16 Paris Hepatology Conference

Hybrid PHC 2024

Institut Pasteur - Paris

18 - 19 March

Encephalopathy Revisited 2024

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Service d'hépato-gastroentérologie

Brain Liver Pitié-Salpêtrière Study Group, INSERM UMR_S 938, CDR Saint-Antoine
& Institut de Cardiométabolisme et Nutrition ICAN

AP-HP.Sorbonne Université, Site Hôpital Pitié-Salpêtrière
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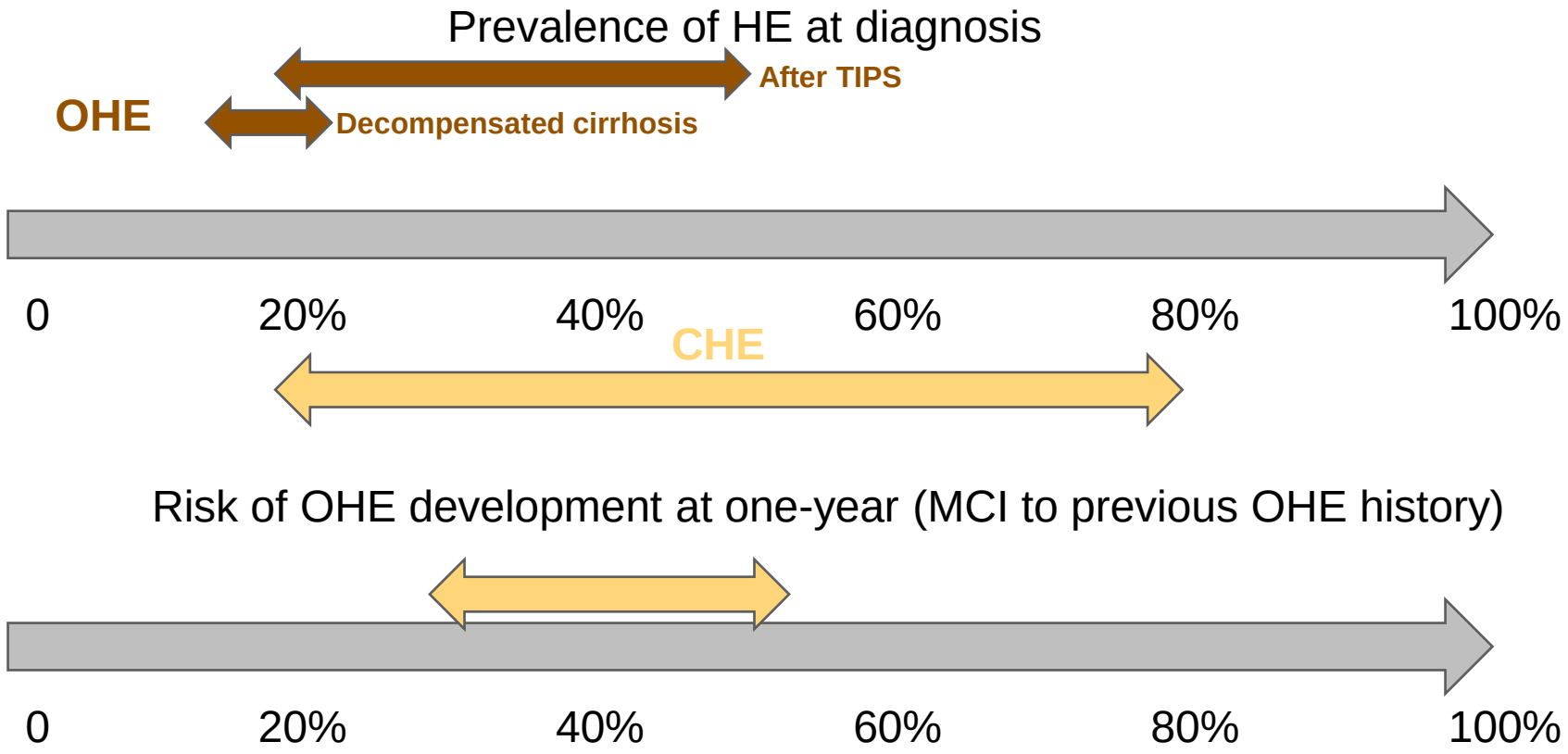
BLIPS

Disclosures

- Conferences: Gore, Gilead
- Board: Gore, Gilead, Abbvie, Alfasigma, Biocryst, Bayer

The Burden of Hepatic Encephalopathy



Hepatic Encephalopathy and ACLF

B

Patient Group	Prevalence	28-Day Mortality	Assigned Grade
	% of patients		
Absence of OF	68.3	4.4	Absence of ACLF
Single, nonkidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1
Single, nonkidney OF with KD or BD	4.2	27.8	ACLF-1
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3
Four to six OFs	1.4	88.9	ACLF-3

