“Update Hepatic Encephalopathy in Cirrhosis – potential Role of L-Ornithin-L-Aspartate”

Online Education 11/Mar/2021

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HE – Classification

HE – Description + Clinical Example

EASL/AASLD Clinical Practice Guidelines, JHEP 2014; 61: 642

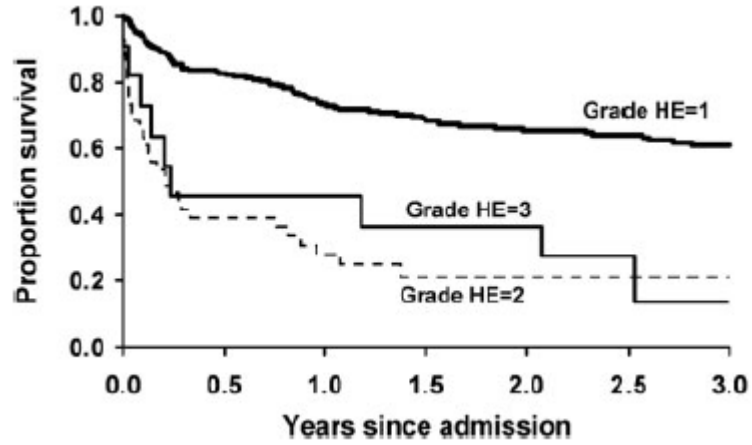
<table>
<tr><th>Type</th><th colspan="2">Grade</th><th>Time course</th><th>Spontaneous or precipitated</th></tr>
<tr><td rowspan="2">A</td><td>MHE</td><td rowspan="2">Covert</td><td rowspan="2">Episodic</td><td rowspan="3">Spontaneous</td></tr>
<tr><td>1</td></tr>
<tr><td rowspan="2">B</td><td>2</td><td rowspan="3">Overt</td><td rowspan="2">Recurrent</td></tr>
<tr><td>3</td><td rowspan="2">Precipitated (specify)</td></tr>
<tr><td>C</td><td>4</td><td>Persistent</td></tr>
</table>

The HE patient should be characterized by one component from each of the four columns. Example of a recommended description of a patient with HE: "The patient has HE, Type C, Grade 3, Recurrent, Precipitated (by urinary tract infection)." The description may be supplemented with operative classifications (e.g., the Glasgow Coma Score or psychometric performance).

HE: Impact on Patients Survival

Stewart *et al.*, LT 2007; 13: 1366

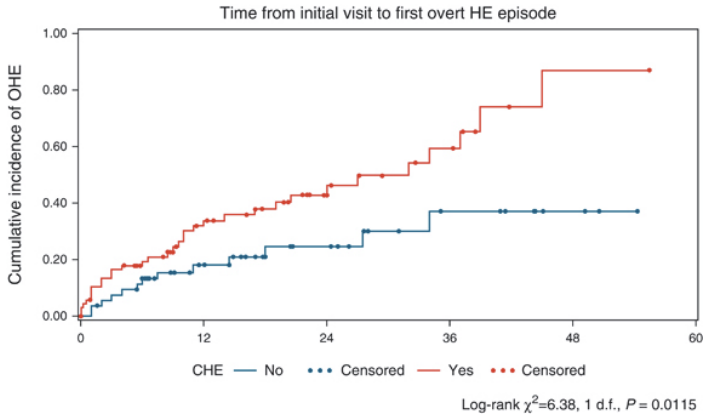
- Retrospective Analysis
  - 223 patients admitted for TIPS
  - 271 cirrhotics hospitalized for decompensation
- Univariate:
  - HE highly significantly associated with survival in both groups
- Multivariate (adjusted for MELD)
  - HE significantly associated in decompensated cirrhotics (HR 2.6)

