Hepatic encephalopathy in clinical practice - more than just brain fog – a typical case presentation

Liver webinar march 11, 2021

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Disclaimer:

This talk was prepared by the presenting author and reflects his own opinion.

Disclosures:

Jörg Petersen has received honoraria for presentations and/or Advisory Boards from AbbVie, Arrowhead, Assembly Pharma, BMS, Contravir, Falk, Gilead, GSK, Hepion, Intercept, Janssen, Merck/MSD, Merz, Novira, Roche, Shionogi, Shire, Takeda.

Case

- 48 yo male from Croatia, 94 kg, 179 cm, smoker, BMI 29,2
- COVID-19 positive Apr 2020, ventilation therapy for 12 days
- After hospitalisation first presentation ambulatory care at IFI institute:
- „Moderate“ alcohol intake
- Diabetes mellitus II, Hypercholesterolemia
- Medication: Spironolacton 100mg QD, Carvedilol 6,25 mg BID, Metformin 850mg BID, Rosuvastatin 5mg QD, Ibuprofen occasionally (backpain)
- ALT 80, AST 85, GGT 178, AP 116, Platelets 100/nl, total Bilirubin 1,2 mg/dl, Albumin 3,5 g/l, INR normal range
- Ultrasound Abdomen : Steatosis and cirrhosis, hepatomegaly, splenomegaly
- Upper endoscopy: esophagal varices I-II ° , no red spots
- **Child Pugh A (6)**

Case fatality rates from different points in the disease course following SARS-CoV-2 infection according to stage of liver disease

	Case fatality rate		
	Once hospitalised	Once admitted to ICU	Once receiving Invasive ventilation
CLD without cirrhosis	8%	20%	21%
CTP-A	22%	40%	52%
CTP-B	39%	62%	74%
CTP-C	54%	79%	90%

Key point

There are diminishing chances of survival as CLD patients require increasing levels of medical support

And...

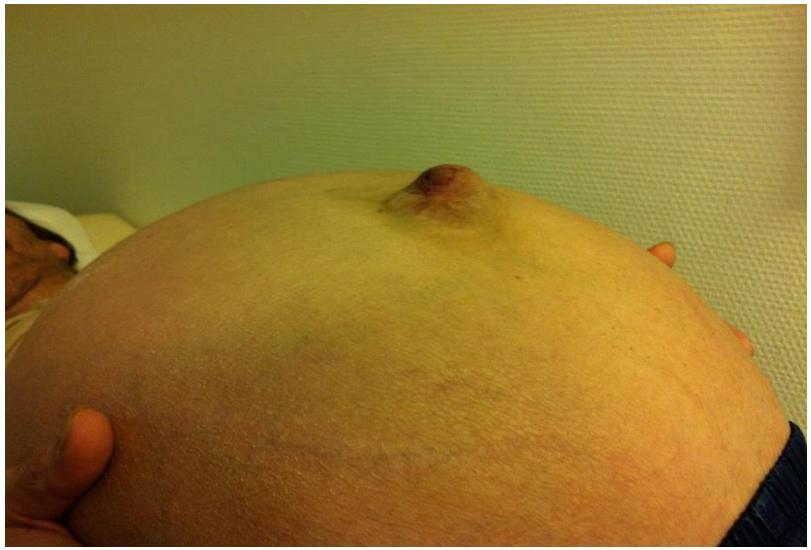
Diminishing chances with more severe baseline liver disease

Thomas Marjot, University of Oxford, ILC digital 2020

COVID-Hep and SECURE-cirrhosis data unpublished as of 14th Aug

Case

- Three months later…
- AST 165 U/l, ALT 98U/l, GGT 292 U/l, Hb 10,6mg/dl, **Platelet 80/nl**, leukocytes 9,8/nl, HbA1c 6,5%, **Albumine 3,1 g/dl**, **total bilirubine 1.7mg/dl, INR 1,4, Creatinine 1,3 mg/dl**, **AFP 28 ug/l**
- „no regular work, started drinking (again), did not take care of myself at all..“
- Ultrasound: Ascites +++, no tumor appearance (MRI neither)
- Ascites: 8l, not entirely clear, albumine substitution, neutrophil count and total leucocytes in ascites fluid elevated