Organ System	1 Point	2 Points	3 Points
Liver	Bilirubin <6 mg/dl	Bilirubin 6.0–11.9 mg/dl	Bilirubin ≥12 mg/dl
Kidney	Creatinine <1.5 mg/dl Creatinine 1.5–1.9 mg/dl	Creatinine 2.0–3.4 mg/dl	Creatinine ≥3.5 mg/dl or RRT
Brain (West Haven criteria)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR <2.0	INR 2.0–2.4	INR ≥2.5
Circulation	MAP ≥70 mm Hg	MAP <70 mm Hg	Vasopressor requirement
Respiration	Pao_2/Fio_2 >300 Spo_2/Fio_2 >357	Pao_2/Fio_2 201–300 Spo_2/Fio_2 215–357	Pao_2/Fio_2 ≤200 Spo_2/Fio_2 ≤214

Brain dysfunction or Brain Failure = Acute Encephalopathy

Arroyo V et al., NEJM 2020

Agenda (against dogmas)

- Acute Encephalopathy: always HE in cirrhotic patients ?
- Cognitive disorders in cirrhotic patients: always Covert Hepatic Encephalopathy ?
- TIPS and HE: friends or foes ?

Agenda (against dogmas)

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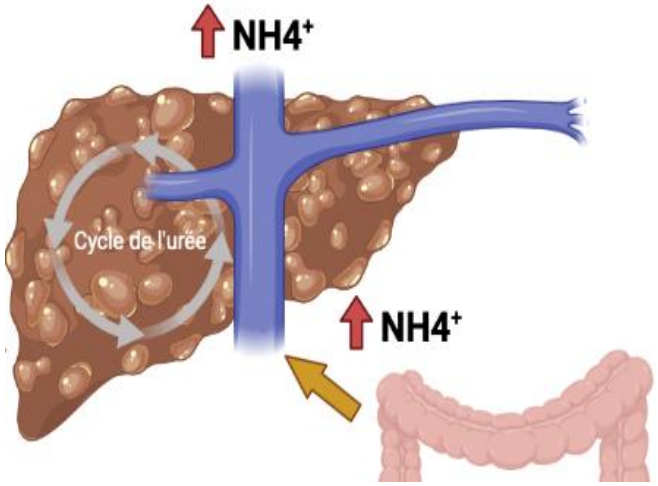
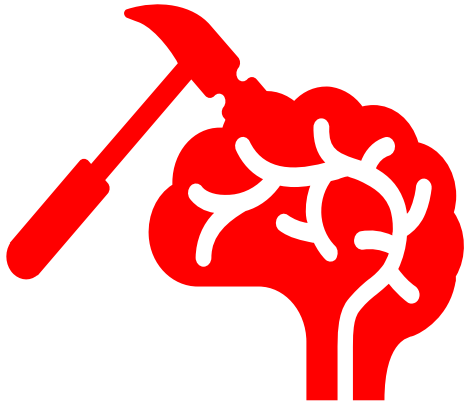
First Cause of Acute Encephalopathy: Hepatic Encephalopathy





Recommendation

- In patients with delirium/encephalopathy and liver disease, plasma ammonia measurement should be performed, as a normal value brings the diagnosis of HE into question **(LoE 4, strong recommendation, 95% consensus).**

Neurological trouble **caused** by acute or chronic liver injury/portosystemic shunt (Does NOT consider the UNDERLYING cause of liver disease nor other causes of delirium)

Vilstrup et al. Hepatology 2014

EASL CPG, J Hepatol 2022

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Ammonia levels: >20 years of medical litterature…

Certainties

1. Ammonia levels **are always elevated in case of HE**
2. Ammonia levels correlate with the severity/grade of HE (True ?)
3. Ammonia levels may be elevated without any HE symptoms
4. When follow-up data are available, ammonia levels remain sometimes stable and elevated, even among patients no longer presenting with overt HE

Pitfalls of the studies

1. Differential diagnosis of HE was never studied
2. Other causes of cerebral injuries were never assessed
3. MHE was poorly studied (lots of confounding factors … obesity, MASH …)

Shalimar KD et al., Hepatology 2019
Reuter B et al., APT 2018

Quero et al. Hepatology 1996
Vilstrup H et al., Hepatology 2014

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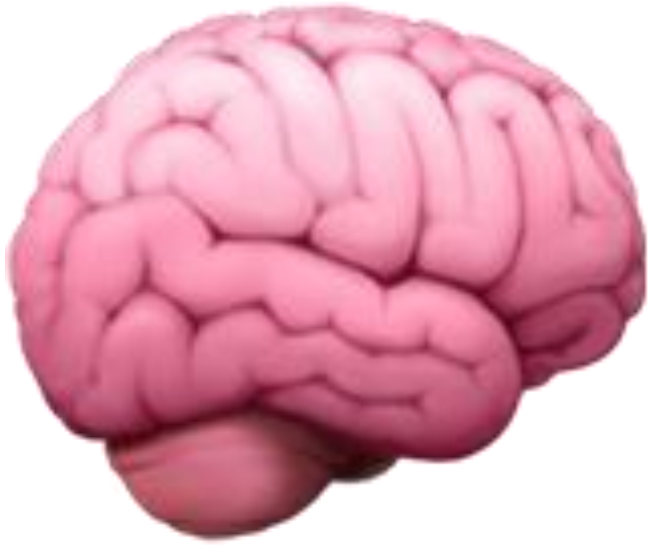
Causes of Acute Encephalopathy in ACLF pts

