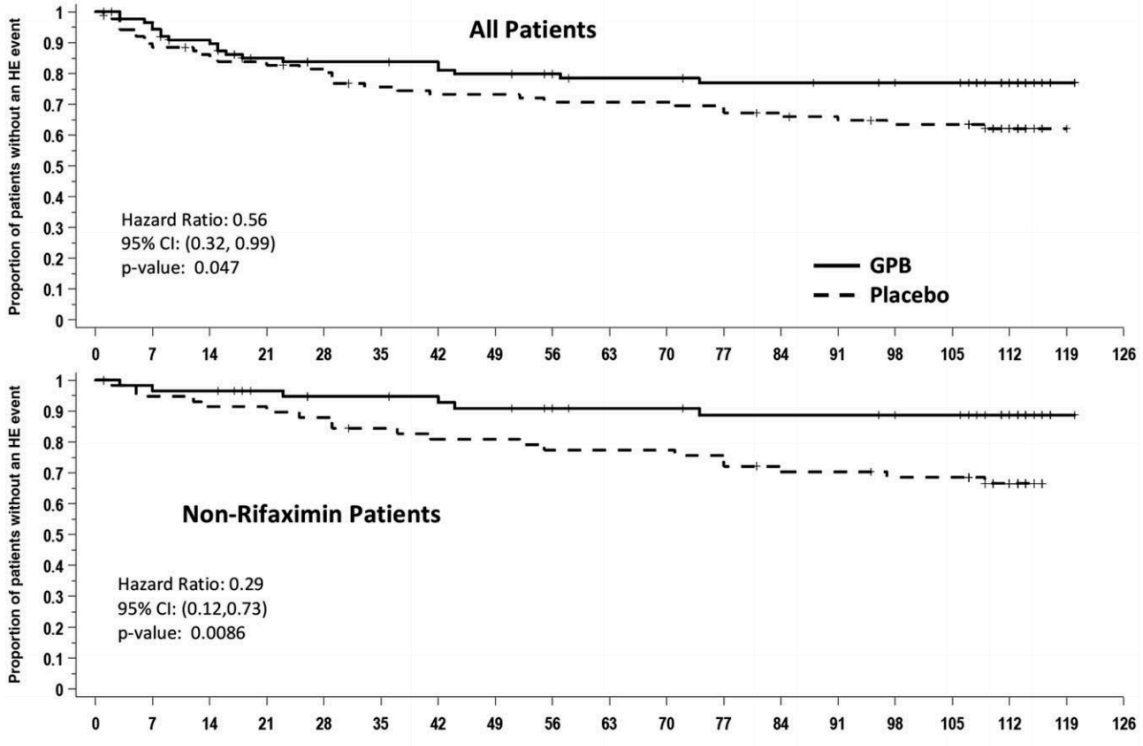


Upregulation of orn – gln

Shifts ammonia into less toxic form of glutamine

Active secretion of glutamine in urine

Glycerol Phenylbutyrate in Hepatic Encephalopathy



Rockey et al Hepatology 2014

Branched Chain Amino Acids (BCAA)

Possible Targets of BCAA Supplementation in the Treatment of Chronic Liver Disease

Prevention and treatment of cachexia

- Stimulates protein synthesis (improves muscle mass)
- Inhibits proteolysis
- Improves insulin resistance and β-cell function

Repair and regeneration of injured liver

- Energy/protein source
- Enhances production of glutamine – stimulates liver regeneration
- Stimulates hepatocyte growth factor by hepatic stellate cells
- Suppresses angiogenesis and HCC carcinogenesis

Prevention and treatment of encephalopathy

- Facilitates ammonia detoxification (through glutamine synthetase) in skeletal muscle and brain
- Normalizes Fischer's ratio – decrease brain influx of AAA
- Improves CBF

Improvement of quality of life, liver functions and survival ?

