# Hepatic Encephalopathy

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NVH
WERKGROEP
PORTALE HYPERTENSIE

https://www.portalehypertensie.nl/

# Disclosures

- Advisory boards/speaker: Gilead, Norgine, Gore
- Grants: ZonMW, Gastrostart, KWF

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# Teaching aims

- Forms of presentation of hepatic encephalopathy (HE)
- Pathophysiology of HE
- Diagnosis of HE
- Treatment options

# Casus: De heer A, 72 jaar

- **Voorgeschiedenis:**
  - 1995: DM bij metabool syndroom.
  - 2015 presentatie ivm gedecompenseerde levercirrose obv (N)ASH.
  - Na compensatie en gewichtsreductie stabiel CP-A (6 punten)
- **Medicatie**
  - Metformine 2dd 850, gliclazide 30mg 1dd, Lantus 14 EH 1dd
  - Simvastatine 40mg 1dd
  - Lisinopril 20mg 1dd
- **Laatste poliklinische bezoek 4 maanden geleden:**
  - Compos mentis; BMI 33.7 kg/L$^2$
  - Albumine 32 g/L; bilirubine totaal/direct 27/23 µmol/L; INR 1.17
  - ALT 54 IU/L; AST 38 IU/L; gamma-GT 143 IU/L; AF 98 IU/L
  - HbA1c 54 mmol/mol (50)

# Scenario 1

- **Presentatie SEH**
  - Laatste weken 10kg gewichtstoename.
  - Nu progressief slaperig. Nog wel wekbaar. Antwoordt niet coherent/onsamenhangend.
- **Lichamelijk onderzoek:**
  - Ascites
  - Geen flapping tremor.
- **Aanvullend onderzoek:**
  - oa. $NH_3$ 178 µmol/L
  - PMN in ascites 450
- **Conclusie:**
  - Verdenking HE obv SBP

- U wil de ernst van de HE scoren volgens de West Haven criteria.

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# Vraag 1: Wat is het stadium van HE (volgens West Haven)

A. Graad 1

B. Graad 2

C. Graad 3

D. Graad 4

# Vraag 2: Welke behandeling start u (naast ceftriaxon)?

A. Lactulose klysma´s, wanneer wakker over op lactulose oraal 25mg 2dd.

B. Lactulose klysma´s + rifaximin 550 mg 2dd, wanneer wakker over op lactulose oraal 25mg 2dd.

C. Kleanprep via maagsonde, wanneer wakker over op lactulose oraal 25mg 2dd.

D. Behandeling A en B kunnen beide.

E. Behandeling A en C kunnen beide.

# Scenario 2

- **Poliklinische afspraak vervroegd door echtgenote**
  - Moeite met krant lezen en slapen.
  - Echtgenote vertelt dat patiënt elke nacht gaat “dwalen door het huis”
  - Huisarts dacht aan HE en is lactulose gestart. Heeft daar 2dd brijige ontlasting bij, maar heeft geen effect gehad op klachten.
- **Lichamelijk onderzoek**
  - Niet ziek, compos mentis, oogt wat bradyfreen, geen flapping tremor.
  - Geen shifting dullness, geen perifeer oedeem
- **Aanvullend onderzoek:**
  - $NH_3$ 54 µmol/L
  - Nuchter glucose 9.5 mmol/L
  - HbA1c 56 mmol/mol
  - Echo abdomen: Geen afwijkingen, geen ascites, geen focale leverafwijkingen.
  - Urine: gb

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# Vraag 3: Is hier nu ook sprake van HE?

A. Ja, klassiek minimale hepatische encefalopathie (mHE)

B. Mogelijk, maar ik weet niet zeker. Ik ga wat aanvullende testjes doen

C. Nee, patiënt lijkt delirant.

# Vraag 3: Is hier nu ook sprake van HE?

A. Ja, klassiek minimale hepatische encefalopathie (mHE)

B. Mogelijk, maar ik weet niet zeker. Ik ga wat aanvullende testjes doen.
   - NCT: 58 seconden

C. Nee, patiënt is lijkt delirant.

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# Vraag 4: Wat doet u nu?

A. Ik verwijs patiënt naar de geriater

B. Ik start rifaximin 550mg 2dd

C. Ik hoog de dosis lactulose verder op.

# Scenario 3

- **Blijft polikliniek frequent bezoeken**
  - Na starten lactulose en rifaximine aanvankelijk verbeterd.
  - Nu weer dezelfde klachten.
  - Endocrinoloog heeft diabetesmedicatie aangepast
    - HbA1c 45 mmol/mol
  - Opnieuw bij lichamelijk onderzoek en aanvullend onderzoek geen afwijkingen.

# Vraag 4: En nu?

A. Ik verhoog rifaximin naar 3dd

B. Ik geef vertakte-keten aminozuren (BCAAs)

C. Ik geef glycerolfenylbuturaat

D. Alles is mogelijk.

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# Hepatic encephalopathy

# Hepatic Encephalopathy (HE)

- Brain dysfunction caused by liver injury or portosystemic shunting.
- Wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.
- Prevalence
  - 10%–14% in general cirrhosis population
  - 16%–21% in those with decompensated cirrhosis
  - 10%–50% in patients with transjugular intrahepatic portosystemic shunt (TIPS).
  - Will occur in 30-40% during clinical course

EASL/AASLD clinical guidelines on HE J. Hepatology. 2014 Aug;60(2):715-35

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# Hepatic Encephalopathy (HE)

- Types of HE:
  - Type A → acute liver failure
  - Type B → portosystemic bypass
  - Type C → cirrhosis + portal hypertension

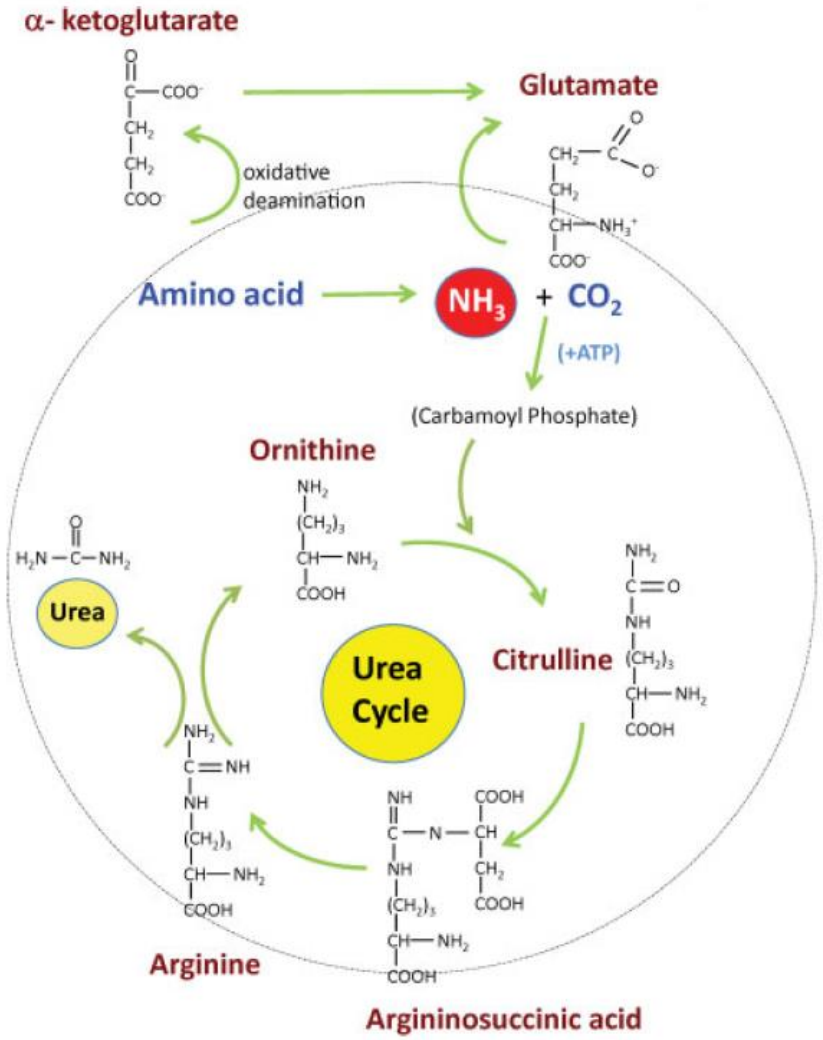
- Impaired quality of life

- Long-term effect on cognition and learning

- Increased mortality risk → Child Pugh classification.

