Hepatic Encephalopathy in chronic liver disease:

Target-based treatment between the Ammonia hypothesis and a fragile Gut-Liver-Brain Axis

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Survival after a first Episode of Hepatic Encephalopathy

Survival

Months

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

Actual Facts and Limitations

- A complex pathogenesis not yet fully elucidated
- No universally accepted standards for the treatment
- Lack of consistency in nomenclature and general standards hindering progress in clinical research
Ammonia and Gut-Brain-liver axis

Ammonia (NH₃) is produced by the liver and intestine. It can be converted to urea in the liver, which is then excreted in urine. In the intestine, ammonia can be converted to glutamine. Feces also contain ammonia. The brain can take up ammonia, which can cause neurotoxicity. Glutamine can be converted to ammonia in the liver and intestine.
Ammonia and Gut-Brain-liver axis

- Ammonia (NH₃) is produced in the liver and can be converted to urea.
- Urea is excreted in urine.
- Glutamine is an amino acid that can be converted to ammonia in the gut.
- Feces contain ammonia and glutamine.
- Urea is also found in urine.
Inflammation in Hepatic Encephalopathy

TREATMENT OF HEPATIC ENCEPHALOPATHY: TARGETING THE GUT-LIVER-BRAIN AXIS  Summary of Presentations from the Norgine Sponsored Satellite Symposium, UEG Week, Berlin, Germany, 12th–16th October 2013
Lactulose

• Metabolized by colon bacterial flora to short chain fatty acids altering luminal pH

Probability of developing recurrent OHE in patients receiving prophylactic therapy with lactulose following an episode of OHE

PEG

- Encouraging data on polyethylene glycol preparation use

Rifaximin

- For the treatment of a first episode of overt hepatic encephalopathy


- Rifaximin added to lactulose: best-documented agent to maintain remission


- Treatment of minimal and covert HE (When indicated)

Antibiotics

• Neomycin: FDA approved for HE, extensive side-effect
  

• Metronidazole: Not FDA approved
  

• Erythromycin: (250 mg OD)
  Reduction in hospital stay and ALT
  
Ammonia and Gut-Brain-liver axis

NH₃

Glutamine

Ureap

Feces

Urea

Urine

NH₄⁺
Nutrition

- Daily energy intakes should be 35-40 kcal/kg ideal body weight
- Daily protein intake should be 1.2-1.5 g/kg/day

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the EASL and the AASLD. J Hepatol (2014) dx.doi.org/10.1016/j.jhep.2014.05.042

A short trial of protein restriction for a few days may ameliorate hepatic encephalopathy without significant loss of total body protein turnover


- Intolerant to dietary protein: Oral BCAA supplementation may allow recommended nitrogen intake to be achieved and maintained in patients

- Zinc : conflicting data

Embolization of Portosystemic Shunt

- Recurrent hepatic encephalopathy: improved survival and liver function


Ammonia and Gut-Brain-liver axis

- Urine
- Feces
- Urea
- NH₃
- Glutamine
- NH₄⁺
Metabolic ammonia scavengers

- Ornithine phenylacetate: (Continuous iv infusion)
  Safe and well tolerated


- Glycerol Phenylbutyrate: (6 ml orally twice daily)
  Safe and well tolerated

Ammonia and Gut-Brain-liver axis

- Urine
- Feces
- Urea
- NH$_3$
- Glutamine
- NH$_4^+$
Oral BCAA’s

- Safe and improve manifestations of HE but have no effect on survival
- Oral dose: 0.25 g /kg (body weight) /day

Gluud LL et al. Oral branched chain amino acids have a beneficial effect on manifestations of hepatic encephalopathy in a systematic review with meta-analyses of randomized controlled trials. J Nutr 2013;143:1263–1268
Extracorporeal Albumin Dialysis

- may be associated with an earlier and more frequent improvement of HE


Albumin infusions?! 

- No effect on resolution of HE, but was related to better postdischarge survival.

Liver transplantation

- Hepatic encephalopathy by itself is not considered an indication for LT unless associated with poor liver function

- Remains the only treatment option for HE that does not improve on any other treatment (risks ++)

Outpatient Follow up

- Patients and caregivers education on medication, importance of compliance, side effects and early signs of recurrence
- Precipitating and risk factors for development of HE should be recognized
- Out-patient postdischarge consultations should be planned to adjust treatment and prevent the reappearance of precipitating factors

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by the EASL and the AASLD. J Hepatol (2014) dx.doi.org/10.1016/j.jhep.2014.05.042
Ongoing researches and strategies
Glutaminase inhibitors

- THDP-17 compound could be a good candidate for HE management (by lowering ammonia production)

Blood-Brain Barrier

- Sodium Benzoate and Rifaximin are able to restore Blood-brain barrier integrity in cirrhotic rats with hepatic encephalopathy

S. Mouri et al. Sodium Benzoate and Rifaximin Are Able to Restore Blood–Brain Barrier Integrity in Cirrhotic Rats With Hepatic Encephalopathy. Poster section at the EASL international liver congress 2015
CSF Metabolomics

- In cirrhotic patients with HE, several altered metabolite pathways linked to ammonia metabolism, neurotransmission and energy metabolism which could constitute interesting new therapeutic targets.

*Weiss et al. HEPATIC ENCEPHALOPATHY: CEREBROSPINAL FLUID METABOLOMICS HIGHLIGHTS ALTERATION OF MULTIPLE METABOLIC PATHWAYS REPRESENTING NEW POTENTIAL THERAPEUTIC TARGETS, Poster section at the EASL international liver congress 2015*
A proposed physiology-driven protocol for the treatment of hepatic encephalopathy

1. Identify and treat precipitating factors
2. Reduce ammonia production and enhance ammonia elimination
3. Reduce systemic inflammation
4. Preserve and enhance nutritional status

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<th>Covert hepatic encephalopathy (or after the first overt episode)</th>
<th>Overt hepatic encephalopathy</th>
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<tr>
<td><strong>First-line therapies</strong></td>
<td><strong>Suggested approach</strong></td>
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<tr>
<td>Discontinue sedatives and narcotics</td>
<td>Examine carefully for infection: culture ascites, urine, and blood</td>
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<tr>
<td>Lactulose 30 cc BID-TID; titrate exact dose to symptoms</td>
<td>Ensure euvolemia consider fluid bolus temporarily hold diuretics</td>
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<tr>
<td>Rifaximin 550 mg BID</td>
<td>Replete potassium if hypokalemic</td>
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<td>Nutritional evaluation and support as needed with meal supplements</td>
<td>Lactulose (q2-q4 dosing until mental clearance then TID)</td>
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<tr>
<td>Ensure eukalemia and intravascular enoemla</td>
<td>Albumin dialysis if refractory and high grade</td>
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<tr>
<td>Consideration of transplant evaluation</td>
<td>Discontinue sedatives and narcotics</td>
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<td></td>
<td>Ensure adequate nutritional intake</td>
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<td>Glycerol phenylbutyrate or l-ornithine l-aspartate</td>
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Thank you