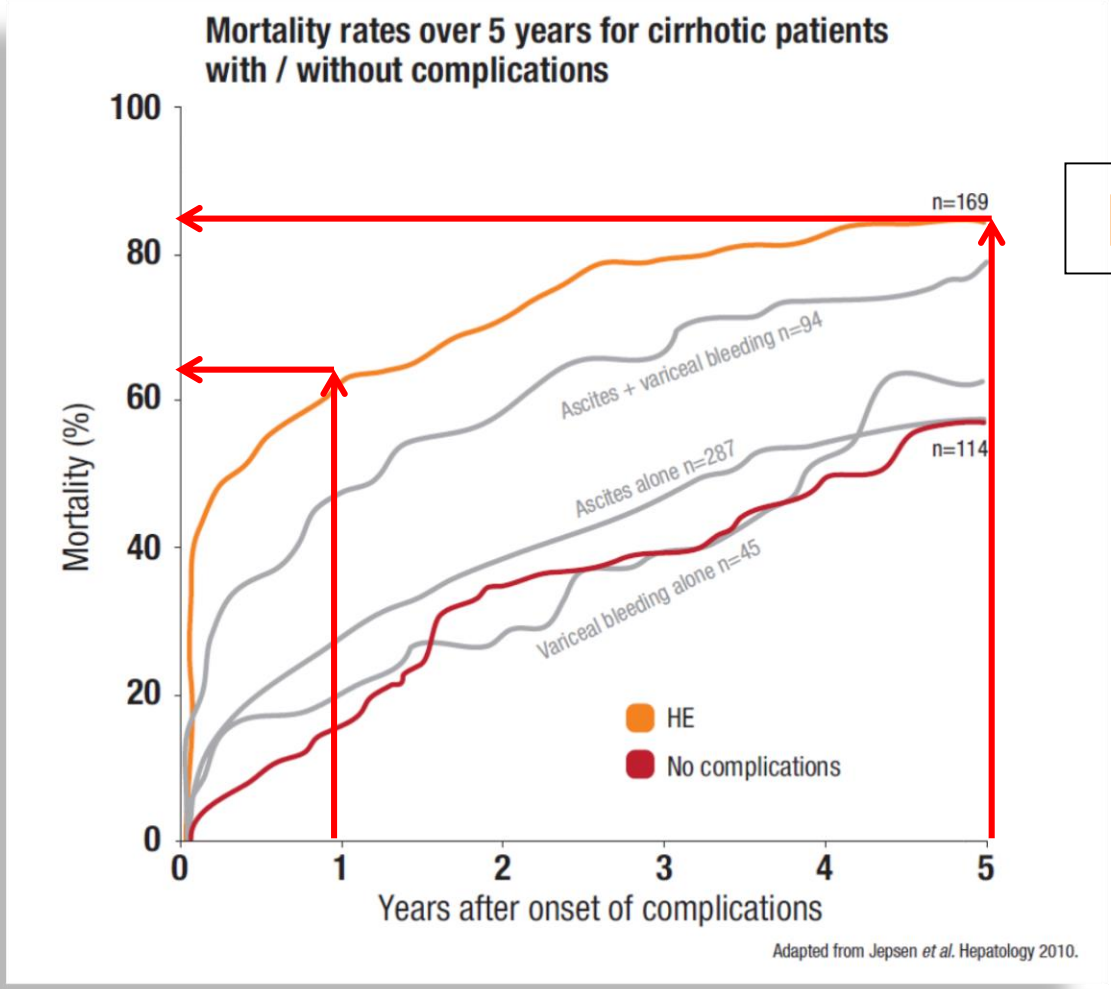
Case

- Ceftriaxon 2g iv QD (SBP), secondary prophylaxis with norfloxacin 400mg QD
- Other medication: Metformin 850mg TID, Rosuvastatin 5mg QD, Spironolacton 100mg QD, Ibuprofen, Carvedilol 6,25 mg TID
- Torasemid 10mg TID
- Nutrition and dietary counseling, no alcohol intake, daily weight protocol

Case

- Ascites well controlled, patient went finally even back to work (warehouse worker)
- Child Pugh B (7)
- Patients wife:
  - “falling asleep during daytime”, “ showing less physical activity”
  - patient denied that, driving his car every day 15 km to work….

Mortality rates in cirrhotic patients w/wo complications



HE

HE - Symptoms

Often late diagnosed

Patient:

- „Fatigue“
- „Problems to concentrate“
- „altered sleep pattern“…..