EASL/AASLD clinical guidelines on HE J. Hepatology. 2014 Aug;60(2):715-35
Bajaj JS, et al. Gastroenterology. 2010;138:2332–40

# $NH_3$ metabolism




Rahimi RS et. al. Semin Liver Dis 2016; 48-55

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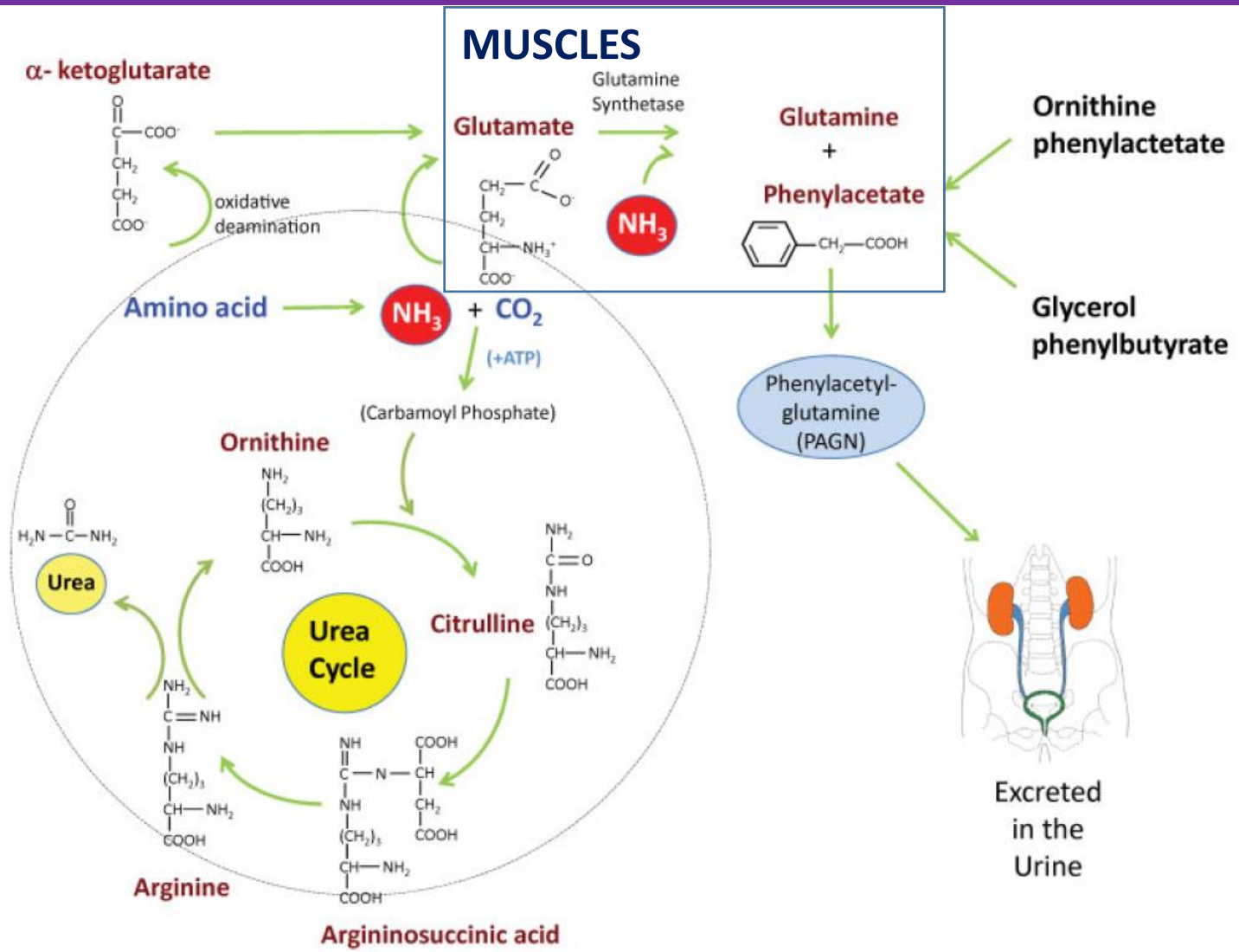
# $NH_3$ metabolism




Rahimi RS et. al. Semin Liver Dis 2016; 48-55

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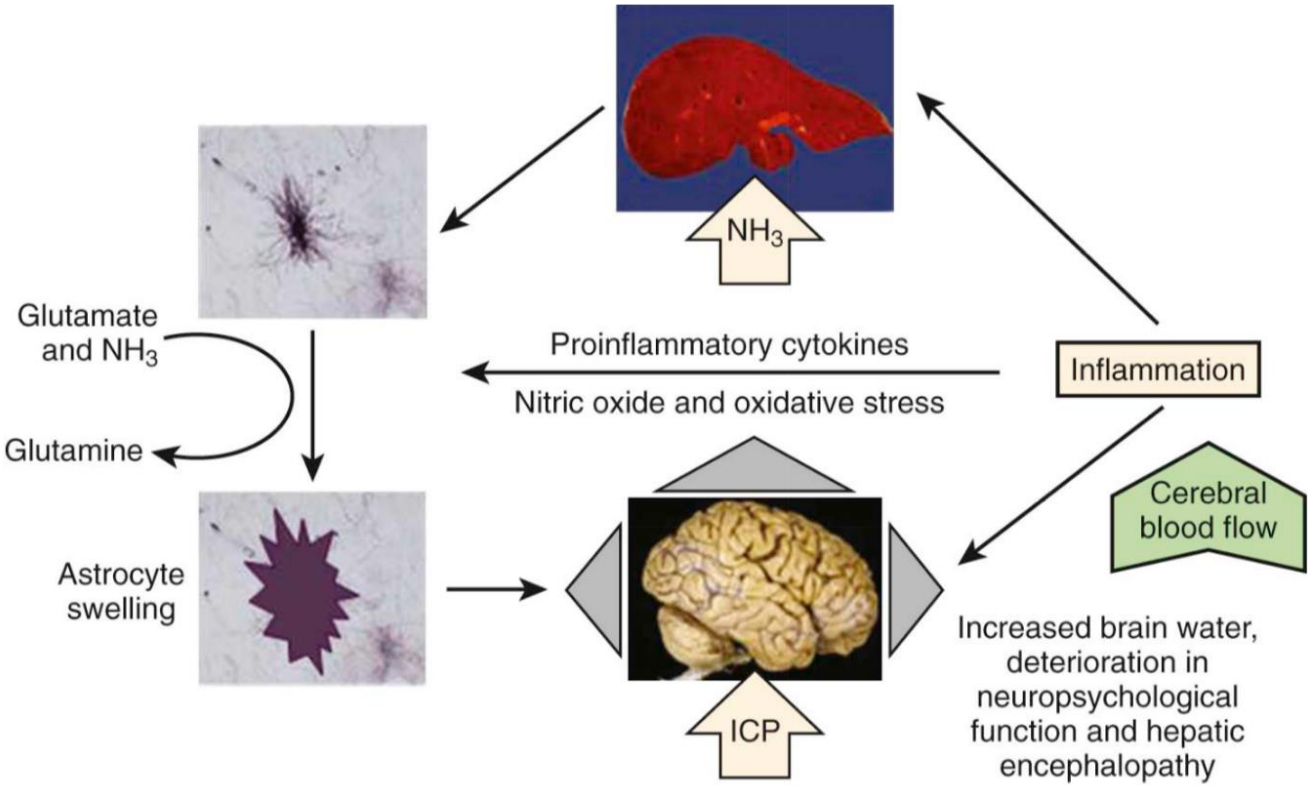
# Pathogenesis of HE

**Hyperammonia**

- $NH_3$ from Gut Bacteria
- $NH_3$ produced by enterocytes
  - Glutamine → Glutamate + $NH_3$
- ↓ ability of hepatocytes to metabolize $NH_3$
- Sarcopenia/muscle waisting
- Portal hypertension → shunting of $NH_3$




Rahimi RS et. al. Semin Liver Dis 2016; 48-55

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# Classification: West-Haven/ Conn criteria

## I (covert HE)

- Minimal behavior changes
- Altered sleep rhythm
- Shortened attention span

## II (overt HE)

- Disorientation
- Drunk feeling
- Inappropriate behavior
- Asterixes (not always)

## III (overt HE)

- Clear disorientation
- Inconsistent speak
- Drowsy

## IV (overt HE)

- Coma
- No response to pain

Atterbury et al. Am J Dig Dis 1978

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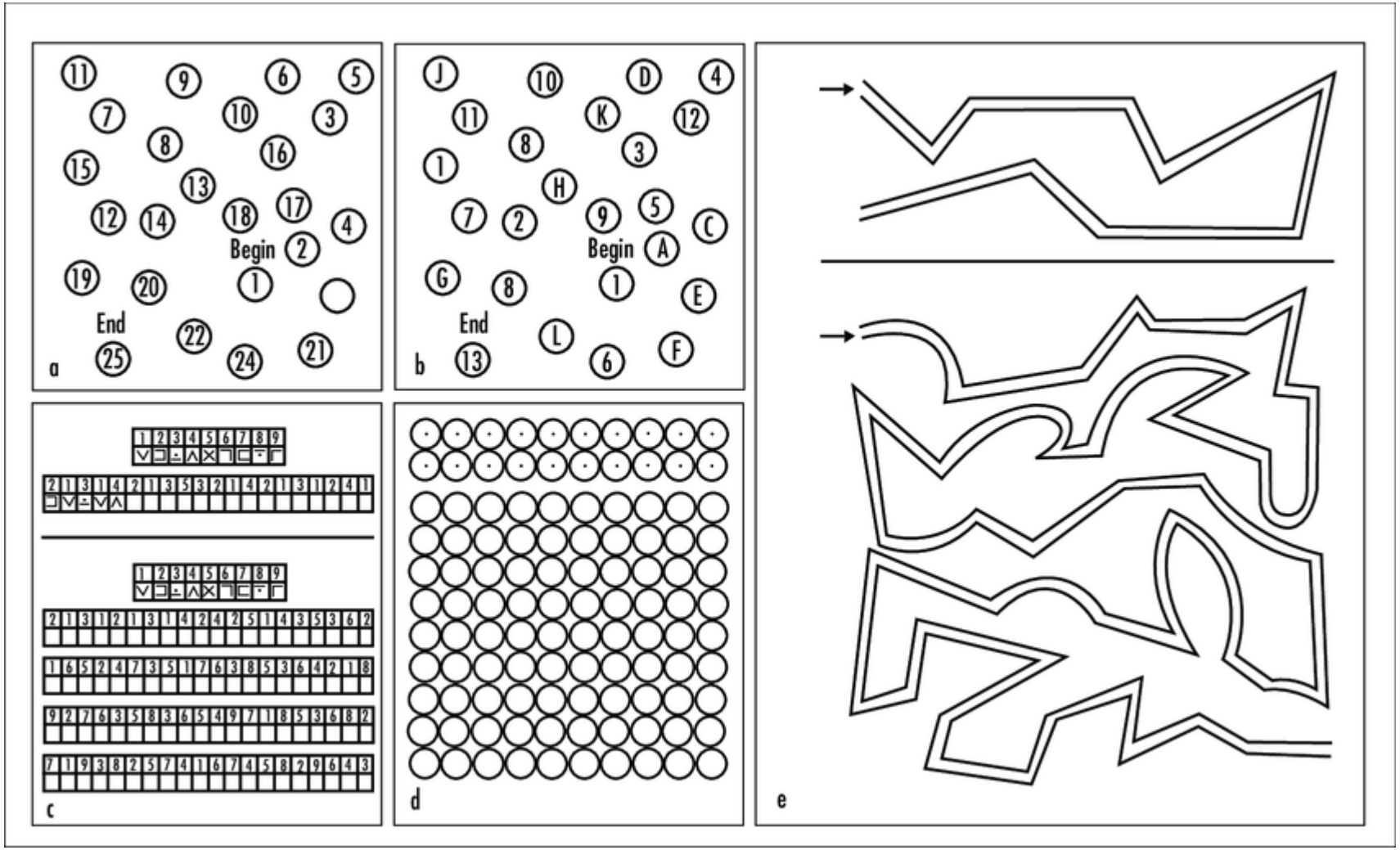
# Diagnosis: Psychometric hepatic encephalopathy score (PHES)