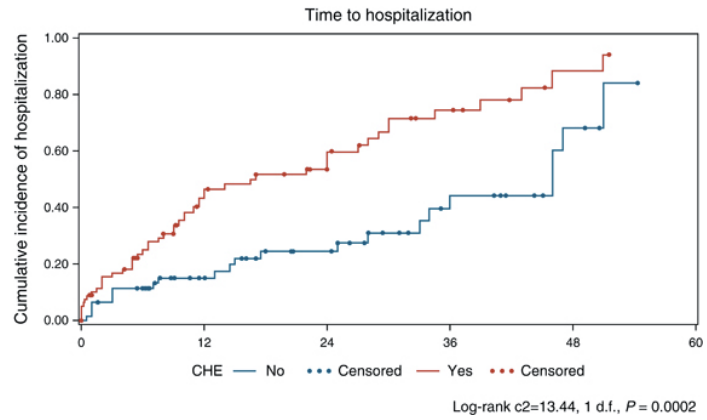


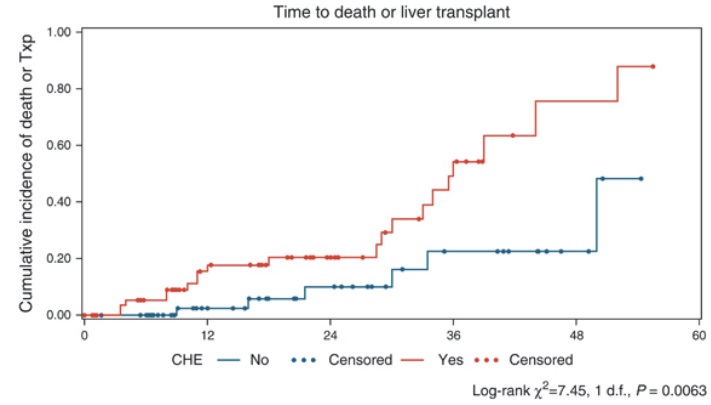
mHE: Impact on Survival

Patidar *et al.*, Am J Gastro 2014; 109: 1757

- 170 cirrhotics w/o HE-episode (53% HCV, 20% NAFLD)
- Mean MELD 9; 56% mHE; 13 months prospective follow-up
- 30% developed HE, 19% died
- Multivariate analysis: mHE risk factor for HE, hospitalization & death