Relatives / friends:

- Change of character
- Behaviour changes as being more aggressive or showing inattention
- Reported problems at work

Important to include relatives / friends for history and diagnosis of HE

HE – diagnosis in clinical practice

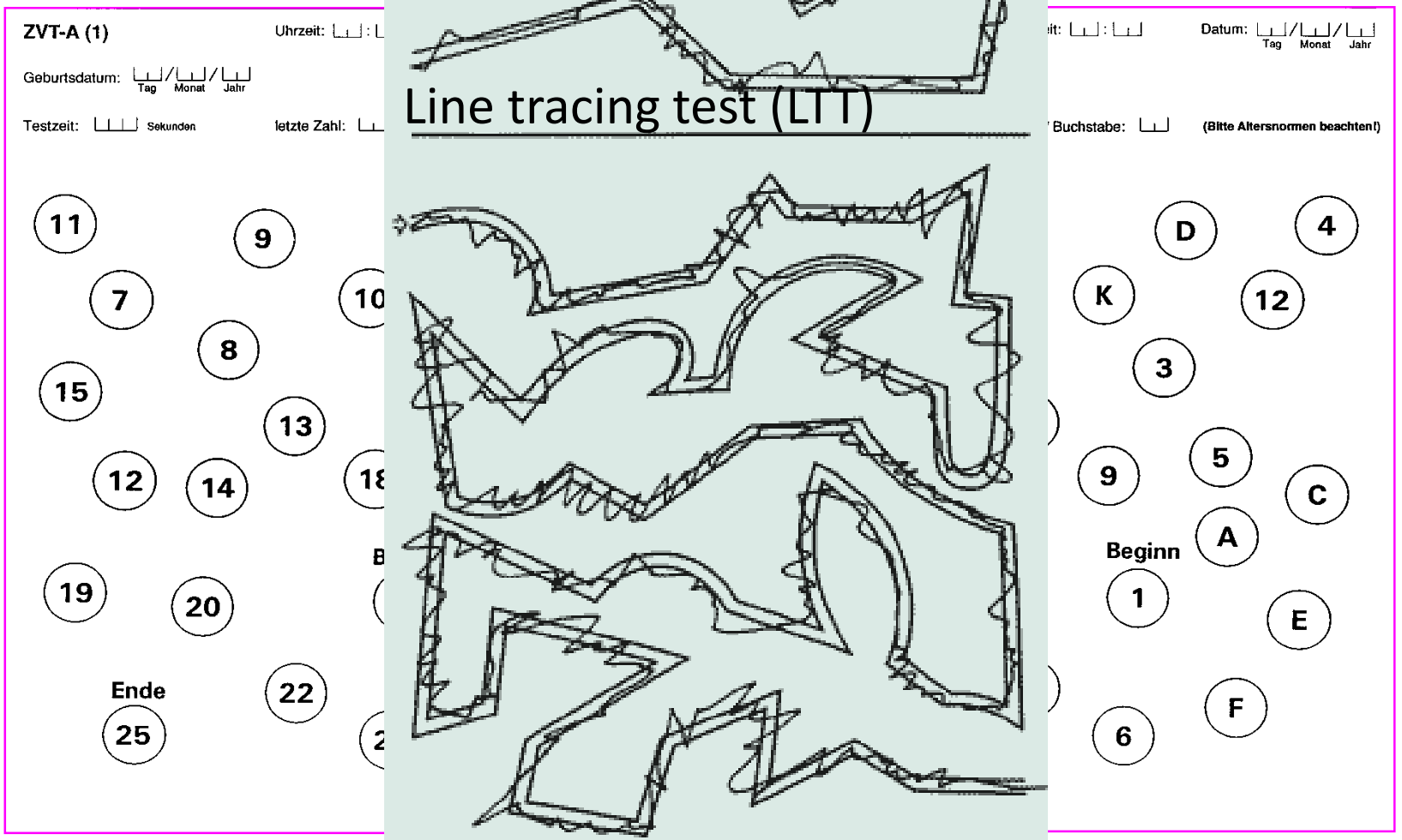
Not overt HE – difficult to diagnose grade I
(and sometimes grade II)

- Clinical impression
- Psychometric tests
- Lab for reasoning of HE
- No routine ammonium levels – correlation problems
- Critical flicker frequency CFF
- West Haven Criteria

Grades of Hepatic Encephalopathy (West Haven Criteria)		
Covert	**Grade 1**	Inattention, euphoria/ anxiety, **altered sleep pattern**, ↓attention span
Overt	**Grade 2**	Lethargy, behavior Δs, time disorientation, **asterixis**, personality Δs, hypoactive DTRs
	Grade 3	**Somnolence** to semistupor, responsive to stimuli, time & place disorientation, asterixis, hyperactive DTRs
	Grade 4	**Coma**

Psychometric tests

Number con … CT-B



Line tracing test (LTT)