1. Number connection test-A
2. Number connection test-B
3. Digit-symbol test
4. Serial dotting test
5. Line tracing

Amodio et al, 1999

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# (Differential) Diagnosis

# simplified 1-minute Animal Naming Test (S-ANT$_1$)

- Naming as much as animals as you can in 1 minute
- Corrected for education → 3 animals for < 8 years of education
- Corrected for age → 6 animals for age > 80 years

| | Controls | | Patients With Cirrhosis (n = 327) | | | | |
|---|---|---|---|---|---|---|---|
| | Healthy Subjects (n = 208) | IBD (n = 40) | Unimpaired (n = 169) | Pooled MHE and Grade 1 HE (HE <Grade 2) (n = 126) | MHE (n = 76) | Grade 1 HE (n = 50) | HE ≥Grade 2 (n = 32) |
| S-ANT$_1$ | 23 ± 0.5* | 25 ± 1.0 | 16 ± 0.7† | 12 ± 0.4†,‡ | 13 ± 0.5†,§ | 11 ± 0.6†,§ | 4 ± 0.9†,‖ |

Campagna et al, Hepatology 2017 (66): 198-208

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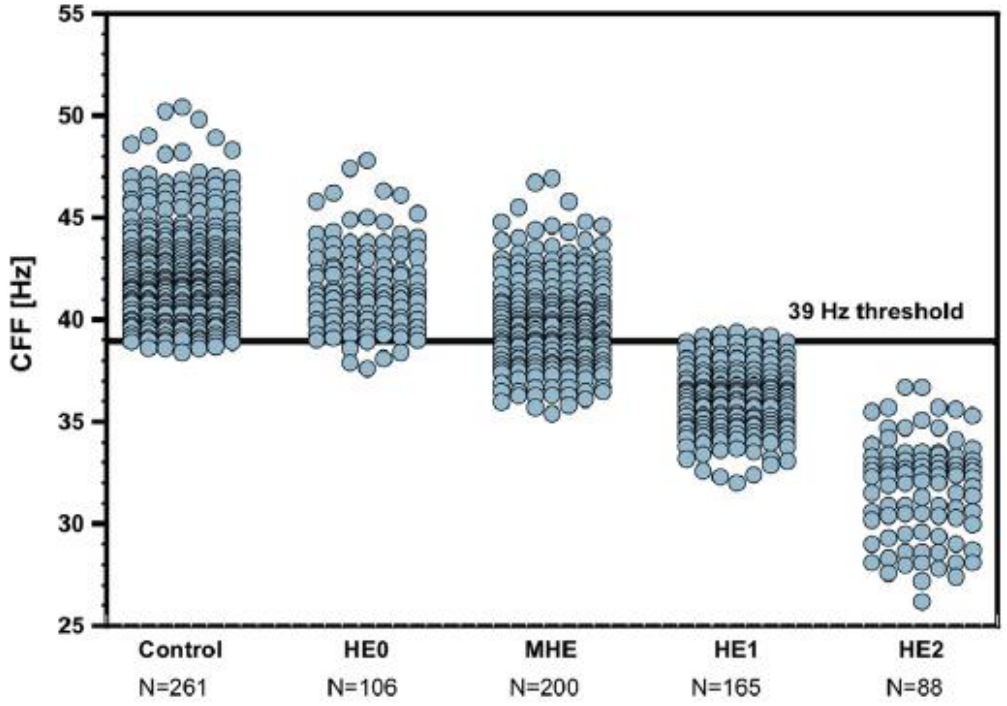
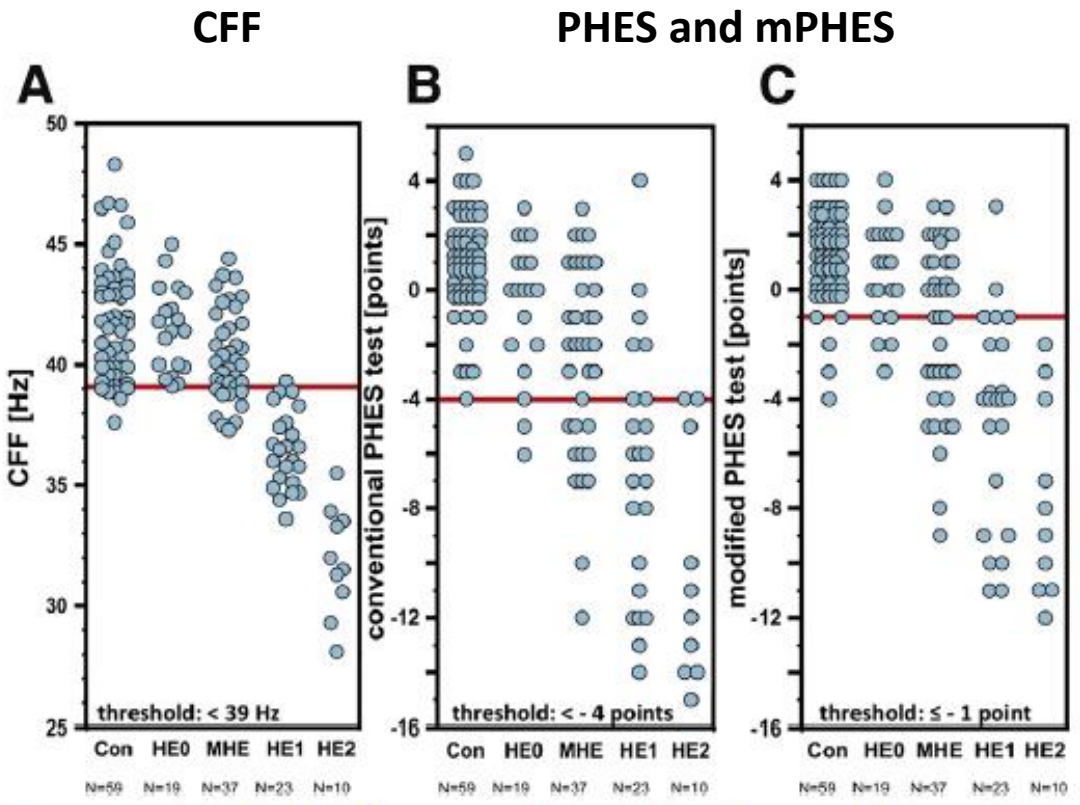
# Critical Flicker Frequency (CFF)




Kircheis et al, Gastroenterology 2014 (146): 961-969

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# CT-scan?

- Risk of intracerebral hemorrhage is 5-fold increased patients with cirrhosis presenting with a first episode of altered consciousness.

- Most patients with grade > 2 will undergo a CT-scan.

Grønbaek H, et al. BMC Gastroenterol 2008;8:16.

# Differential diagnosis

- Infection
  - Sepsis, SBP, urinary tract infection, pneumonia
- Drug induced
  - Opioids, sedative, alcohol
- Noncompliance
- Metabolic
  - Hyperglycemia, electrolytes disturbance, Wernicke encephalopathy, vitamin B1/B12 deficiency
- Neurologic
  - CVA, subdural hematoma (trauma)
- Systemic organ failure
  - Heart failure, AKI

# Precipitating factors

| | Factor | Mechanism |
|---|---|---|
| 1 | Infection | |
| 2 | GI bleeding | |
| 3 | Hypovolemia and use of diuretics | |
| 4 | AKI | |
| 5 | Constipation | |
| 6 | Psycho-active medication | |
| 7 | TIPS | |
| 8 | Hyponatremia | |
| 9 | Additional liver injury | |
| 10 | Malnutrition | |

1. Bajaj, 2010; 2. Jiang et al., 2008; 3. Blei & Córdoba, 2001

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# Precipitating factors

| | Factor | Mechanism |
|---|---|---|
| 1 | Infection | ↑ $NH_3$ by catabolic metabolism, decreased kidney function and inflammation |
| 2 | GI bleeding | Blood = protein = ↑ intestinal peptides (containing –NH) = ↑ $NH_3$ |
| 3 | Hypovolemia and use of diuretics | Hypokalemia and alkalosis increase $NH_3$ production<br>Dehydration worseness brain dysfunction |
| 4 | AKI | ↓ clearance of $NH_3$ |
| 5 | Constipation | Persistent intra-intestinal production of $NH_3$ |
| 6 | Psycho-active medication | Worsening of HE |
| 7 | TIPS | By-passing $NH_3$ and toxins → up-to 30% of patients |
| 8 | Hyponatremia | ↑ astrocyte swelling |
| 9 | Additional liver injury | ↓ catabolism $NH_3$ |
| 10 | Malnutrition | Increased production and ↓ catabolism $NH_3$ |