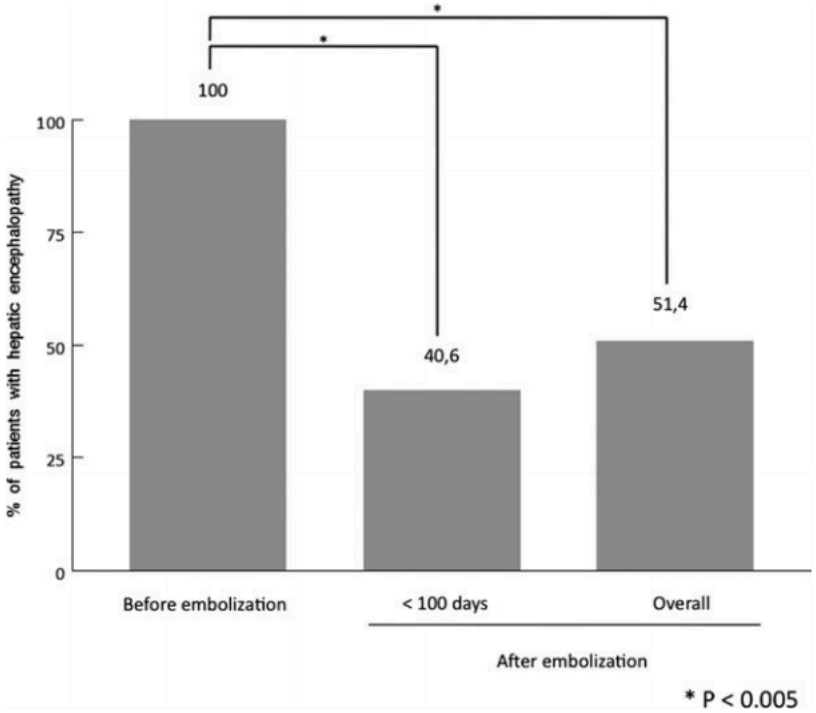
Adapted from Holecek M. Nutrition 2010 and Kawaguchi T, et al. Hepatology 2011

RCT: Oral BCAA for Cirrhotic Patients

Study	Patients	Interventions	Outcomes
Cochrane meta-analysis 2003	**11 RCTs* N=556**	**BCAA vs any kind of control FU 6-30 d**	• **↓ HE: RR 1.31 (1.04-1.66)** • **Survival ↔: RR 1.06 (0.98-1.14)** • **AEs ↔: RR 0.97 (0.41-2.31)**
Marchesini et al. (Gastro 2003)	Cirrhosis CP-B/C N=174	BCAA (14.4 gm/d) vs LAB vs MDX FU 1 yr	• ↓ Major events: OR 0.43 (0.19-0.96) vs LAB; OR 0.51 (0.23-1.17) vs MDX • Improved liver functions • ↓ Hospitalization, ↑ HRQoL • Rx adherence 75%
Muto et al. (CGH 2005)	Cirrhosis CP-A/B/C N=646	BCAA 12 gm/d vs CD (protein 1-1.4 gm/kg/d) FU 2 yr	• ↓ Major events: HR 0.67 (0.49-0.93) • ↑ Albumin, ↑ HR-QOL • Rx adherence 90%
Les et al. (AJG 2011)	Cirrhosis w/ previous HE N=116	BCAA 30 gm/d vs MDX FU 56 wk	• ↔ HE-free survival: 47% vs 34%, p=ns • Improved minimal HE, ↑ muscle mass • Hospitalization ↔, LOS ↔, AEs ↔

* Small, short FU, low methodological quality; LAB, lactoalbumin; MDX, maltodextrins; CD, conventional diet