HE and impaired driving capability

Bajaj et al. Clin Gastro and Hepatol, 2008; 6: 1135-1139, MMW 10.2013; 13-18

- **“The role of physicians is a balancing act between the interests of patients compared to society while upholding the law, which often makes the topic uncomfortable to broach and liable to be ignored”**

Tapper EB, et al. J Hepatology 2019;590-92 and 648-57

HE - therapy

- **Causal therapeutic approaches**

- Treatment of GI bleeding
- Correction of electrolyte disbalances
- Stopping of sedatives and over the counter drugs
- Adjusting the amount and classes of diuretics

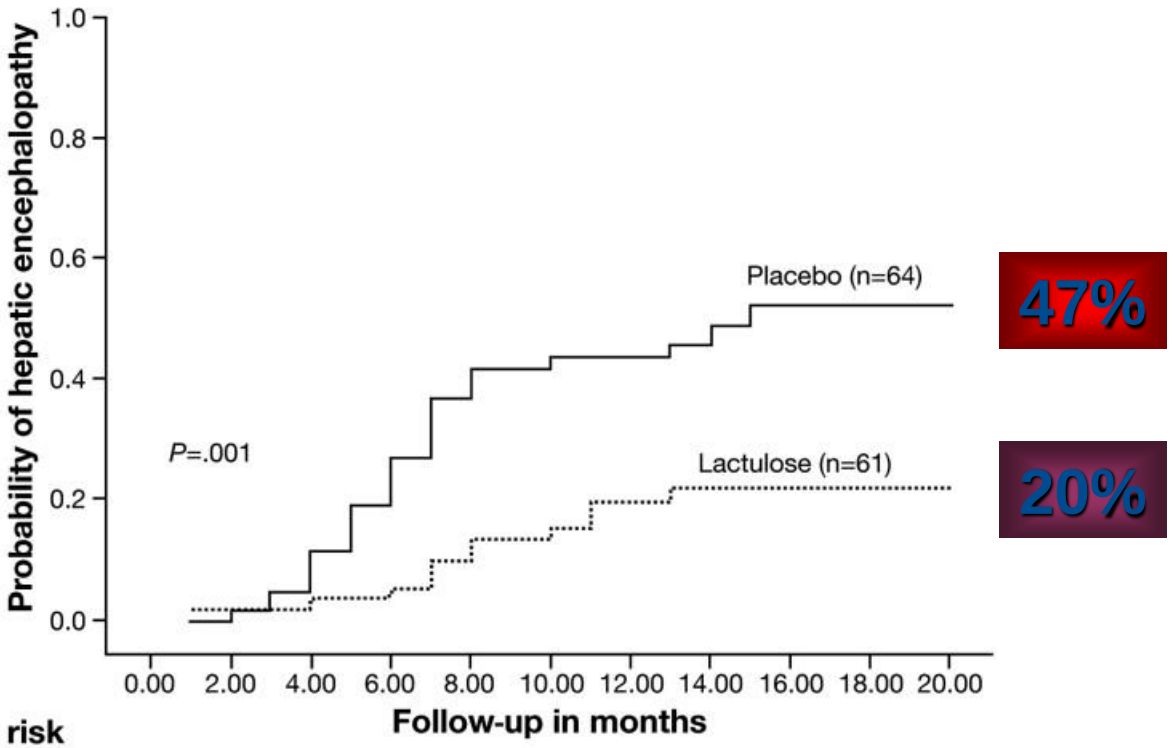
HE – specific therapies

Principle: Reduction of ammonium concentration

- **Reduction of intestinal ammonium generation**
  - Lactulose (pH-reduction, stool frequency elevation)
  - Oral Antibiotics (Rifaximin)
    (Reduction of urea producing bacteria)