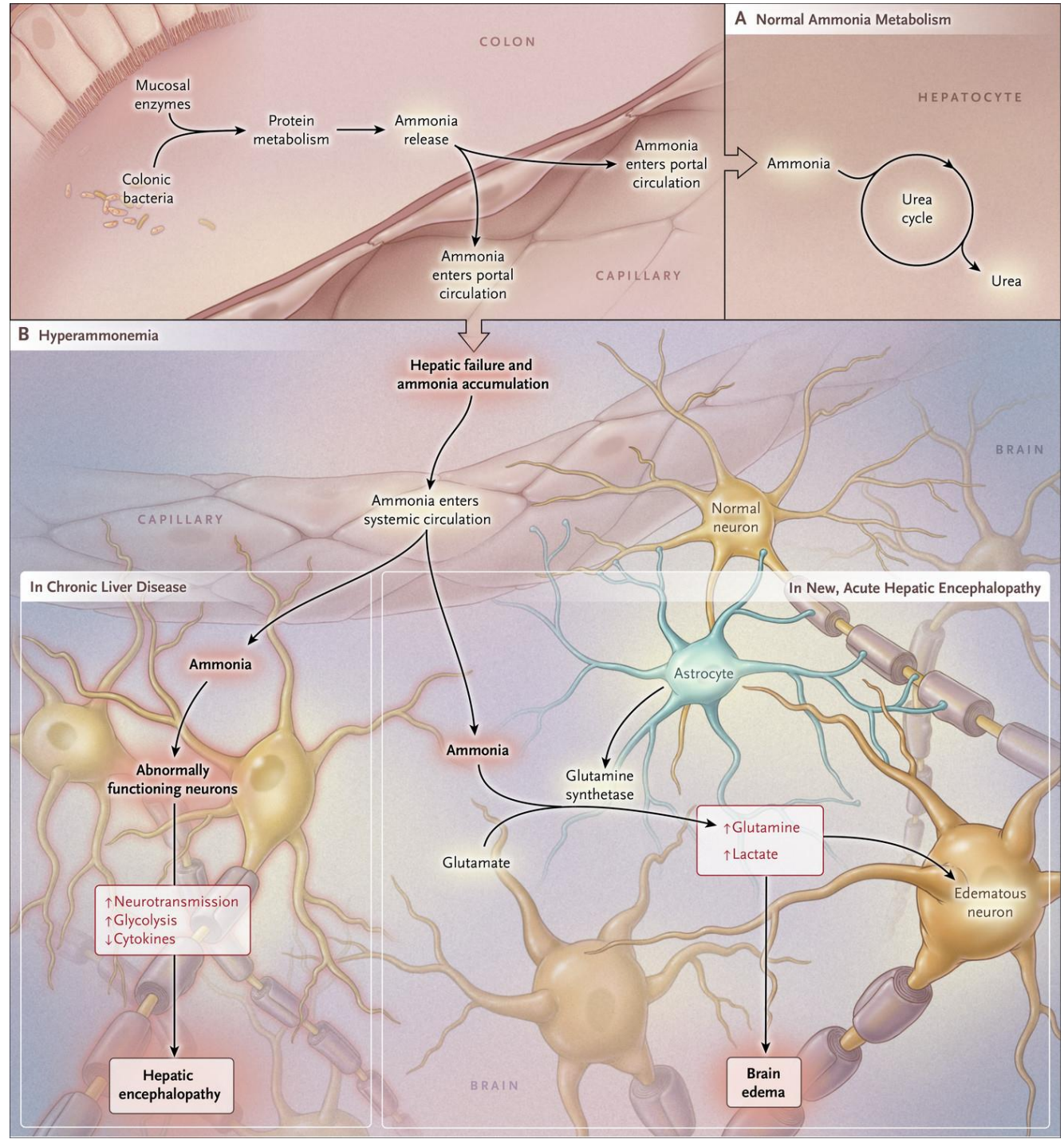




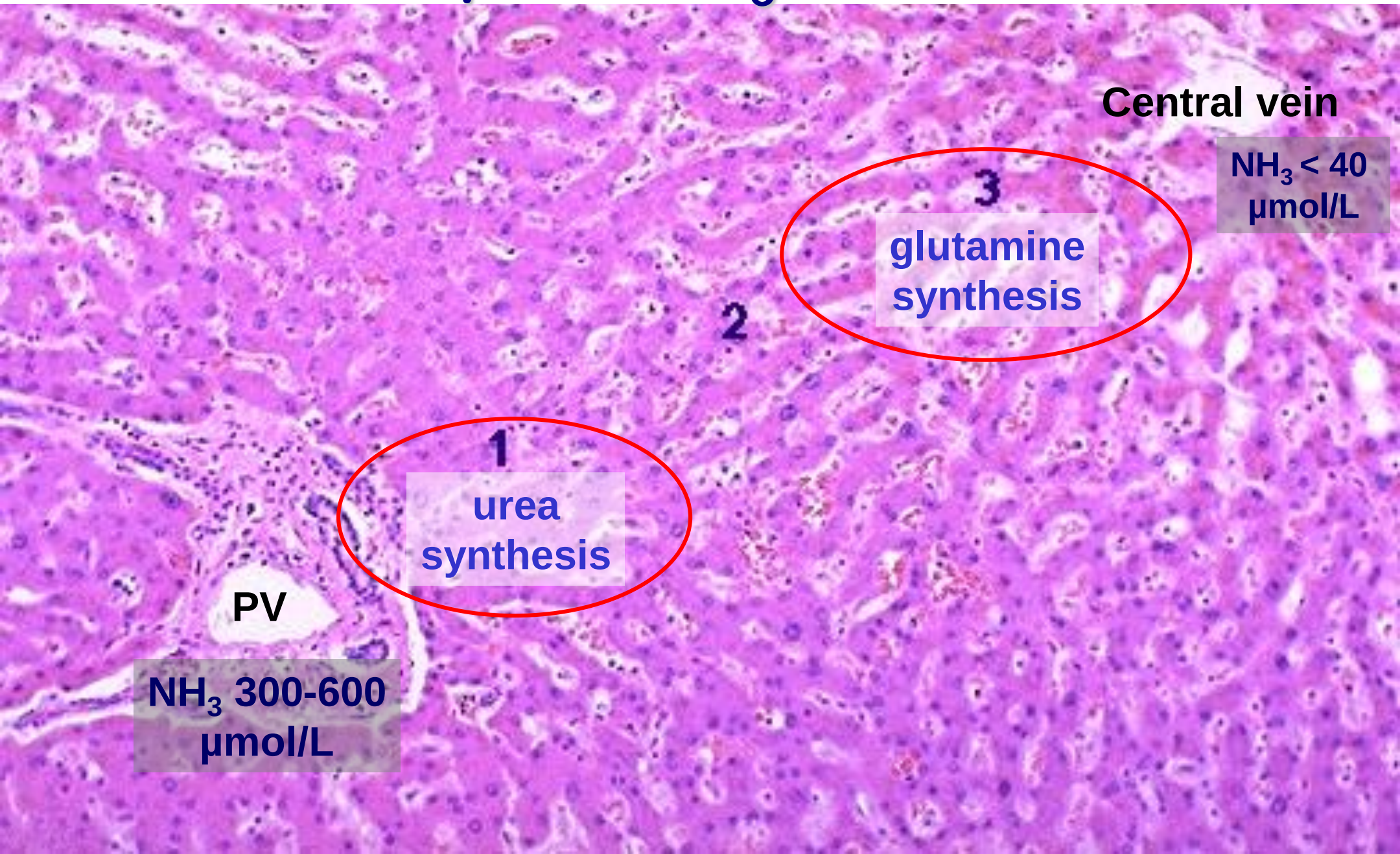
HE – Pathophysiology

Mechanisms HE & Brain Edema

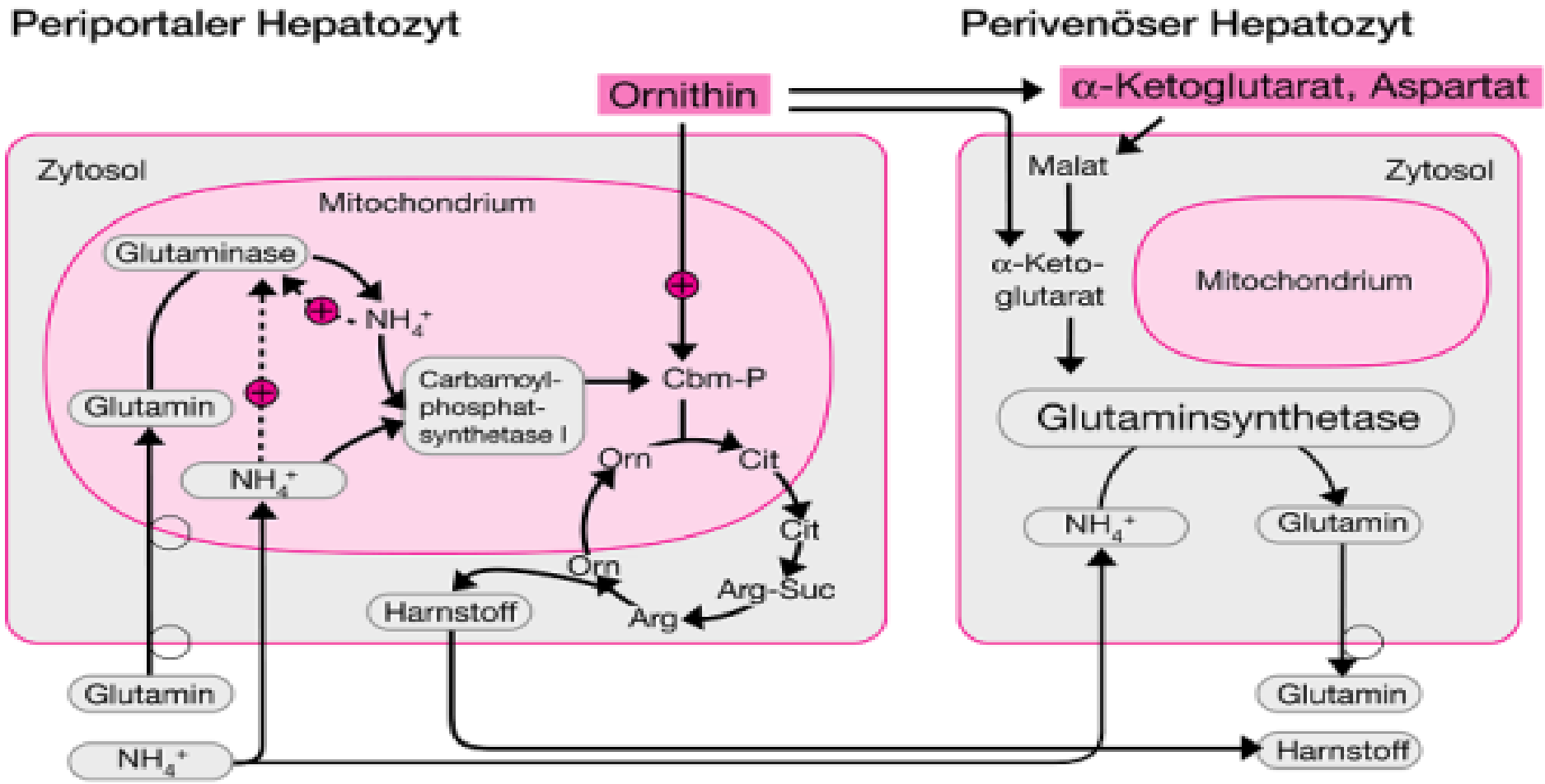