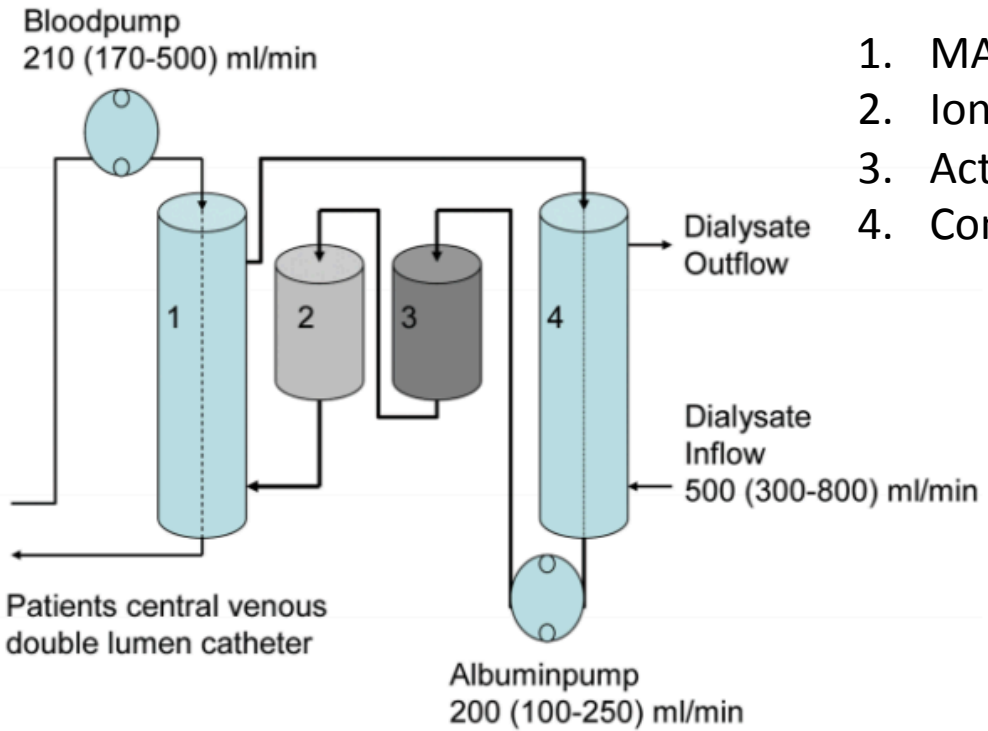
Short- and long-term efficacy of Spontaneous Porto-Systemic Shunt (SPSS)-embolization in the occurrence of HE



Laleman et al Hepatology 2013

Molecular Adsorbent Recirculating System (MARS) Device

Molecular Adsorbent Recirculating System (MARS) Device



1. MARS Flux
2. Ion Exchange Resin Column (IE 250)
3. Activated Charcoal Column (AC 250)
4. Conventional Dialysis Column (DiaFlux)