- **Activation of ammonia detoxification**
  - L-Ornithin-L-Aspartat

Secondary prophylaxis of HE with Lactulosis

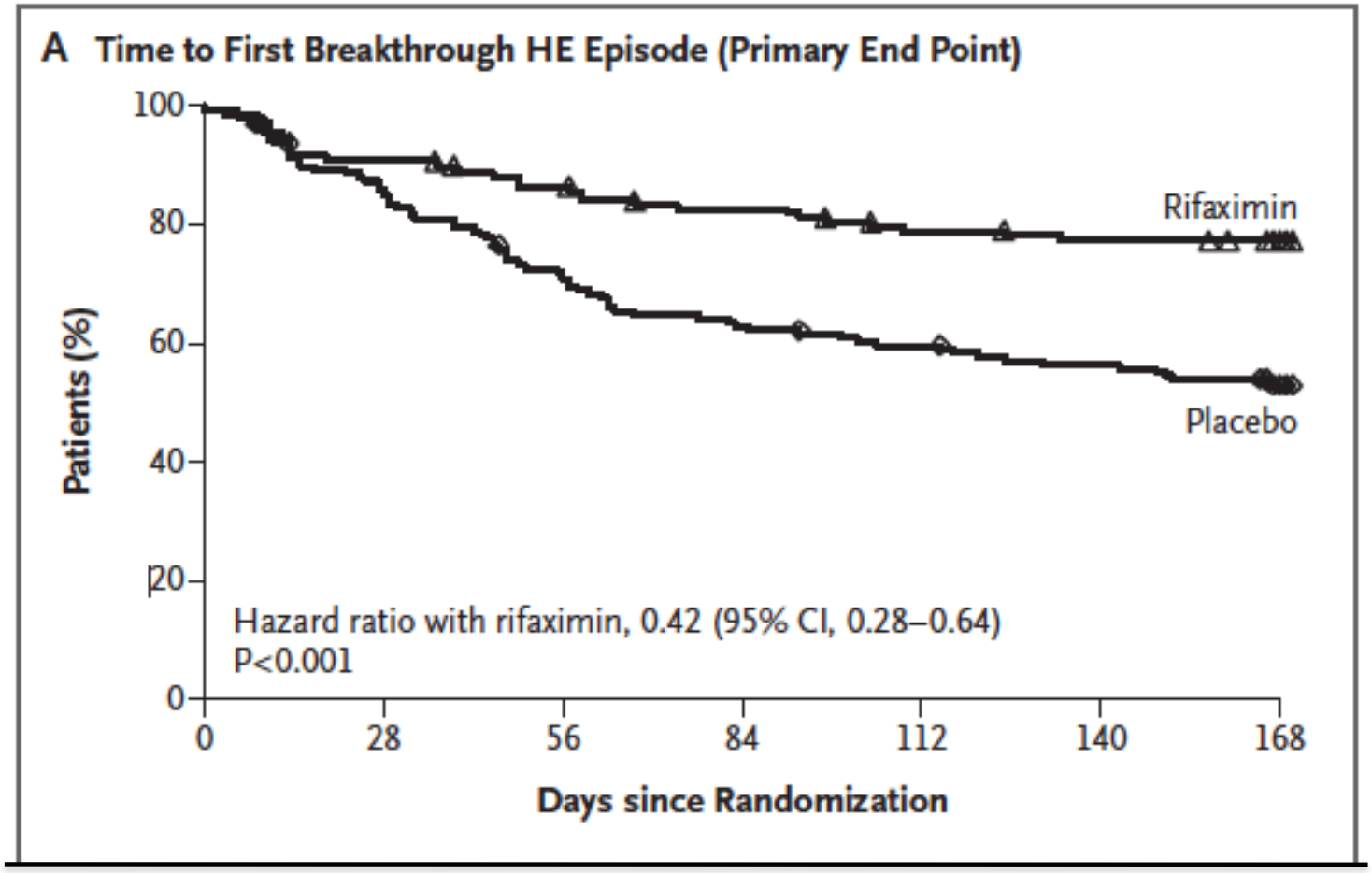


Patients at risk

Lactulose	61	60(1)	59(2)	58(3)	51(8)	45(9)	38(11)	28(12)	10(12)	7(12)	1(12)
Placebo	64	62(1)	59(4)	50(13)	37(24)	33(27)	28(27)	19(29)	13(30)	8(30)	4(30)

Sharma et al, Gastroenetrology 2009

Secondary prophylaxis of HE with Rifaximin



90 % of pts received lactulose

Bass NM et al. NEJM 2010

Case

- **Psychometric tests**:
  - Patient denied, calling these tests „childish, rubbish“

  - **Lactulose 2 x 30 ml**
  - Clinical stabilisation, but bloating and diarrhea, patient stopped medication after thre weeks
  - **L-ornithine L-aspartate (LOLA) 6 g TID**
  - **Rifaximin 550 mg BID (Norfloxacin stopped)**
  - Good tolerability
  - Wife of patient: much more alert and awake, discussions and talks together possible again
  - Car-driving situation unsolved

Clinical Practice Guidelines

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Clinical Practice Guidelines

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

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

L-ornithine L-aspartate (LOLA)
An RCT on patients with persistent HE demonstrated improvement by IV LOLA in psychometric testing and postprandial venous ammonia levels [105]. Oral supplementation with LOLA is ineffective.