Wijdicks,
NEJM 2016; 375: 1660



Intrahepatic NH_3-Metabolism

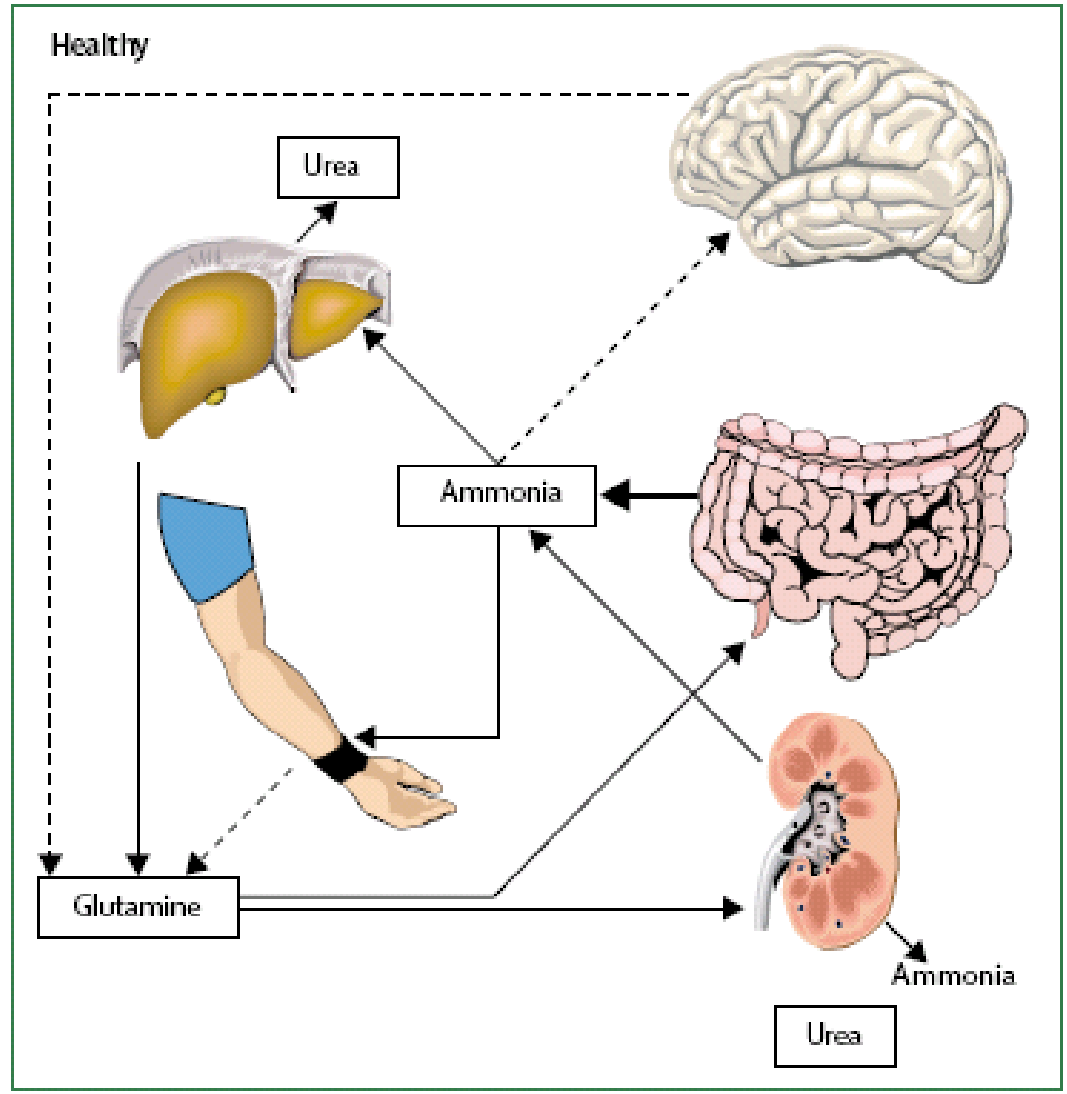


Ornithin-Aspartat (OA)



Interorgan Trafficing of Ammonia

Shawcross *et al.*, Lancet 2005; 365: 431



Factors leading to Acute HE

- acute liver failure
- acute GI-bleeding
- hyponatremia
- dehydration
- infection
- exogenous factors (drugs, etc.)