1. Bajaj, 2010; 2. Jiang et al., 2008; 3. Blei & Córdoba, 2001

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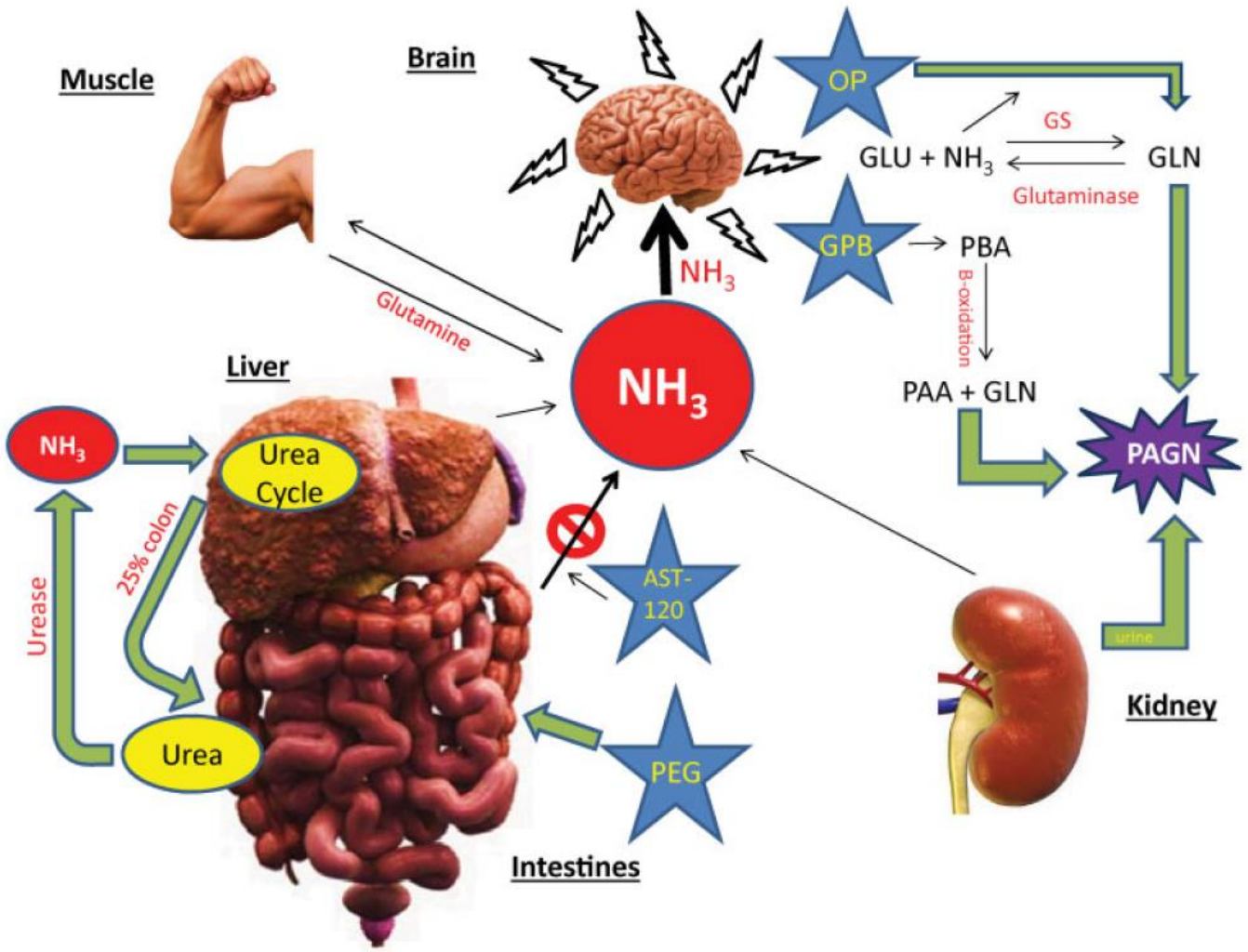
# Treatment options

# 1st line treatment of HE

- **Nonabsorbable disccharides:**
  - **Lactulose**
- Antibiotics:
  - Rifaximin
- Laxatives
  - Poly Ethylene Glycol (PEG) → Kleanprep
- Glycerol Phenylbuturate (GPB)
- Branched chain amino acids (BCAA)
- Benzodiazepine receptor agonists
  - Flumazenil
- Ammonia scavengers
  - L-Ornithine-L-Aspartate (LOLA)
  - Natriumbenzoaat
- Glutaminase inhibitors




EASL/AASLD. J Hepatol. 2014;61:642–59; Rahimi RS, Rockey DC Seminars in Liver disease 2016

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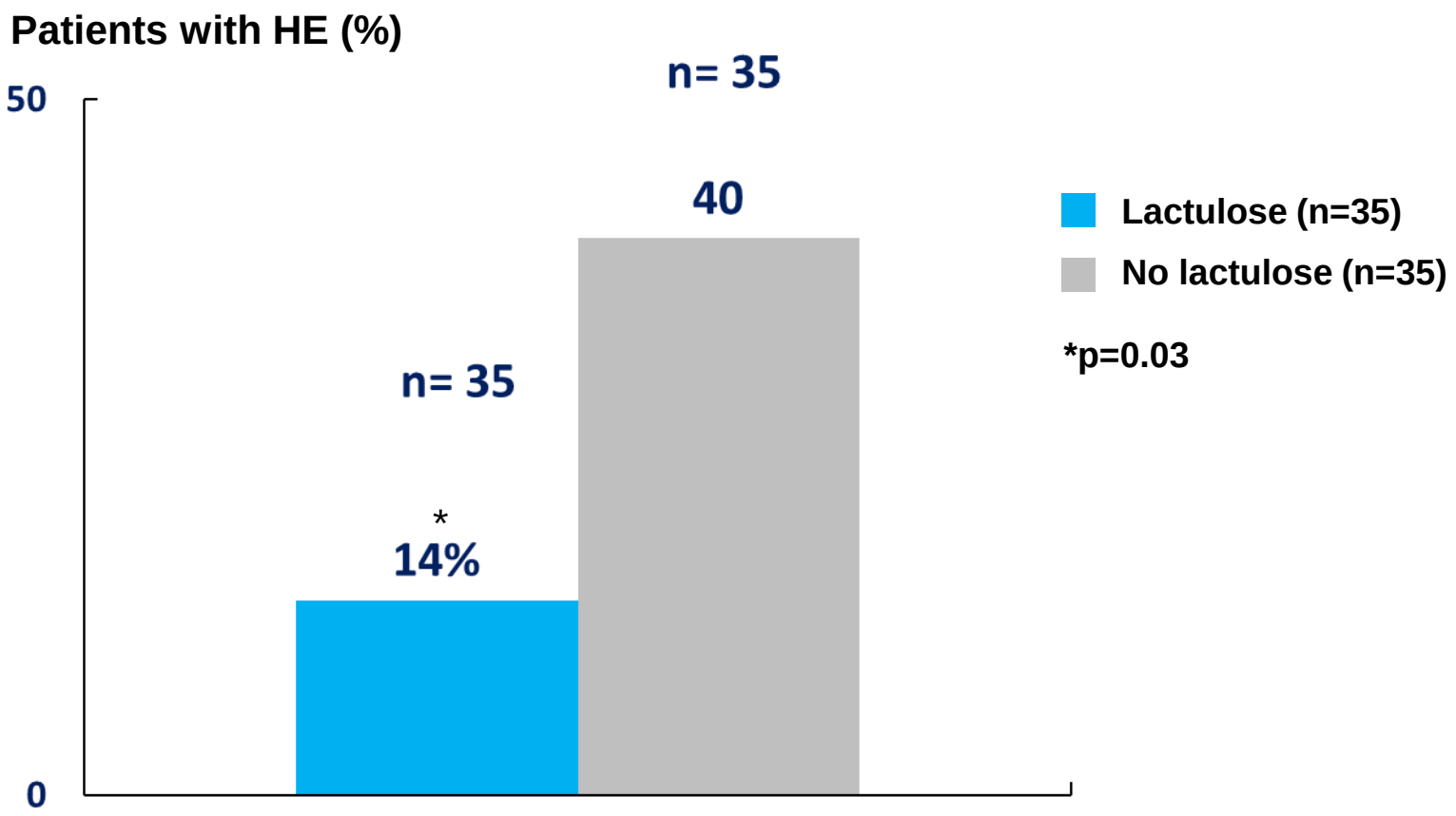
# Treatment of grade 2/3 HE

- Cornerstone = ↓ $NH_3$
- To open the bowels with Nonabsorbable Disaccharides
  - lactulose of lactitol
- Start with 25mg b.i.d.
  - Stool frequency 2-3/day
- Working mechanism:
  - $NH_3 + H^+ \leftrightarrow NH_4^+$
  - ↓ Time of $NH_3$ absorption

Jiang et al., Eur J Gastroenterol Hepatol 2008, Bass et al., N Engl J Med 2010, Wright et al., International Journal of Hepatology 2011
Di Franchis et. al. Journal of Hepatology 2015;63:743–752