22. IV LOLA can be used as an alternative or additional agent to treat patients nonresponsive to conventional therapy
(GRADE I, B, 2)

[105] Kircheis G, Nilius R, Held C, et al. Therapeutic efficacy of L-ornithine-L-aspartate infusions in patients with cirrhosis and hepatic encephalopathy: results of a placebo-controlled, double-blind study. Hepatology. 1997;25(6):1351-1360. doi:10.1002/hep.510250609.

Evidence post-2014 for assessment of efficacy of LOLA for HE in cirrhosis

5 RCTs for treatment / prevention of MHE, OHE and episodic OHE

- Bai et al. 2014
- Sharma et al. 2016
- Higuera-de-la Tijera et al. 2018
- Sidhu et al. 2018
- Varakanahalli et al. 2018

4 systematic reviews / meta-analyses

Reported efficacy of LOLA [iv or oral] for treatment of HE and reversal of MHE / prevention of OHE

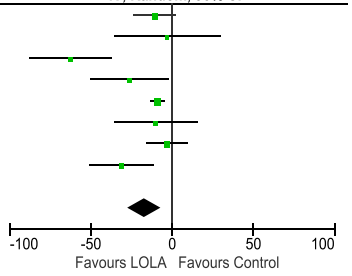
- Butterworth et al. 2018
- Goh et al. 2018
- Dihman et al. 2020
- Butterworth 2020

Evidence post-2014 for assessment of efficacy of LOLA for HE in cirrhosis

Ammonia lowering, all HE trials

Study or Subgroup	LOLA Mean	LOLA SD	LOLA Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI	Year
Kircheis et al	-17.3	37.2	57	-6.4	32.5	60	16.1%	-10.90 [-23.58, 1.78]	1997
Stauch et al	-27	56	33	-24	73	30	6.8%	-3.00 [-35.36, 29.36]	1998
Chen et al	-132	60	45	-69.5	58	40	9.3%	-62.50 [-87.61, -37.39]	2005
Schmid et al	-15	40.1	20	11.1	36.6	20	9.9%	-26.10 [-49.89, -2.31]	2010
Abid et al	-9.6	9.3	32	-0.5	7.8	31	20.6%	-9.10 [-13.33, -4.87]	2011
Mittal et al	-18.8	53.3	60	-8.7	85	60	9.2%	-10.10 [-35.49, 15.29]	2011
Alvares de Silva et al	5	24	28	8.5	26.7	35	16.1%	-3.50 [-16.04, 9.04]	2014
Sidhu et al	-69.8	65.5	80	-38.4	60.4	78	11.9%	-31.40 [-51.04, -11.76]	2018
Total (95% CI)			**355**			**354**	**100.0%**	**-17.50 [-27.73, -7.26]**	

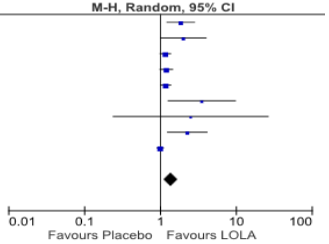
Heterogeneity: Tau² = 128.00; Chi² = 24.24, df = 7 (P = 0.001); I² = 71%
Test for overall effect: Z = 3.35 (P = 0.0008)



Improvement of mental state, all HE trials

Study or Subgroup	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				

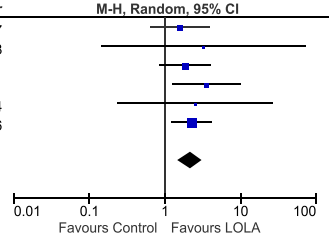
Heterogeneity: Tau² = 0.06; Chi² = 48.38, df = 8 (P < 0.00001); I² = 83%
Test for overall effect: Z = 2.82 (P = 0.005)