Hepatic Encephalopathy

Metabolic
- Renal failure, hyponatremia
- **Drug-induced encephalopathy**
- Hypercalcemia
- Diabetic: hypoglycemia, ketoacidosis, hyperosmolar, lactate acidosis



Septic Encephalopathy

Traumatic
- Subdural hematoma
- Epidural hematoma
- Subarachnoid haemorrhage

Psychiatric disorders

Related to alcohol:
- *Delirium tremens*
- Gayet-Wernicke
- Intoxication
- Status epilepticus

Strokes

Recommendation

- In patients with delirium/encephalopathy and liver disease, brain imaging by CT scan or MRI should be performed in case of diagnostic doubts or non-response to treatment **(LoE 5, strong recommendation, 96% consensus).**

EASL CPG, J Hepatol 2022

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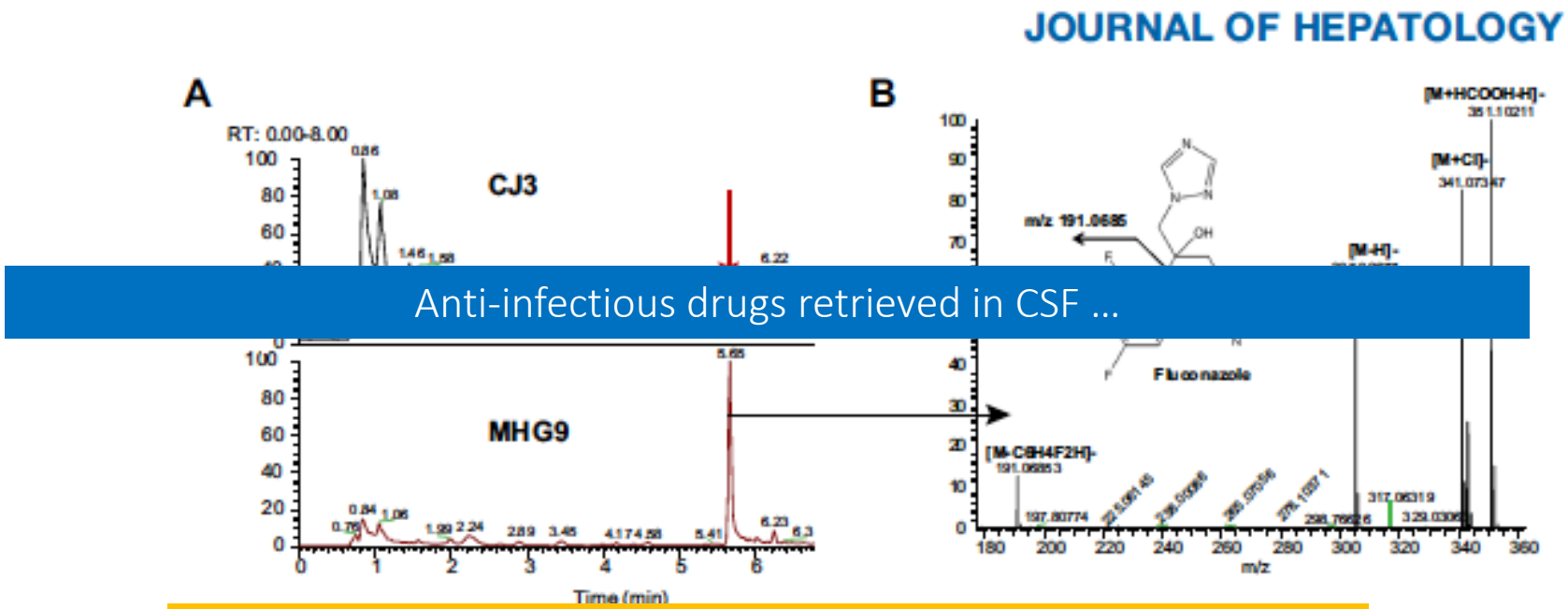
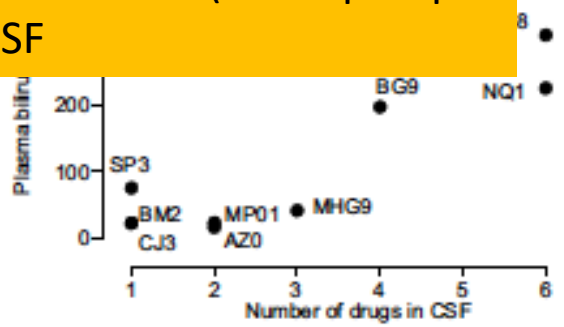
Drug-induced Encephalopathy