# Lactulose can prevent HE after variceal bleed




*p=0.03

Sharma P, et al. J Gastroenterol Hepatol. 2011;26:996–1003

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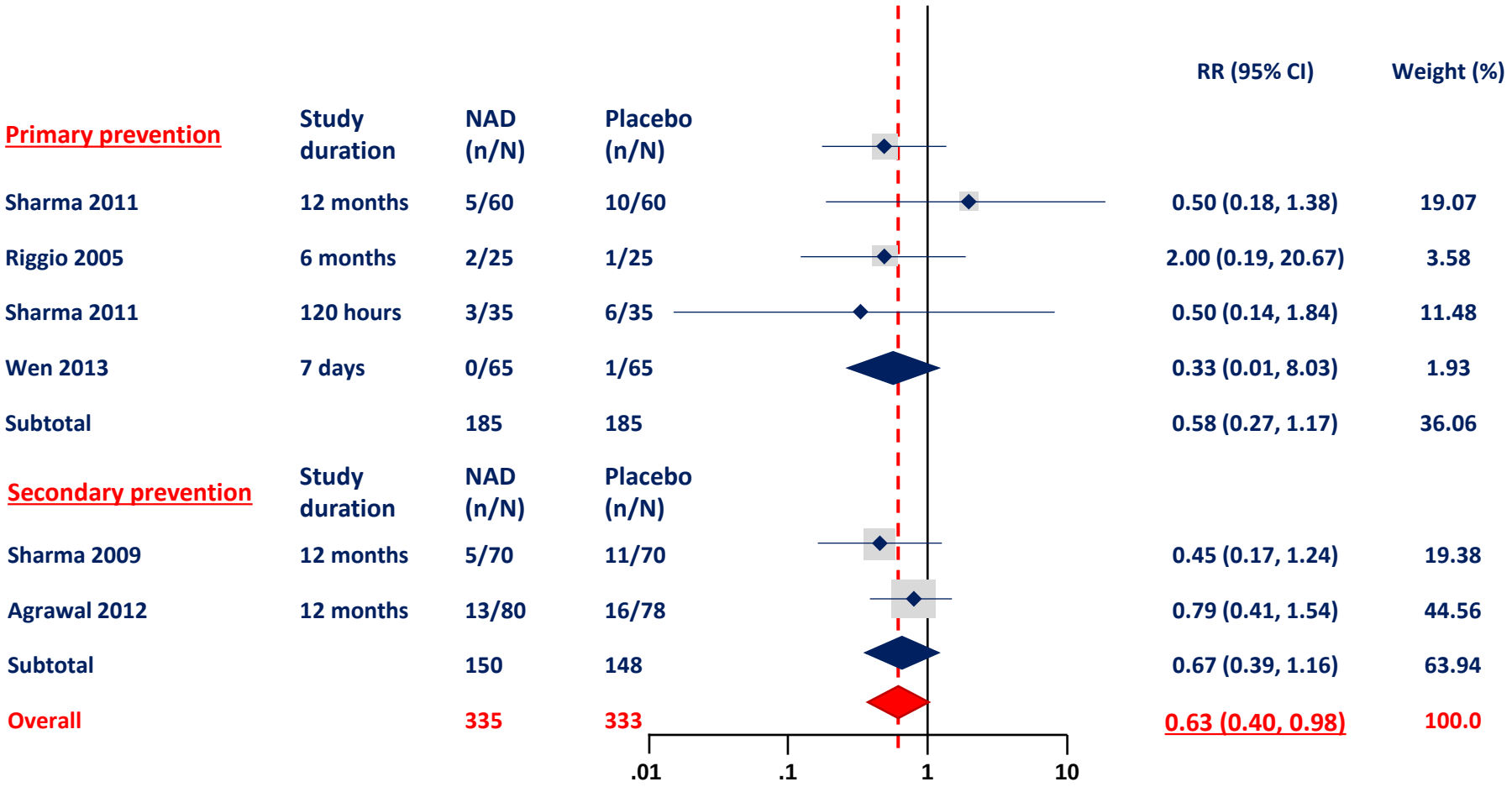
# NADs improve overall survival




Weights are from random effects analysis

Gluud LL, et al. Cochrane Database Syst Rev. 2016;(5):CD003044

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# 2nd line treatment of HE

- Nonabsorbable disccharides:
  - Lactulose
- **Antibiotics:**
  - **Rifaximin**
- Laxatives
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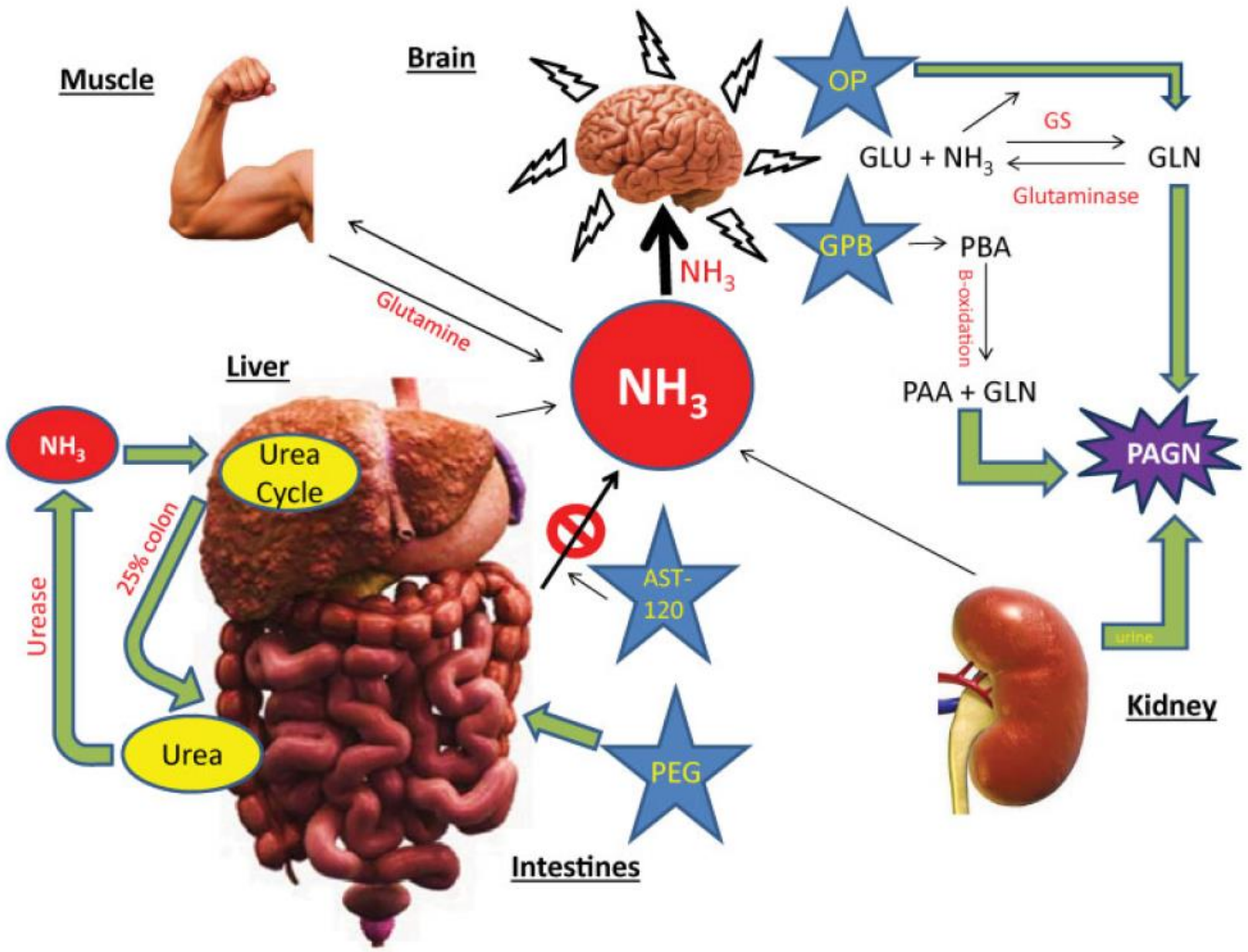


EASL/AASLD. J Hepatol. 2014;61:642–59

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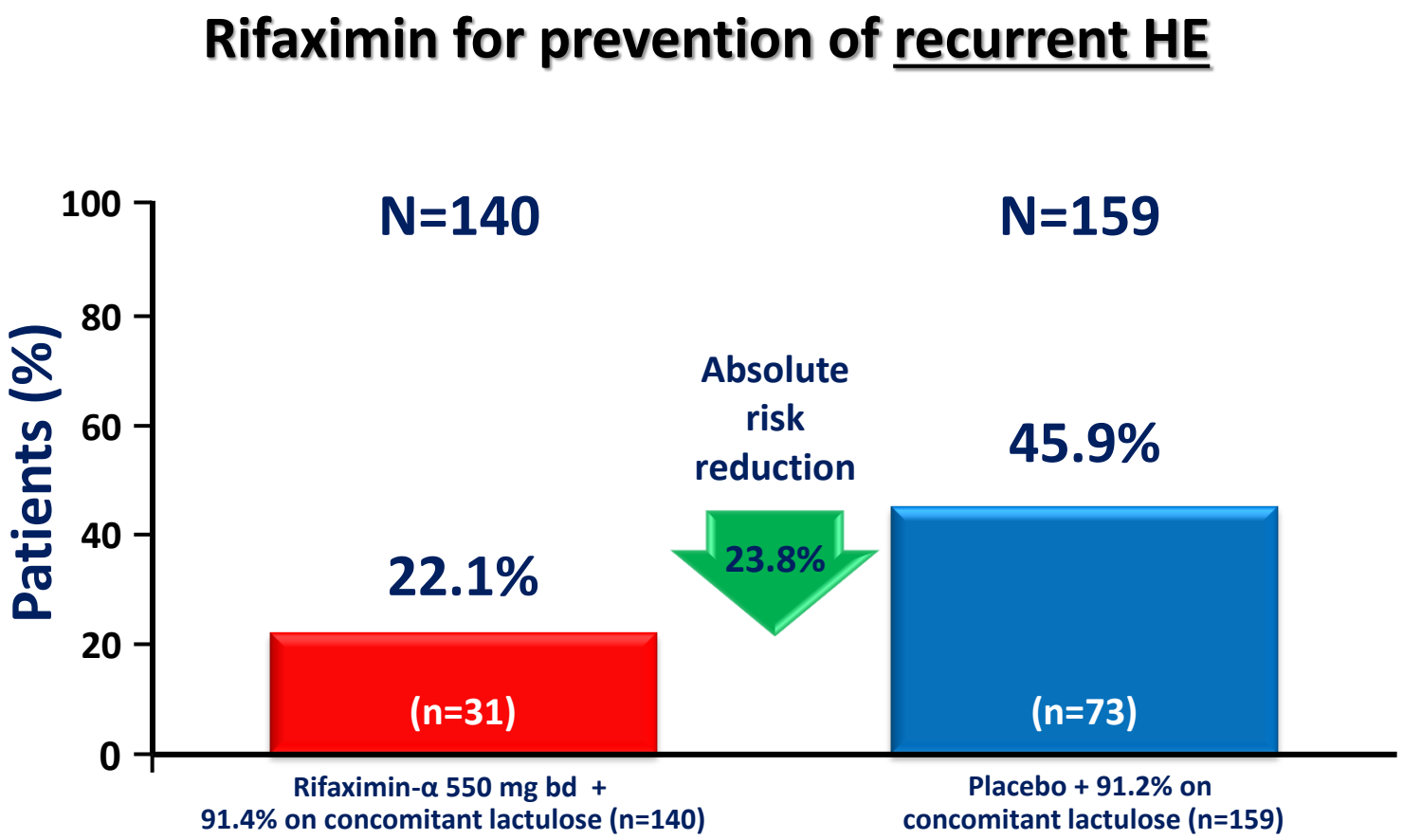
# Lactulose and rifaximin for HE