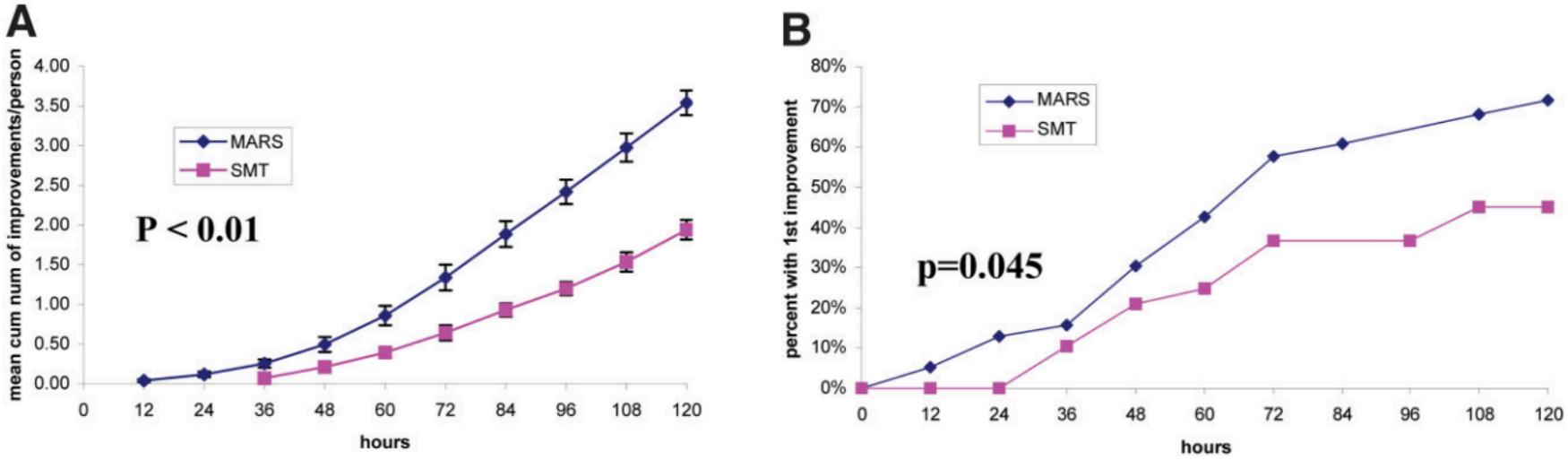
Hassanein et al Hepatology 2007

Elements dialyzed with the MARS therapy organized according to affinity

Water-soluble	Albumin-bound
• Ammonia • Urea • Creatinine	• Bilirubin (indirect, principally) • Bile acids • Tryptophan • Fatty acids (middle- and short-chained) • TNF-a, IL-6 • Copper • Benzodiazepines (diazepam, principally)

Ramón et al Ann Hepatol. 2011

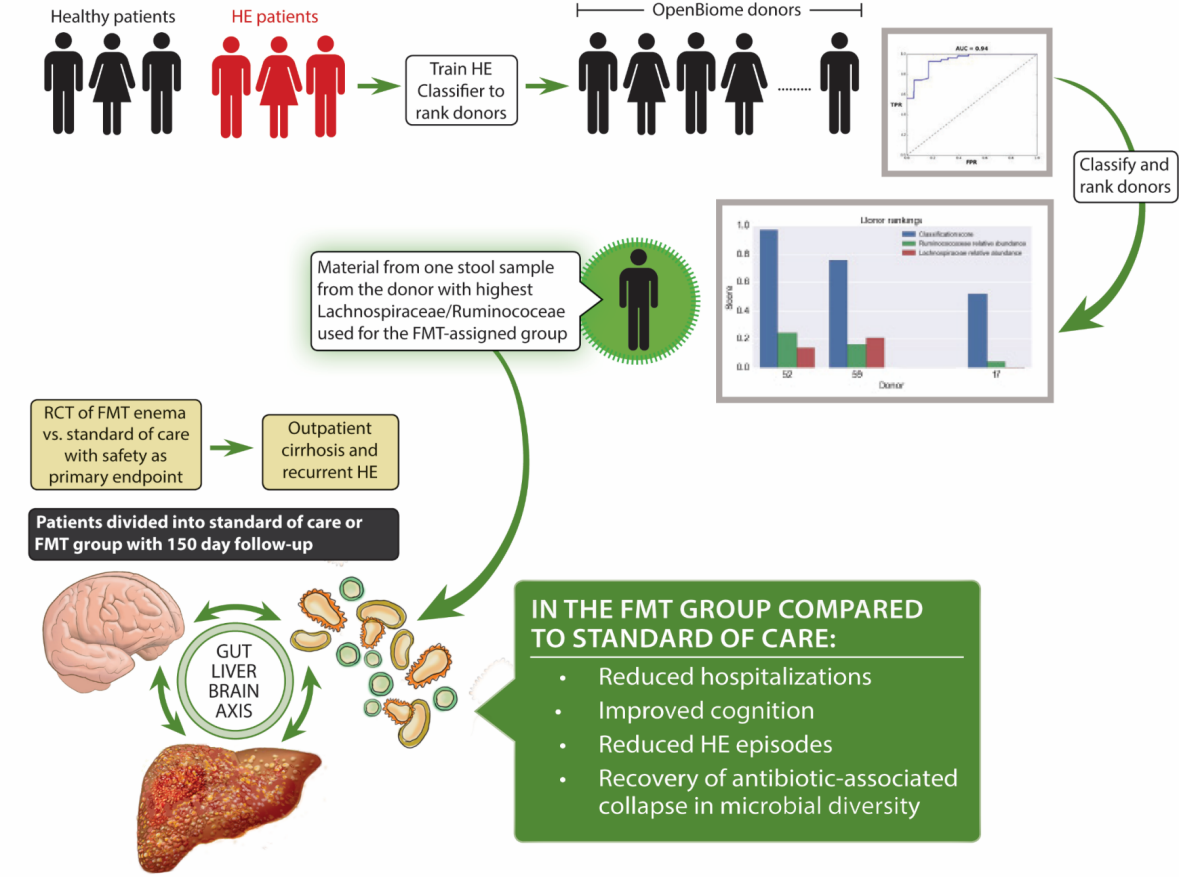
Mean cumulative number of improvements per person and time to first improvement in ECAD vs. SMT