Anti-infectious drugs retrieved in CSF …

Fluconazole, fluoroquinolones, beta-lactamines (efflux pumps substrates) in CSF

Fluconazole	MGH9, NQ1, ZG8, AZ0
Diazepam	BC8, MHG9, MP01, NQ1, ZG8
N-Desmethyldiazepam	BC8, MHG9, MP01, NQ1, ZG8
Tazobactam	BG9, NQ1, ZG8
Piperacillin	BG9, NQ1, ZG8
Ciprofloxacin	AZ0, BG9, NQ1, ZG8, SP3
Norfloxacin	CJ3, BC8



STOP the DRUGS

Weiss et al., J Hepatol 2016
Weiss et al., Liv Int 2016
Assaraf et al., Gastroenterology 2017

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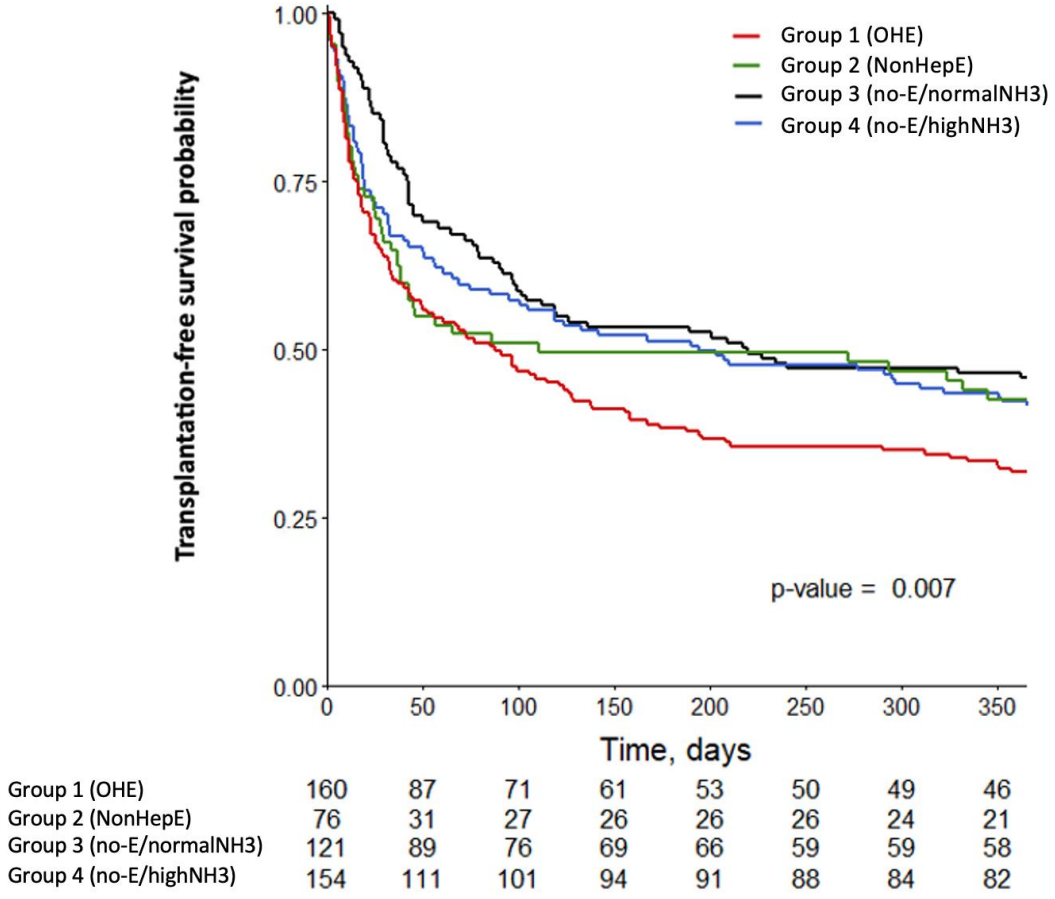
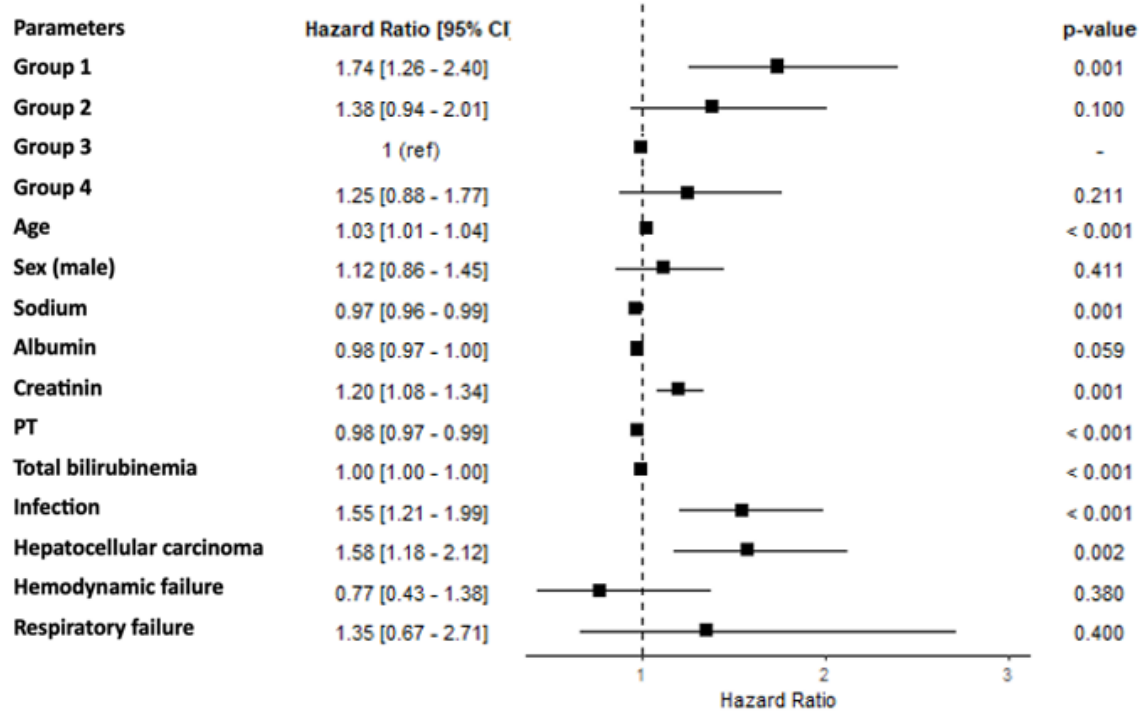
Acute Encephalopathy vs Hepatic Encephalopathy: does it matter ?