- **NNT = 4** to prevent one breakthrough of overt HE episode.
- **NNT = 9** to prevent one hospitalisation involving hepatic encephalopathy

Bass NM, et al. N Eng J Med. 2010;362:1071–81

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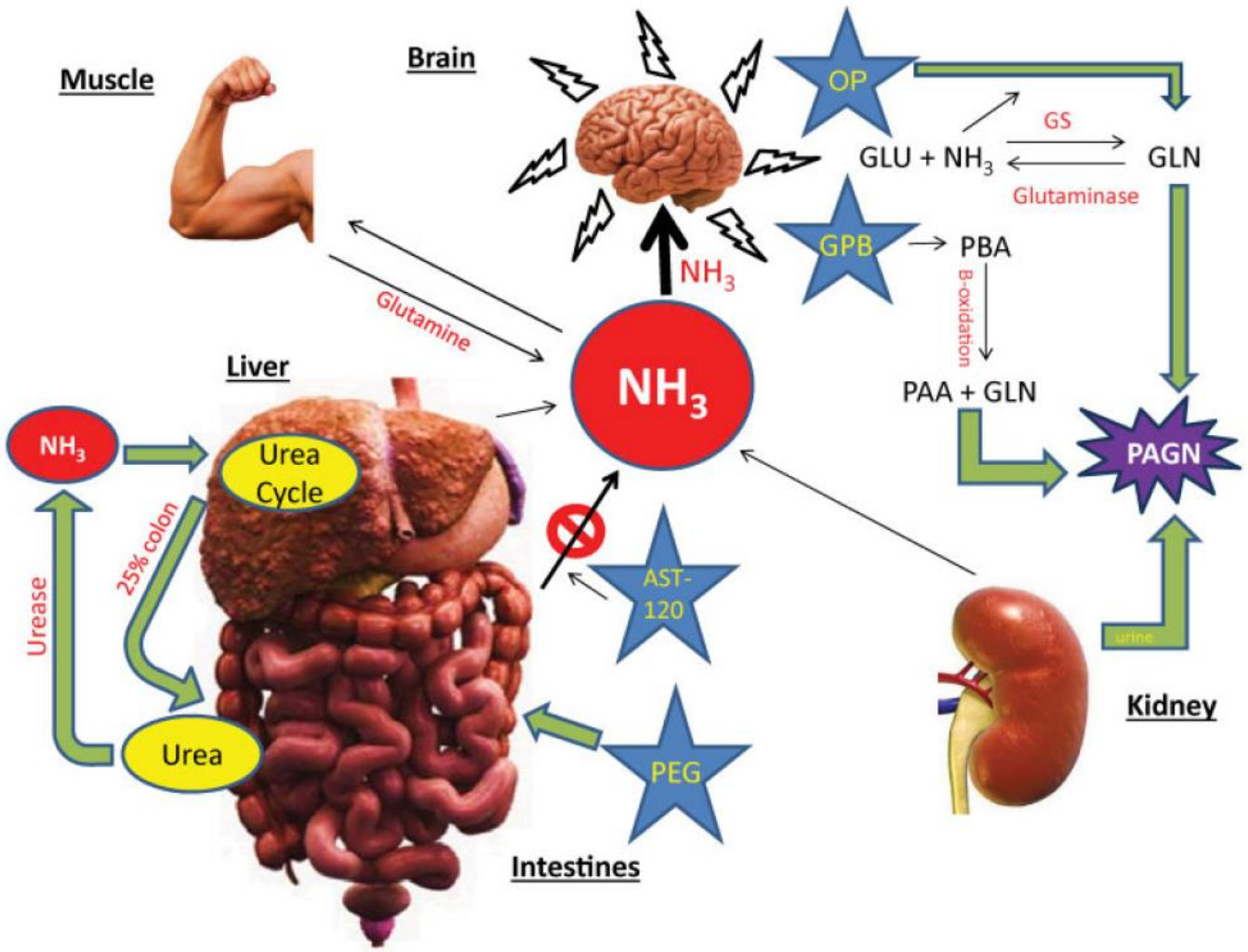


EASL/AASLD. J Hepatol. 2014;61:642–59

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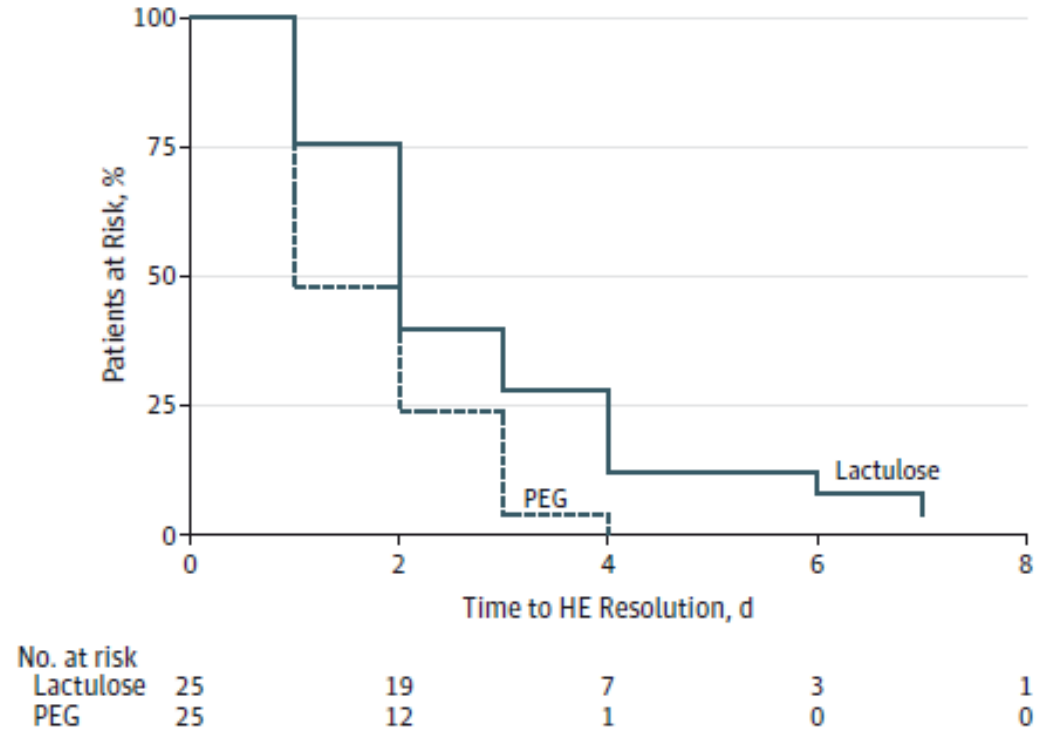
# PEG vs Lactulose for HE

- 50 patients
  - 25 patients receiving standard of care lactulose
    - 20-30 mg 3x a day orally/ nasogastric tube
    - 200 g rectally at the discretion of the physician.
  - 25 patients receiving 4L poly-ethylene-glycol (PEG)

- 91% (PEG) vs 52% (lactulose) had 1 or more points (WH) improvement after 24 hours.

- Time to HE resolvement in PEG group significantly shorter.




Rahimi et al. JAMA Intern Med. 2014;174(11):1727-1733.