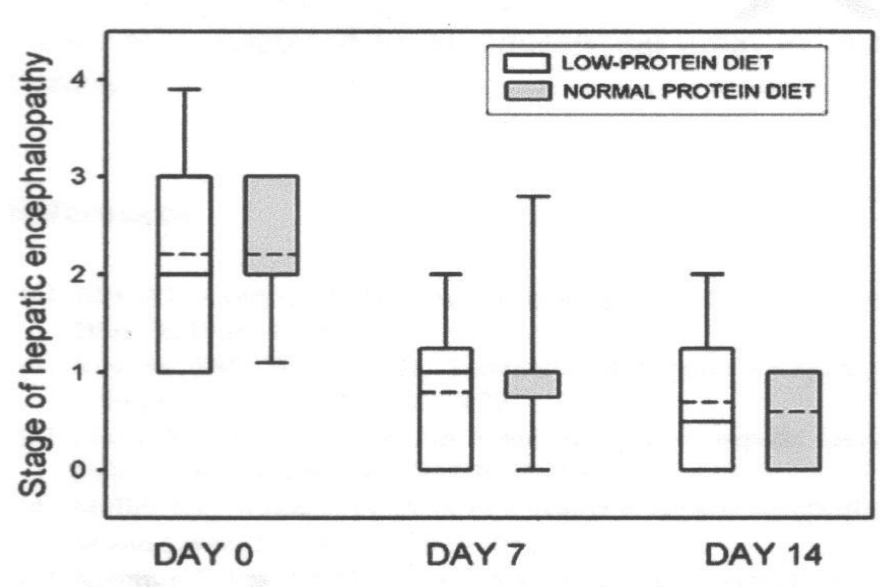
Protein Restriction and HE

Cordoba *et al.*, J. Hepatol. 2004; 41: 38

- 30 cirrhotics admitted for an HE-episode

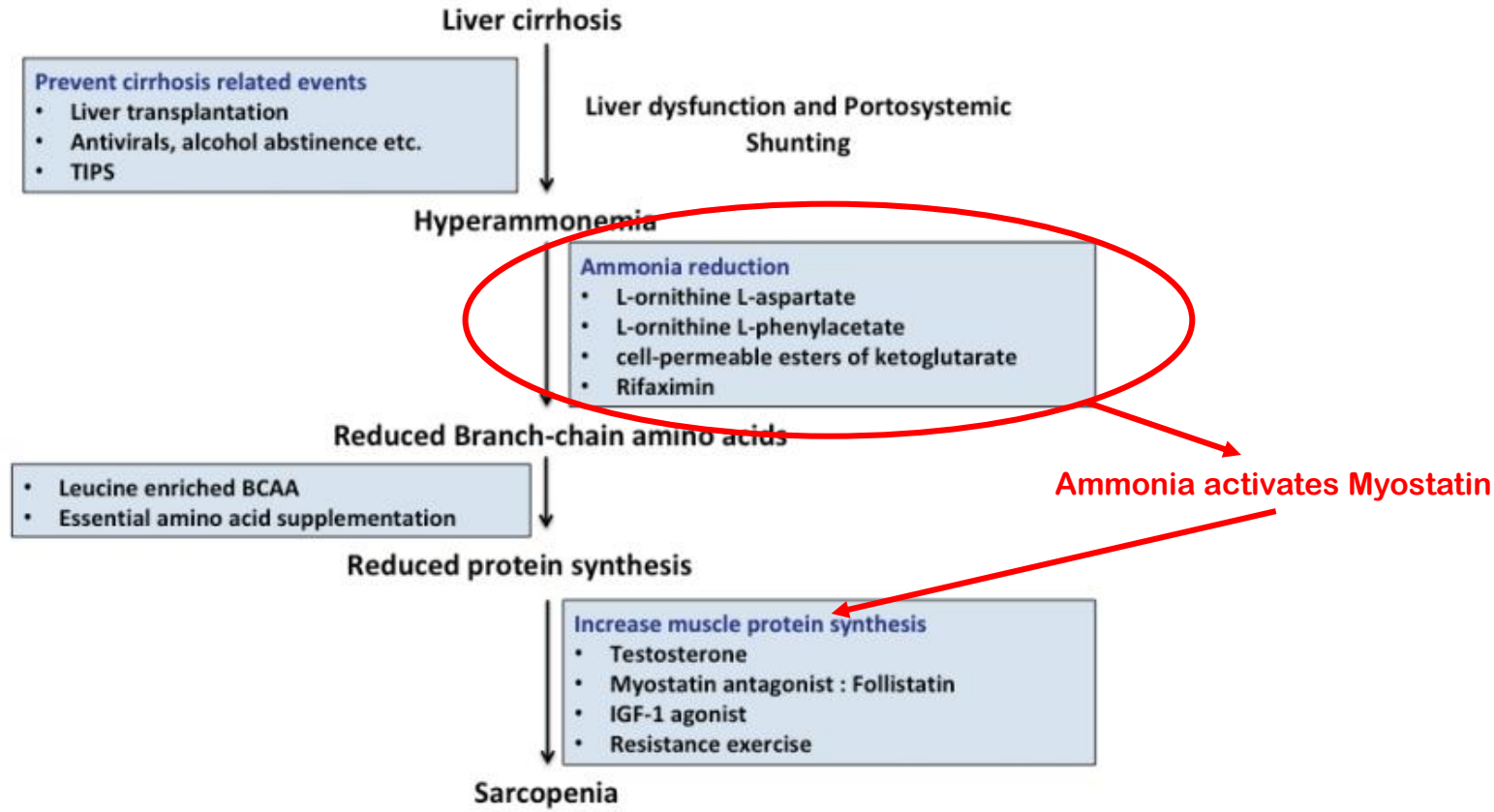
- RCT, low protein (LPD) *vs.* standard protein diet (SPD)
  - LPD (↑ q3d): 0 → 12 → 24 → 48g → 1.2 g protein/kg
  - NPD: 1.2 g protein/kg over 14d

- Results:
  - HE: n.s.
  - Protein synthesis: n.s.
  - Protein breakdown in LPD ↑



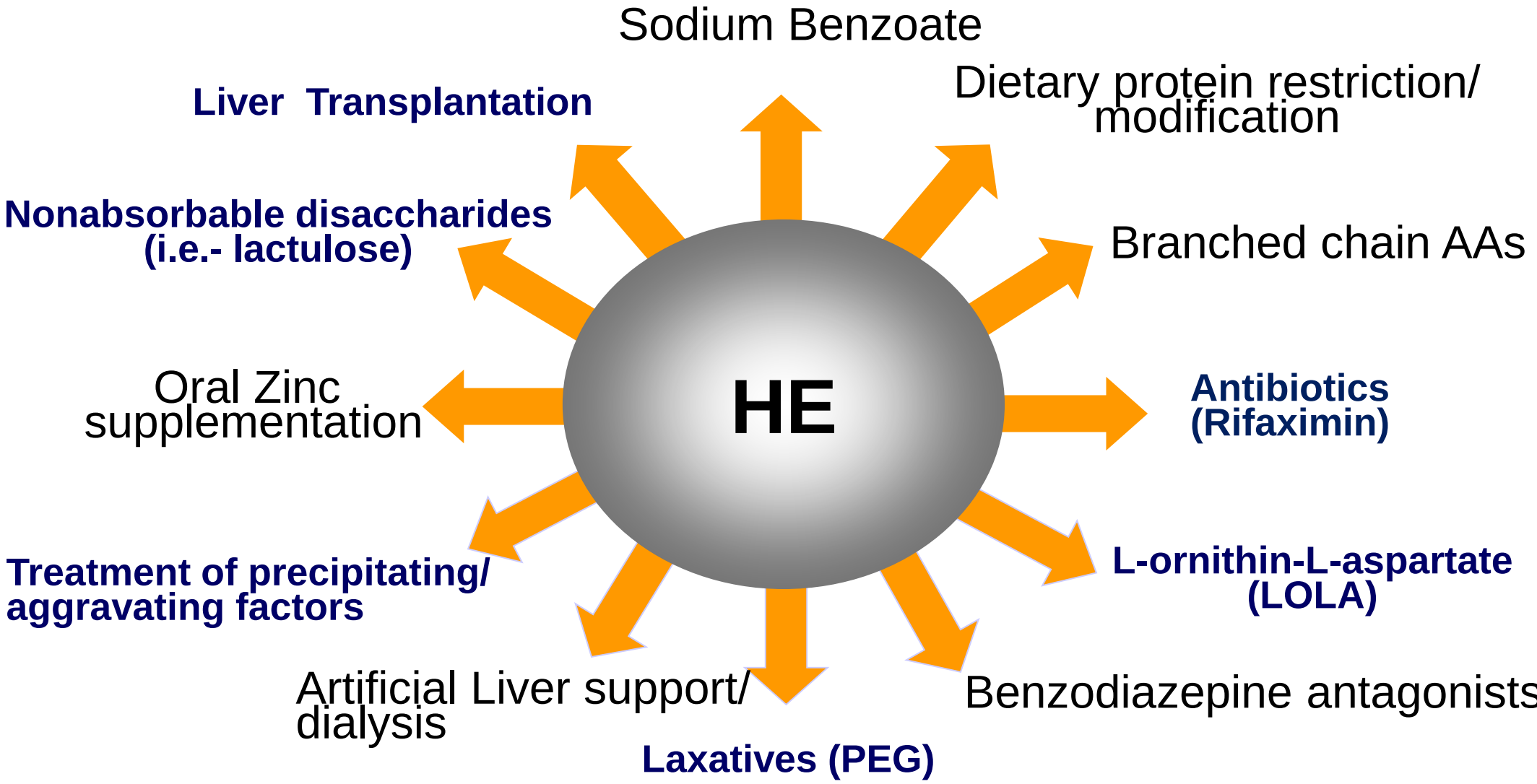
Strategies to Combat Muscle Wasting in Cirrhosis