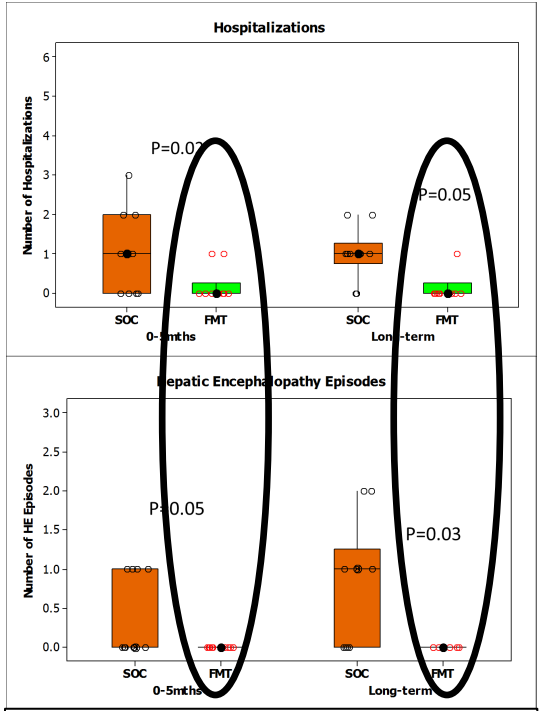


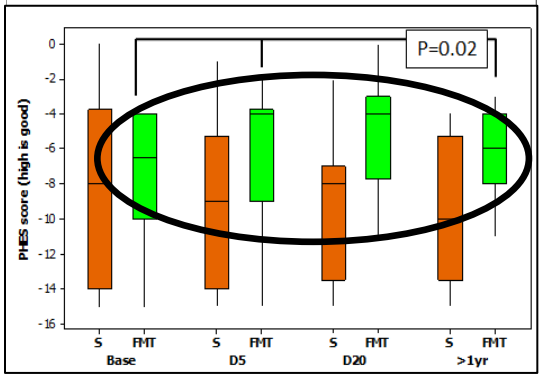
Hassanein et al Hepatology 2007

FMT

Enema FMT is safe short-term and long-term

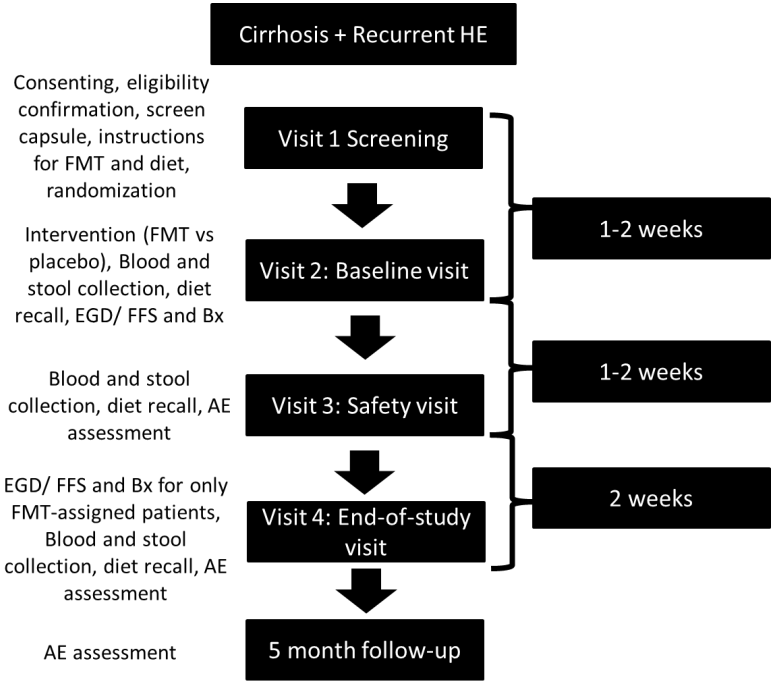


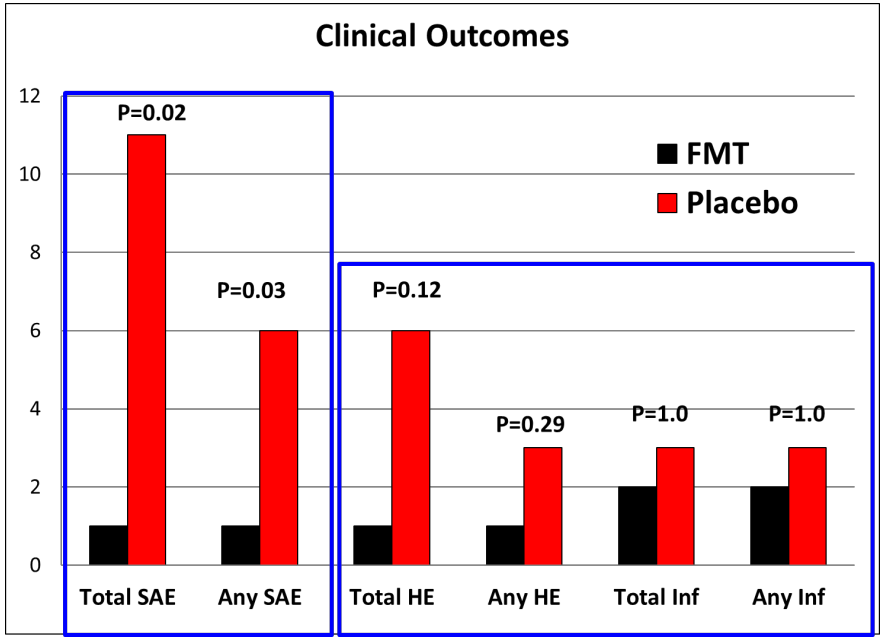