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# 2nd line treatment of HE

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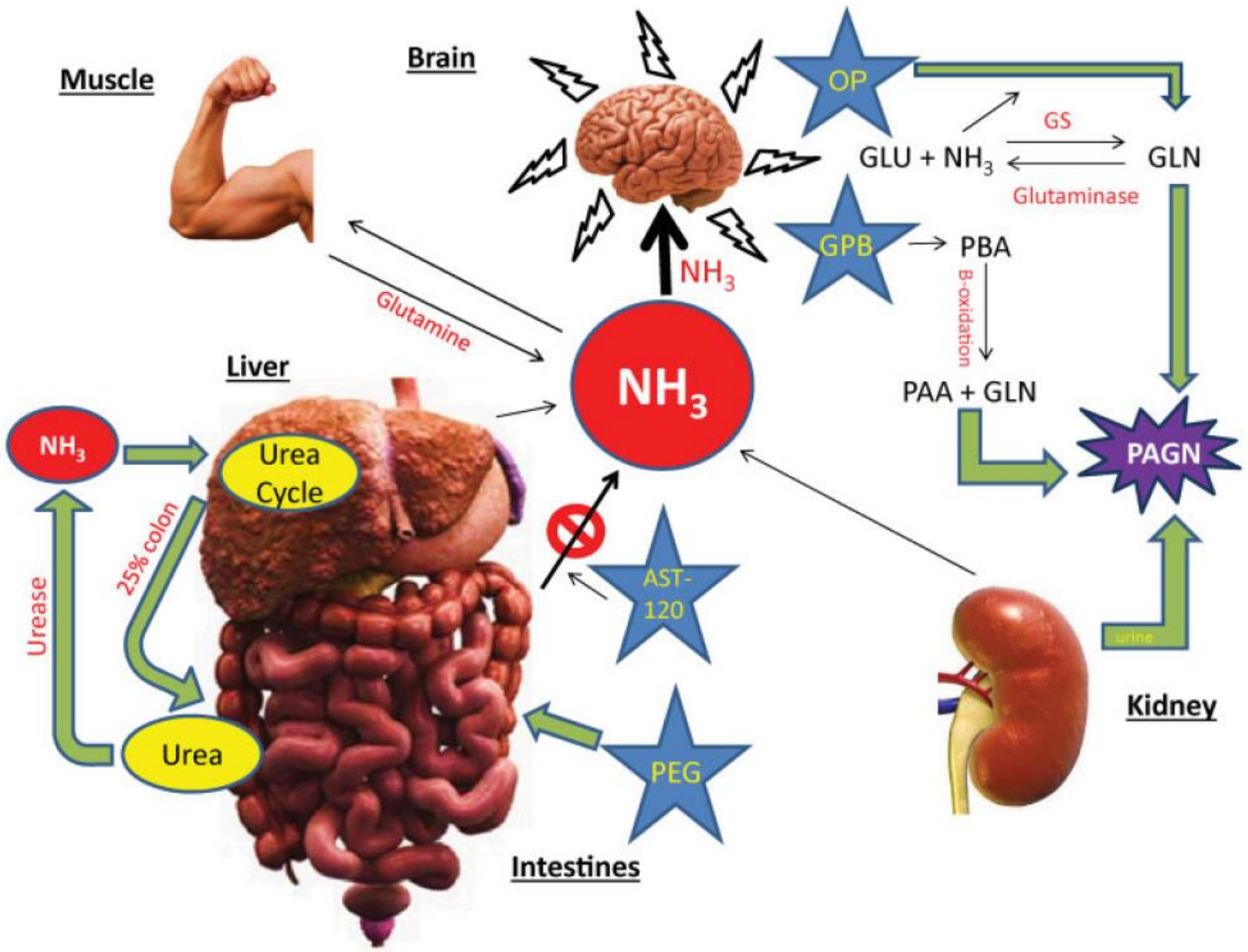


EASL/AASLD. J Hepatol. 2014;61:642–59

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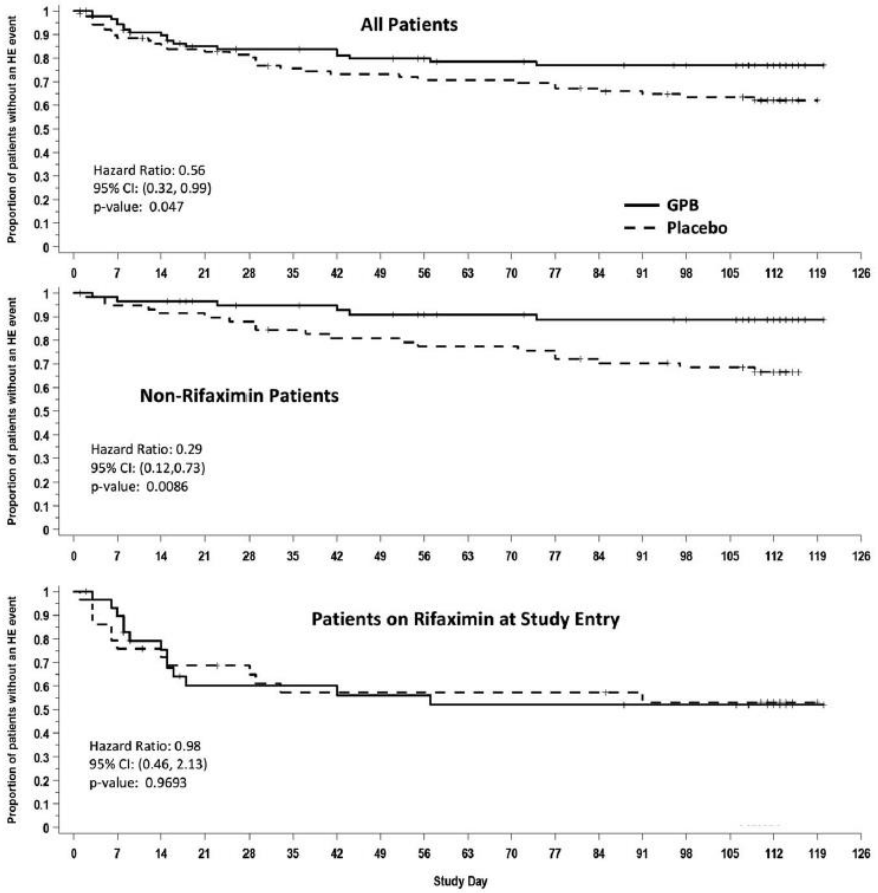
# Glycerol phenylbuturate (GPB)

- Multicenter, randomized, double blind, placebo-controlled phase-II trial.
- 55 patients receiving 16 weeks GPB 6mL twice daily
  - 21% experinced HE event
- 67 patients receiving 16 weeks placebo
  - 36% experienced HE event
- Safe
  - Nausea, peripheral edema, AST increase




Rockey et al Hepatol. 2014;59(3):1071–83

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# 2nd line treatment of HE

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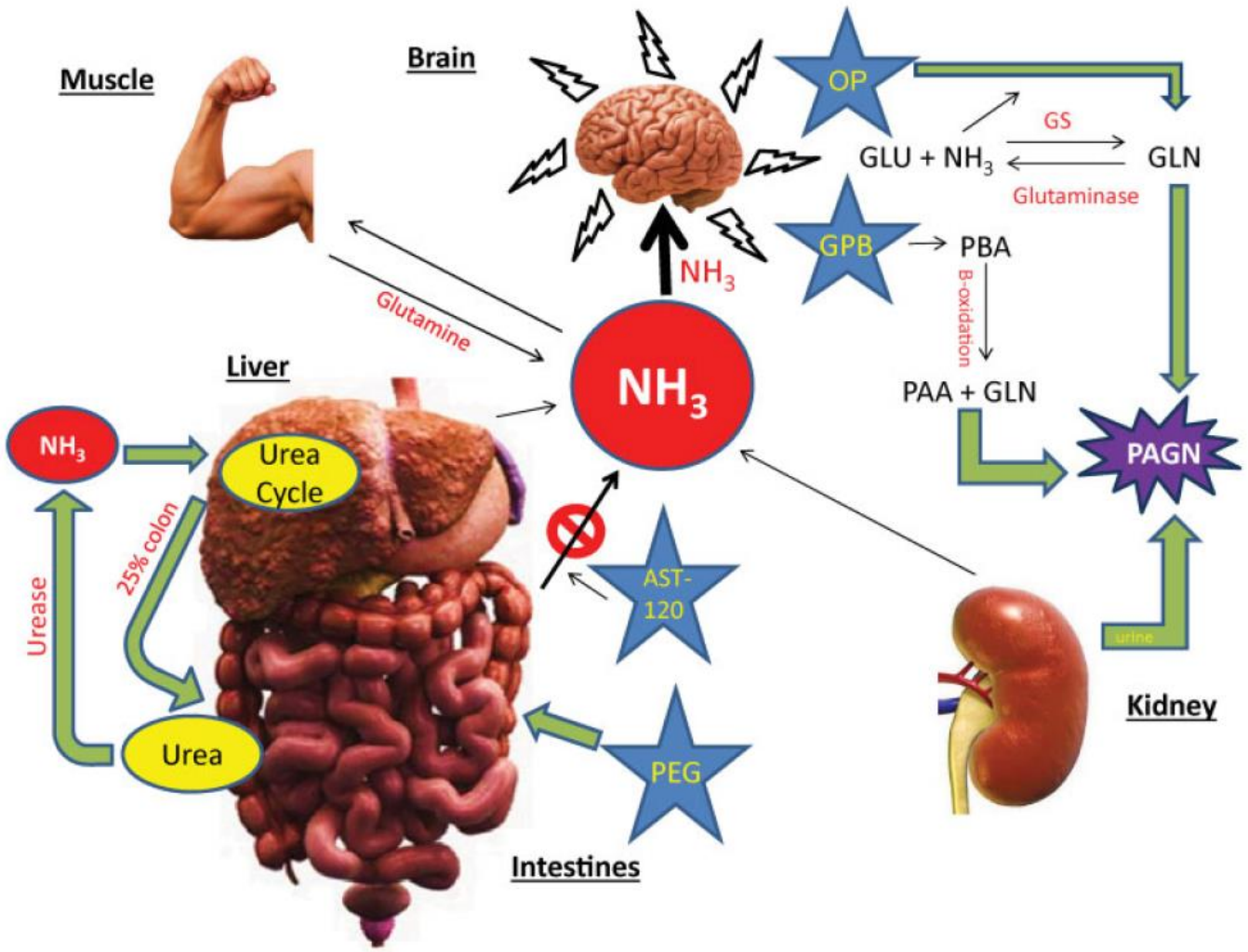