Jindal *et al.*, Clin Mol Hepatol 2019; 25: 270



HE – Treatment

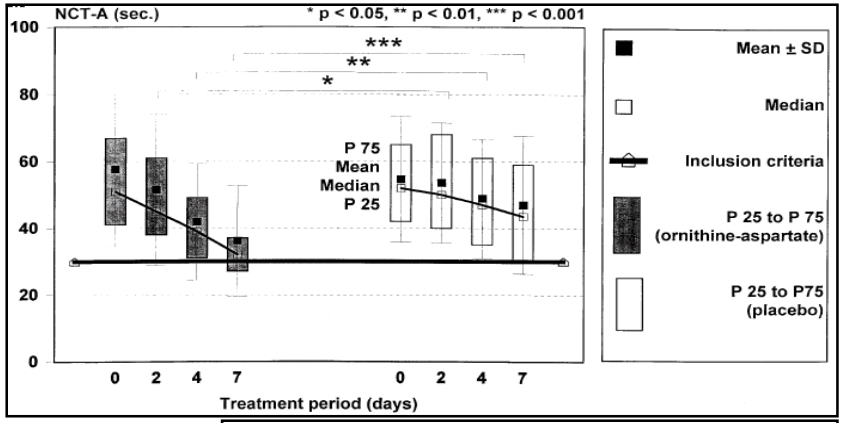
Current Treatment Options for HE

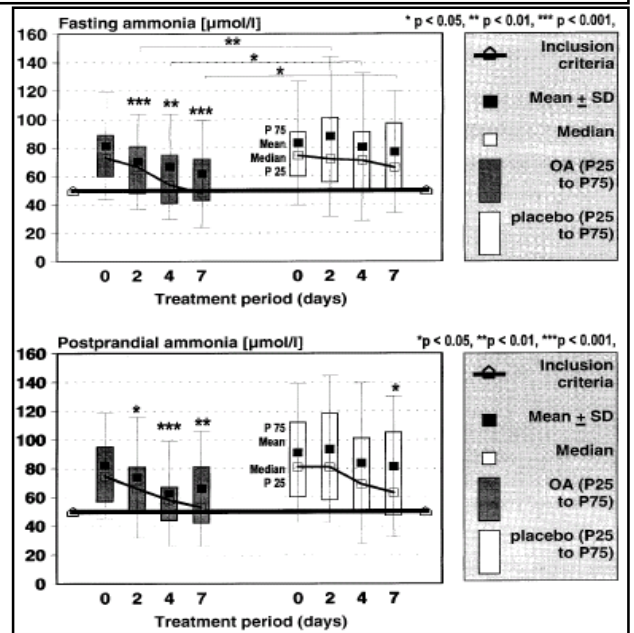


L-Ornithin L-Aspartat (LOLA) for HE

Kircheis *et al.*, Hepatology 1997; 25: 1351

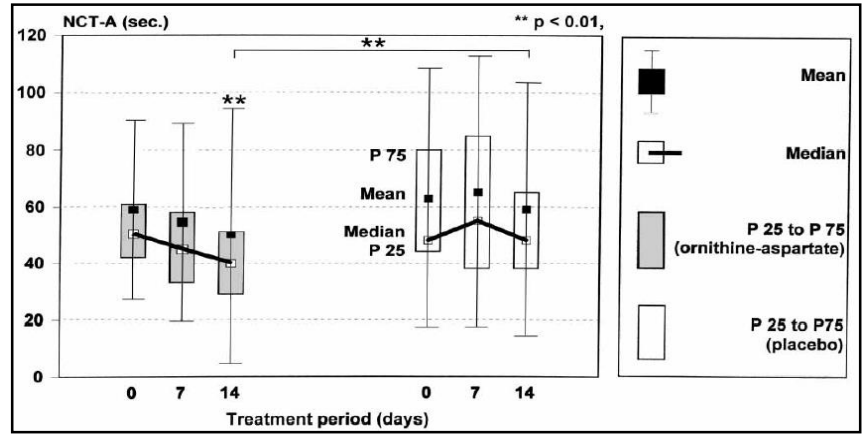
- RCT, 126 patients, SHE – HE II
- 20 g /d LOLA i.v. *vs.* placebo, 7d