- Does ammonia influence prognosis ?
- Is the brain primed by hyperammonemia ?

Desplats V et al., submitted

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Agenda (against dogmas)

- Acute Encephalopathy: always HE in cirrhotic patients ?
- **Cognitive disorders in cirrhotic patients: always Covert Hepatic Encephalopathy ?**
- TIPS and HE: friends or foes ?

Covert Hepatic Encephalopathy vs Other Causes of Neurological Impairment ?

Recommendation

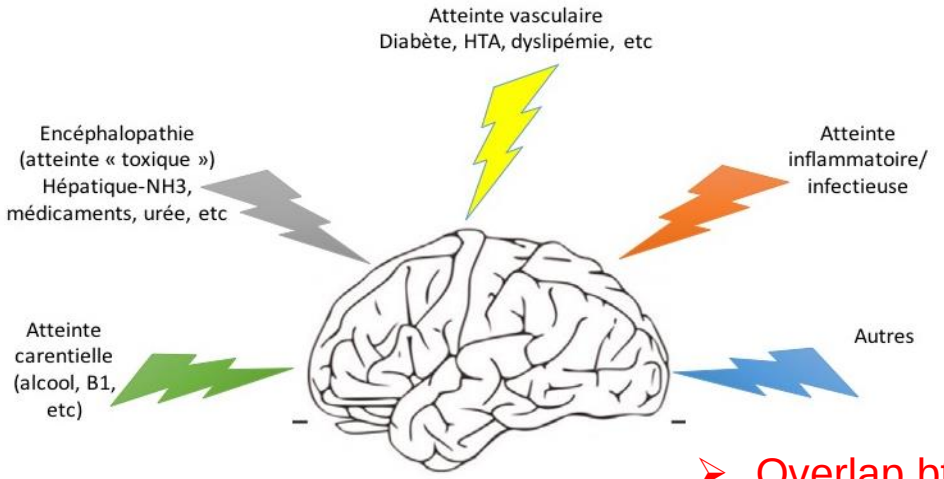
- In patients with cirrhosis and no history of overt HE, screening for covert HE should be performed with tests for which experience/tools and local norms are available. As the only bedside test available to date, the Animal Naming Test is worthy of further study and validation **(LoE 4, strong recommendation, 83% consensus).**

Recommendation

- In patients with covert HE, anti-HE treatment should be considered for the purposes of differential diagnosis and to prevent overt HE **(LoE 5, strong recommendation, 89% consensus).**

EASL CPG, J Hepatol 2022

Covert Hepatic Encephalopathy vs Other Causes of Neurological Impairment ?



71552 Veterans with cirrhosis

↓

5647 with Dementia

↓

Dementia associated with HE (but not ascites)

- Overlap btw diagnosis of HE and dementia ?
- Brain primed ?