Improvement of mental state in MHE

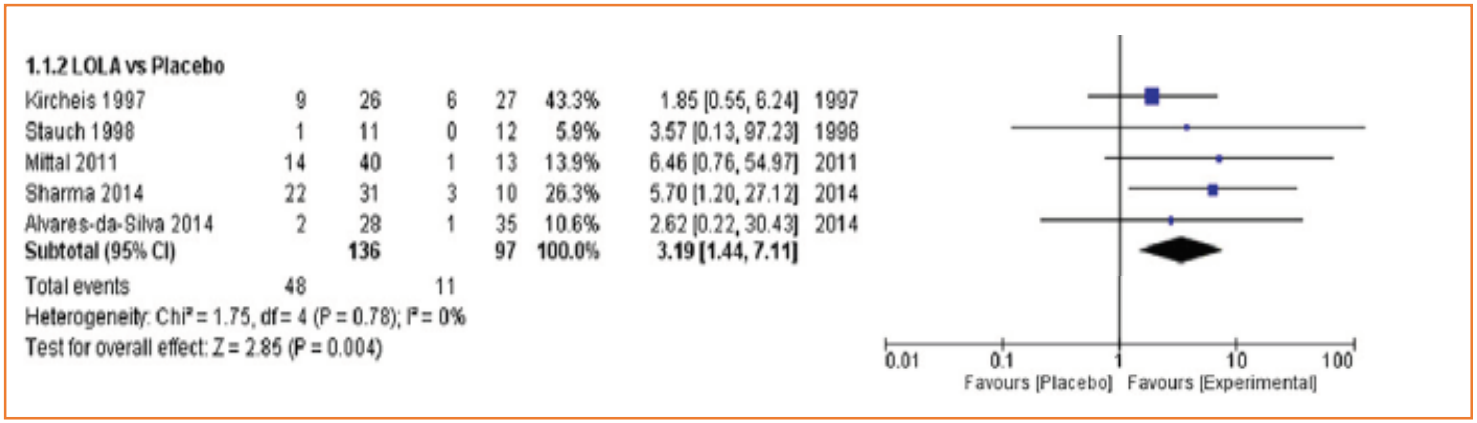
Study or Subgroup	LOLA Events	LOLA Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Kircheis et al	9	26	6	27	18.3%	1.56 [0.65, 3.76]	1997
Stauch et al	1	11	0	12	1.5%	3.25 [0.15, 72.36]	1998
Abid et al	6	6	3	6	24.1%	1.86 [0.86, 4.01]	2011
Mittal et al	14	40	4	40	13.7%	3.50 [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				

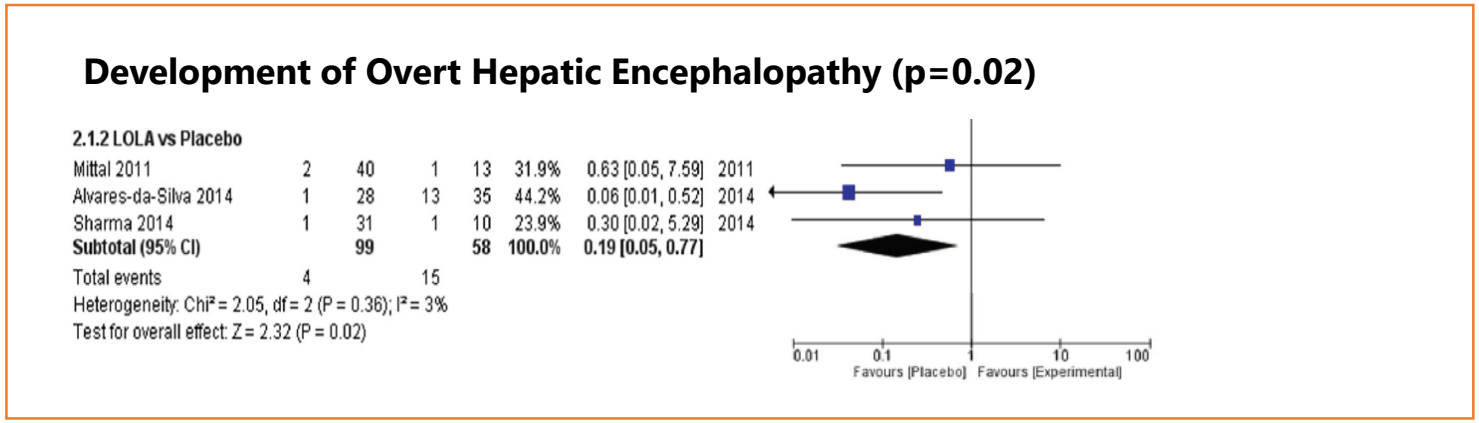
Heterogeneity: Tau² = 0.00; Chi² = 1.70, df = 5 (P = 0.89); I² = 0%
Test for overall effect: Z = 3.98 (P < 0.0001)



Butterworth RF, Kircheis G, Hilger N, McPhail MJW. Efficacy of l-Ornithine l-Aspartate for the Treatment of Hepatic Encephalopathy and Hyperammonemia in Cirrhosis: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J Clin Exp Hepatol*. 2018;8(3):301-313.