Bajaj et al Hepatology 2017, Bajaj et al Gastro 2019

Oral capsular FMT is safe and shows benefit in HE





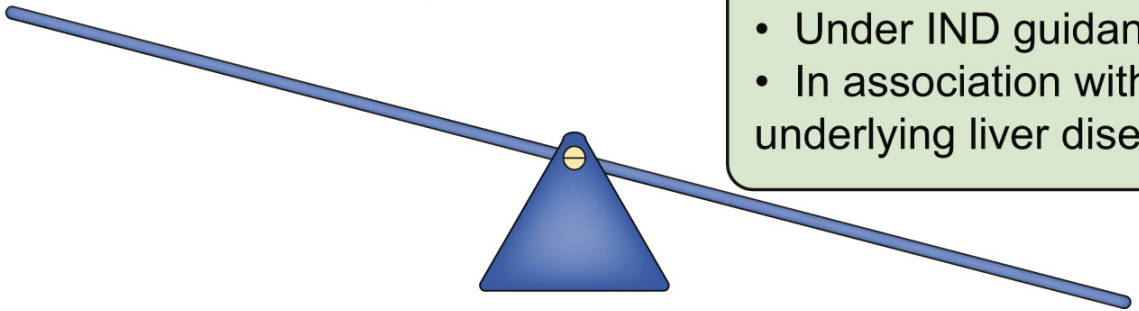
Bajaj JS et al Hepatology 2019

Clinical Equipoise

Risk benefit ratio for intestinal microbiota transplantation in chronic liver disease