Table 3. Multivariable model for dementia using hepatic encephalopathy as the only decompensating event

	aOR (95% CI)	*P* value
Age, per 10 yr	1.070 (1.065–1.075)	<0.0001
Females vs males	0.995 (0.820–1.207)	0.9600
Homelessness	1.590 (1.472–1.717)	<0.0001
Race/ethnicity		
Hispanics vs non-Hispanic Whites	1.147 (1.018–1.293)	0.024
Rural vs urban	0.853 (0.790–0.921)	<0.0001
Census region		
Midwest vs Northeast	1.264 (1.128–1.416)	<0.0001
South vs Northeast	1.18 (1.070–1.308)	0.001
West vs Northeast	0.941 (0.843–1.050)	0.2770
Charlson score	1.406 (1.382–1.429)	<0.0001
Etiology of liver disease		
Alcohol liver disease	1.185 (1.036–1.355)	0.013
Hepatitis C liver disease	0.620 (0.571–0.673)	<0.0001
Nonalcoholic steatohepatitis	0.795 (0.709–0.893)	0.001
Hepatic encephalopathy	2.265 (2.102–2.440)	<0.0001
Chronic medical conditions		
Cerebrovascular disease or stroke	1.443 (1.338–1.556)	<0.0001
Alcohol use disorder	1.303 (1.162–1.462)	<0.0001
Depression	1.819 (1.698–1.950)	<0.0001
Tobacco use disorder	1.115 (1.036–1.200)	0.003
Head injury	2.970 (2.637–3.344)	<0.0001

aOR, adjusted odds ratio; CI, confidence interval.

Statement

- Features of covert HE and MCI of an aetiology other than liver dysfunction show significant overlap **(LoE 2, 90% consensus).**

Adejuma A et al., AJG 2023
EASL CPG, J Hepatol 2022

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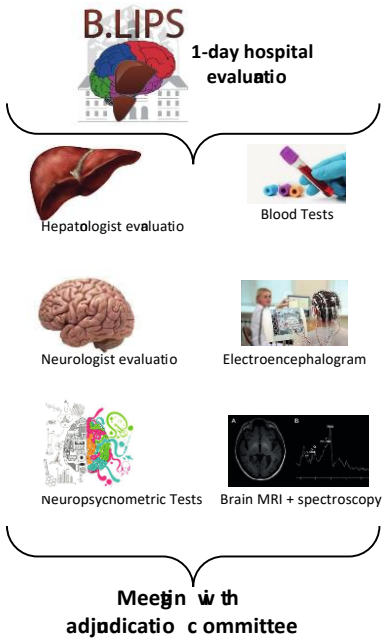
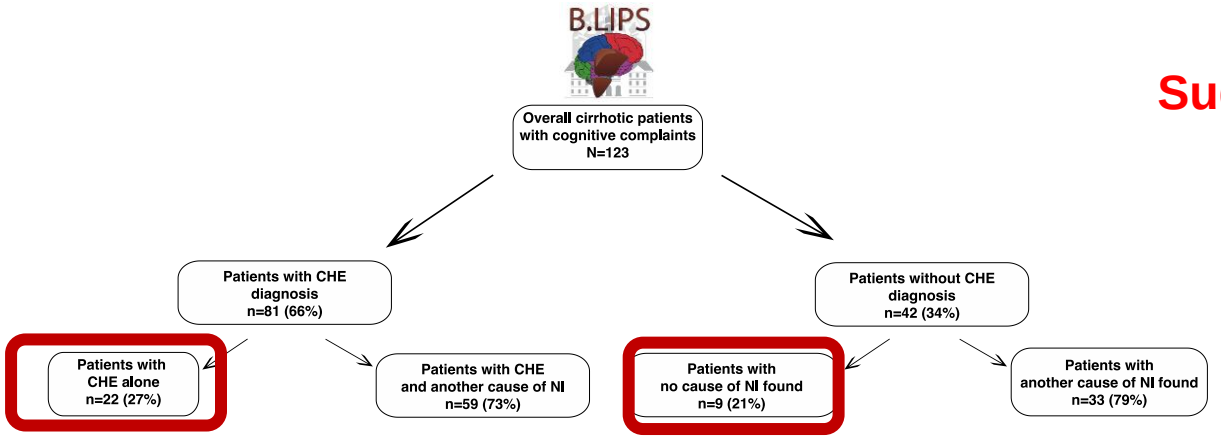
Covert Hepatic Encephalopathy vs Other Causes of Neurological Impairment ?