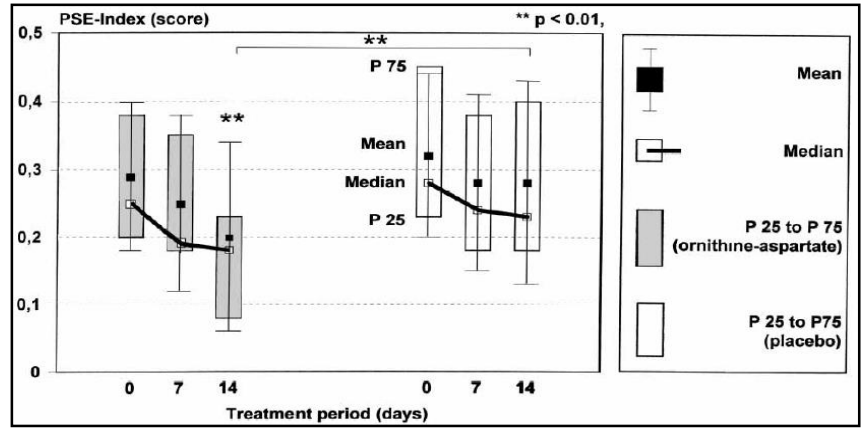




Strauch *et al.*, J. Hepatol. 1998-28-856

- RCT, 66 patients, at least SHE
- 3 x 6 g /d LOLA p.o. *vs.* placebo, 14 d

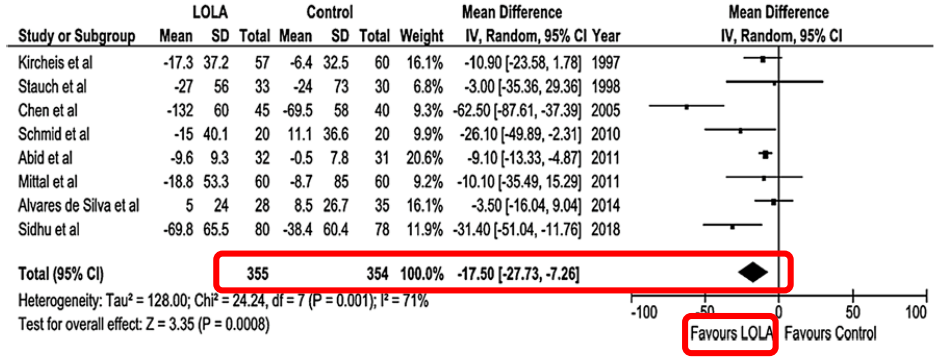




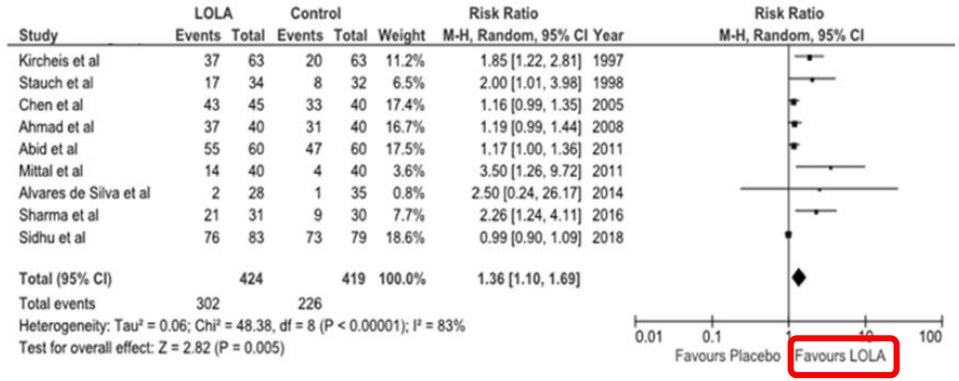
L-Ornithin-L-Aspartate for HE: MA

Butterworth *et al.*, Drugs 2019; 79: 31

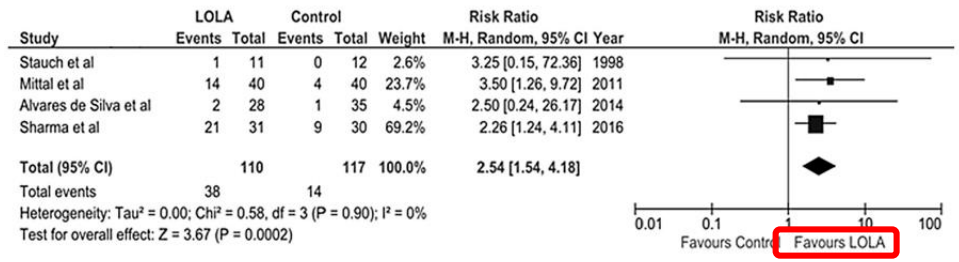
- **Meta-analysis safety & efficacy L-Ornithin-L-Aspartate for HE in cirrhotics**



NH_3-lowering, all patients



Improvement Mental State, all trials



Improvement mHE, oral formulation