EASL/AASLD. J Hepatol. 2014;61:642–59

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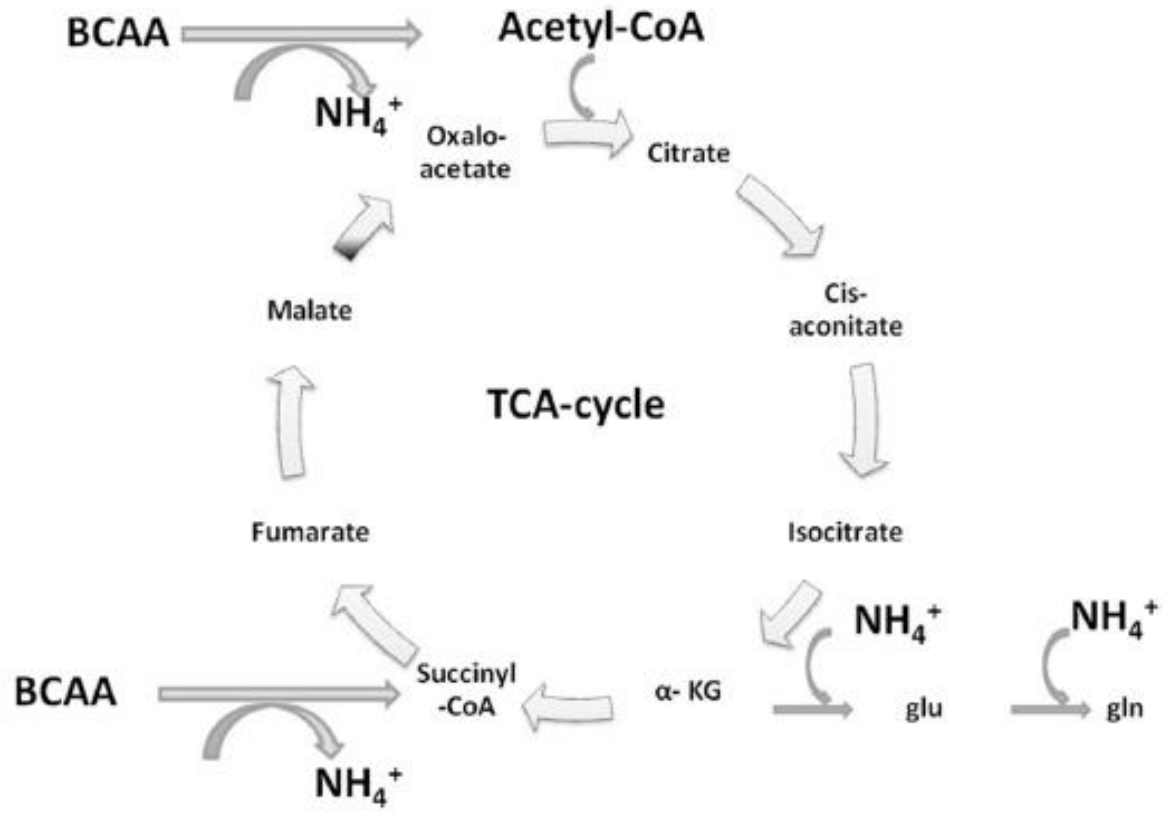
# Branched-chain amino acids supports ammonia detoxification

- BCAAs enhance muscle mass
- Stimulation of protein synthesis
- Meta-analysis:
  - Beneficial effect on HE
  - NNT 5
- 12-30 g/day




Damm et al. J. Clin. Exp. Hepatol 2018;8:448–451

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# 2nd line treatment of HE

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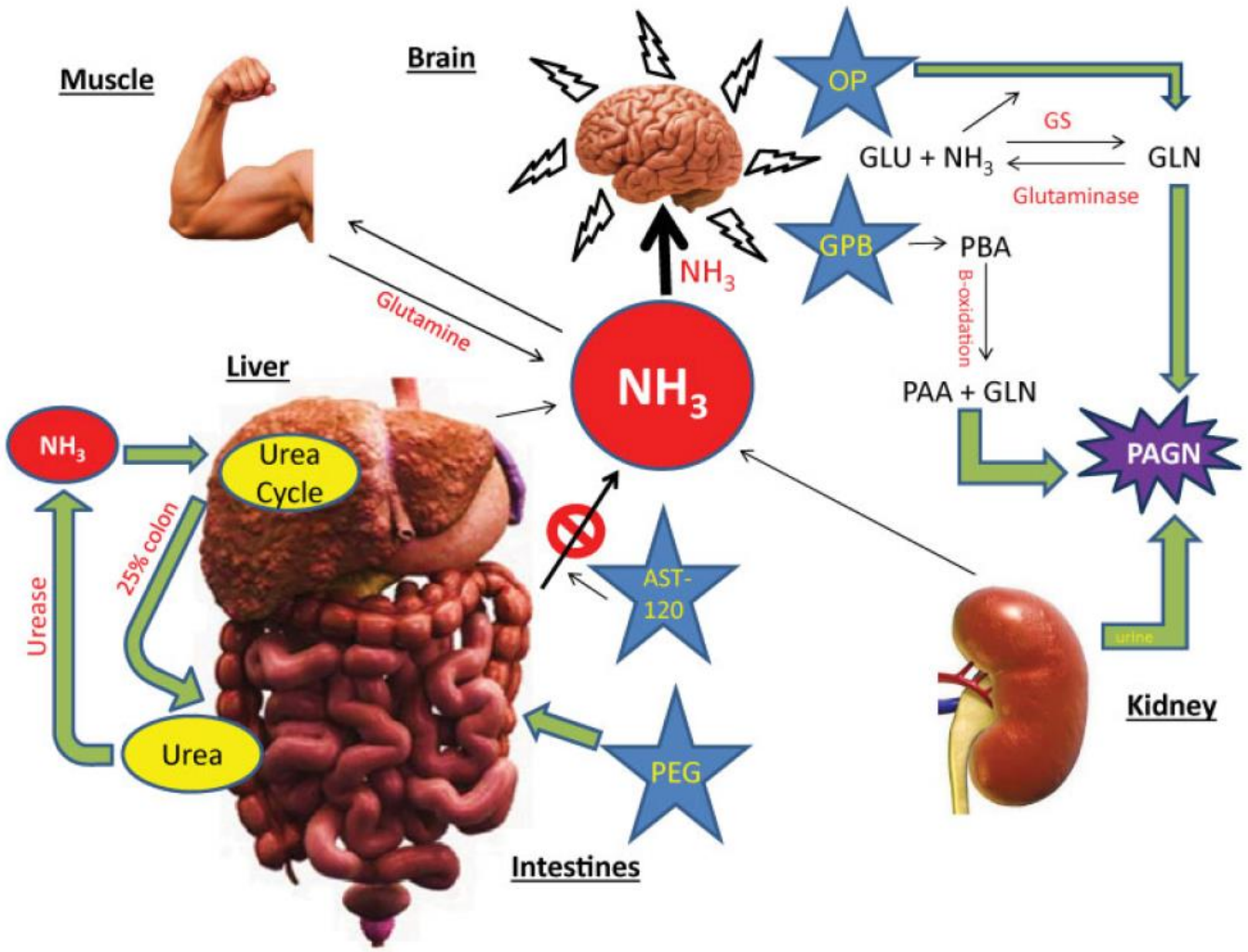
Liver transplantation




EASL/AASLD. J Hepatol. 2014;61:642–59

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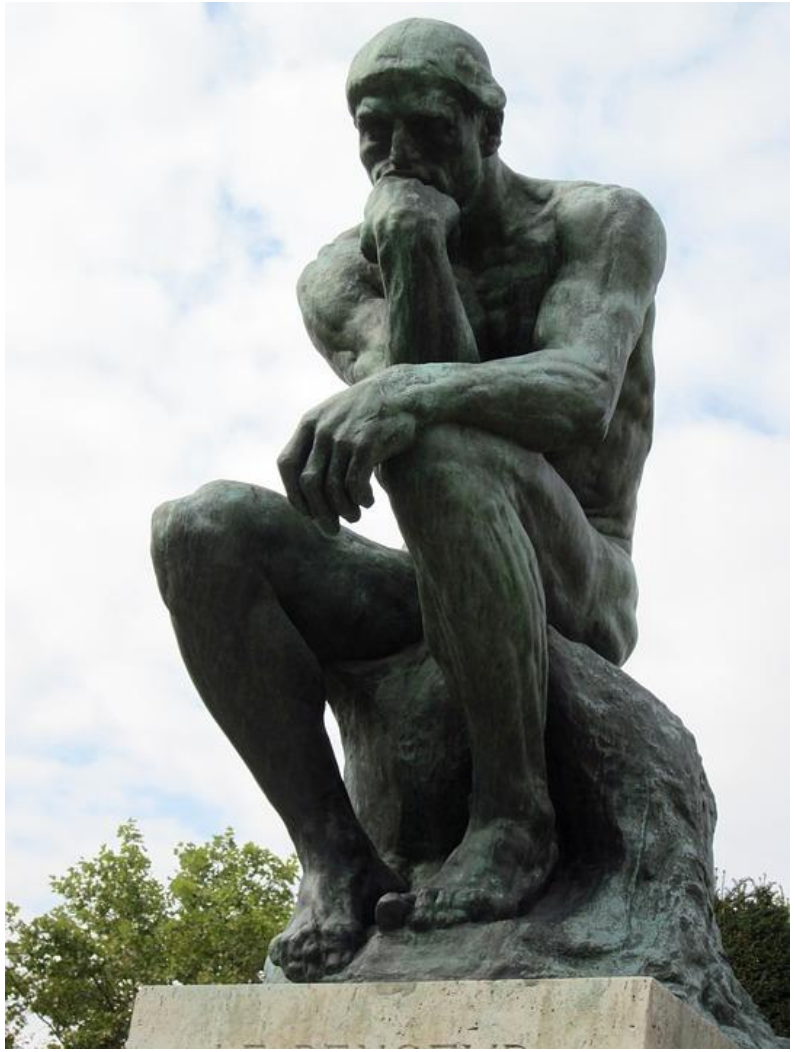
# Conclusions

1. HE is frequently seen in cirrhotic patients
2. Often luxated by precipitating factor
3. Most evidence on NAD for oHE
4. Rifaximin after recurrence (or in nonresponse)
5. Other treatment options when 3 and 4 not effective → be creative

# Questions?



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