123 pts with cognitive complaints & cirrhosis





Suggest other therapies

CHE: covert hepatic encephalopathy (adjudication committee)
NI: neurocognitive impairment

Recommendation

- In patients with suspected HE, alternative or additional causes of neuropsychiatric impairment should be identified to improve prognostic accuracy and the results of treatment **(LoE 4, strong recommendation, 100% consensus).**

Sultanik P et al., submitted

EASL CPG, J Hepatol 2022

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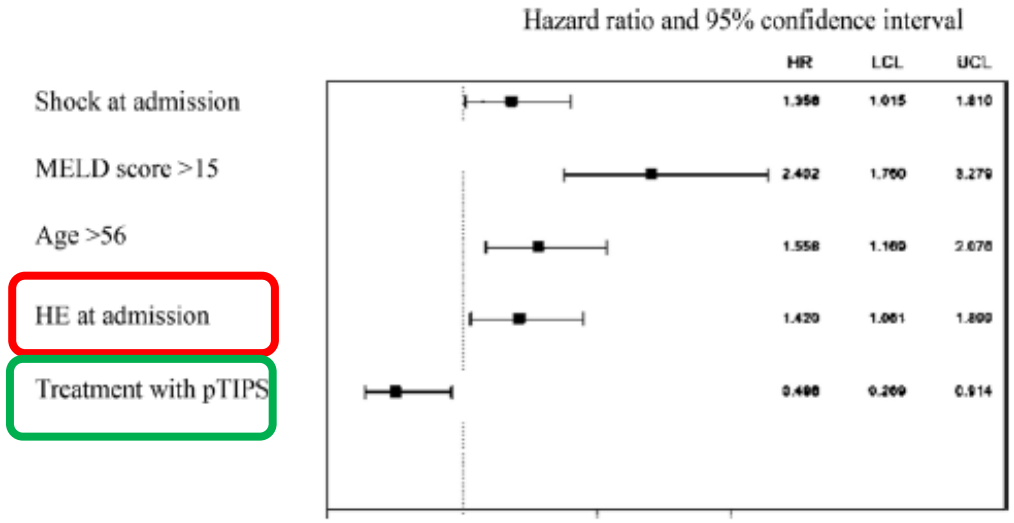
Agenda (against dogmas)

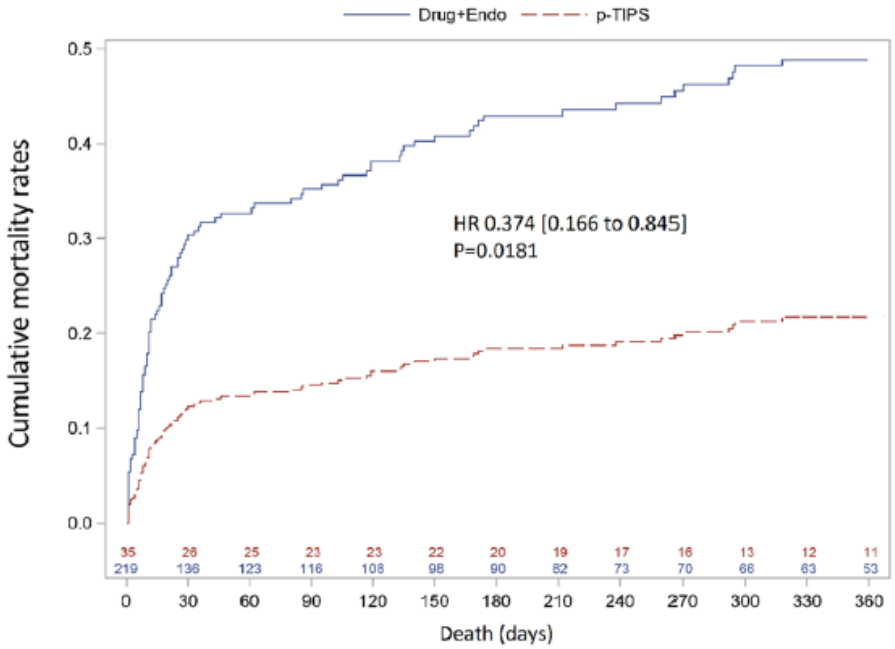
- Acute Encephalopathy: always HE in cirrhotic patients ?
- Cognitive disorders in cirrhotic patients: always Covert Hepatic Encephalopathy ?
- **TIPS and HE: friends or foes ?**

Risk of further HE after preemptive TIPS in pts with HE: pTIPS cohort study

Mortality, all pts (MV)