Risk high

- Safety
- Availability
- Dose/route clarity
- Transmission of other traits
- Acceptability



Benefit high

- No alternatives available
- Additive to current therapies
- Under IND guidance
- In association with treatment of underlying liver disease

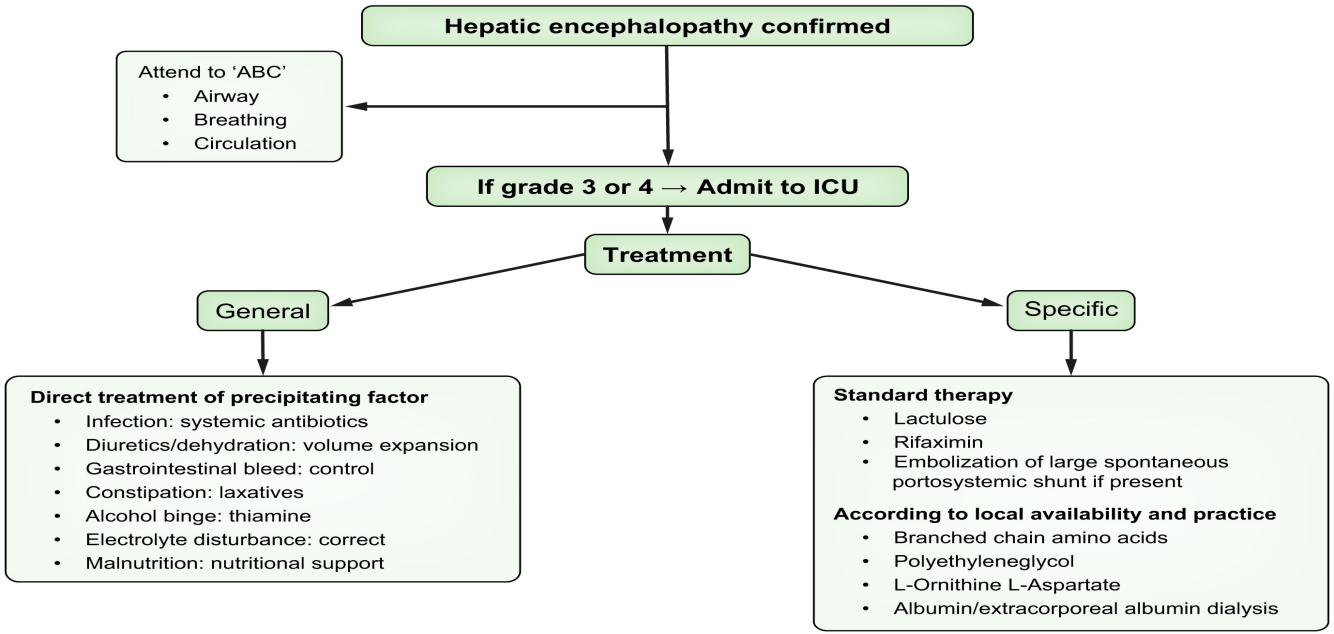
Bajaj, Khoruts J Hepatol 2020

Pre-Clinical Studies

- Liposome-supported Peritoneal Dialysis
- Engineered Bacteria
- Activated carbon microspheres
- GABA modulating steroid antagonists
- Glutamine synthetase replacement

Journal of Hepatology 2020 731526-1547DOI: (10.1016/j.jhep.2020.07.013)

Algorithm for the management of a hospitalized patient with overt hepatic encephalopathy



Journal of Hepatology 2020 731526-1547DOI: (10.1016/j.jhep.2020.07.013)