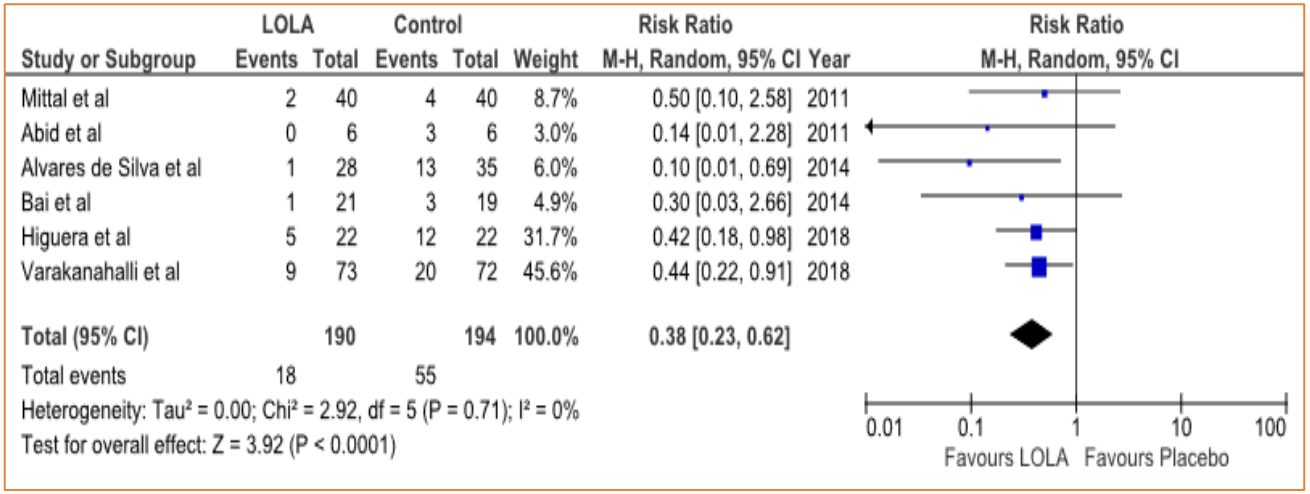
Efficacy of treatment options for minimal and overt hepatic encephalopathy (LOLA)

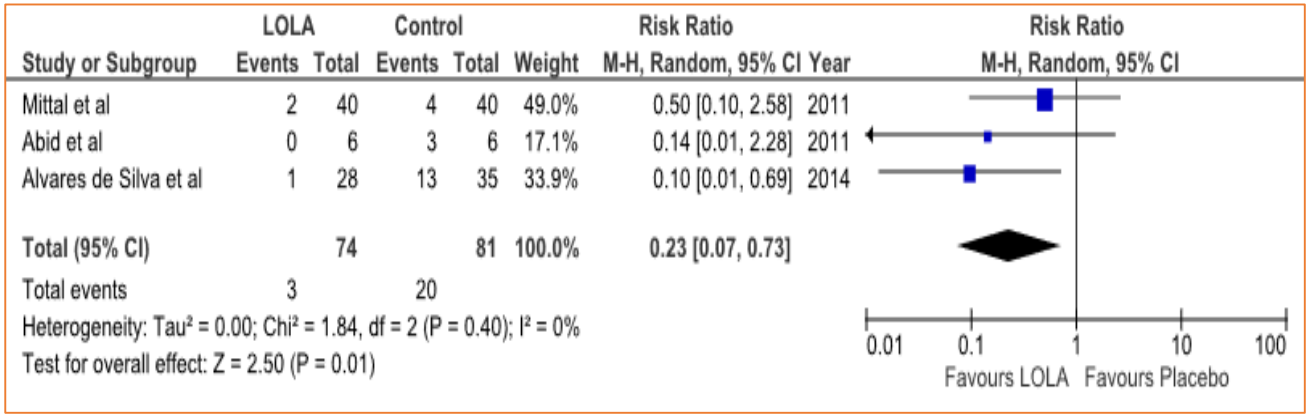




Dhiman RK, Thumburu KK, Verma N, et al. Comparative Efficacy of Treatment Options for Minimal Hepatic Encephalopathy: A Systematic Review and Network Meta-Analysis. Clin Gastroenterol Hepatol. 2020;18(4):800-812.e25. doi:10.1016/j.cgh.2019.08.047

LOLA in Prevention of OHE and HE prophylaxis





Butterworth RF. Beneficial effects of L-ornithine L-aspartate for prevention of overt hepatic encephalopathy in patients with cirrhosis: a systematic review with meta-analysis. *Metab Brain Dis.* 2020;35(1):75-81.

Case

- Clinical stabilisation – Child Pugh B (7)
- Last ultrasound w/o ascites (risk of infection lowered)

- Torasemid stopped, Spironolacton 100mg QD

- HCC surveillance (ultrasound, AFP every six months)

Thank you very much for your attention!

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