Survival in 256/671 pts with HE at admission



Rudler M et al., Gut 2022

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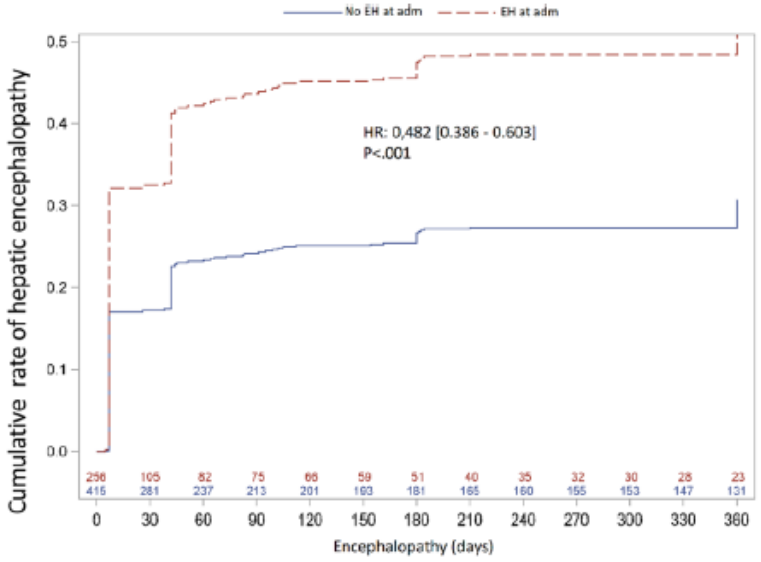
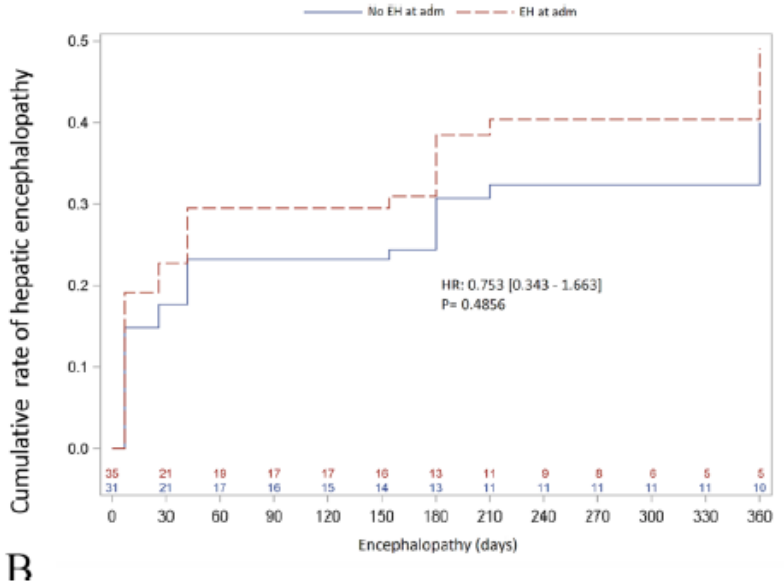
Risk of further HE after preemptive TIPS in pts with HE: pTIPS cohort study

Occurrence of HE according to HE at admission

Control group



TIPS group



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Risk factors for HE?

Ongoing prospective EuroTIPS registry

Rudler M et al., Gut 2022

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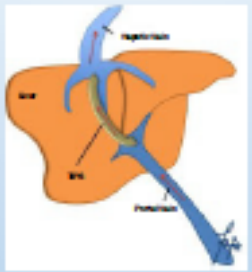
HE after TIPS: is this so simple ?

Patients and methods

614 patients submitted to TIPS for variceal bleeding or refractory ascites in 3 Italian centers



A multicenter non-inferiority observational study to evaluate the mortality rate at 30 months in patients with and without OHE after TIPS, using competing risk analysis

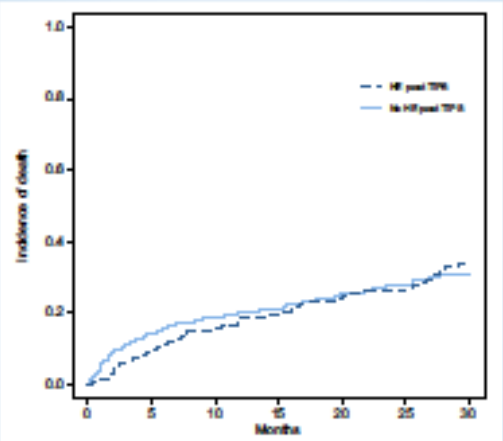
Study population

	No OHE post TIPS (n = 321)	OHE post TIPS (n = 293)	*p* value
Sex (M/F)	222/99	198/95	0.738
Age (y)	59 (50-67)	64 (57-71)	<0.001
Aetiology (virus/alcohol/other)	139/110/72	145/84/64	0.245
MELD score	10 (9-13)	11 (8-14)	0.195
Child-Pugh class (A/B/C)	90/197/34	66/190/37	0.263
Child-Pugh score	7 (6-9)	8 (7-9)	0.101
Previous OHE (no/yes)	292/29	248/45	0.023
Bilirubin (mg/dl)	1.3 (0.9-2.1)	1.3 (0.9-2.1)	0.892
Albumin (g/dl)	3.3 (2.9-3.6)	3.1 (2.8-3.5)	0.023
INR	1.3 (1.2-1.4)	1.3 (1.1-1.4)	0.663
Sodium (mEq/L)	138 (134-140)	137 (133-140)	0.006
TIPS indication (bleeding/ascites)	191/130	165/128	0.473

Results

Multivariable analysis showed that age [sHR 1.04 (1.02-1.05), *p* <0.001] and MELD [sHR 1.09 (1.05;1.13), *p* <0.001], but not post-TIPS OHE, were associated with a higher mortality rate.

Episodic OHE after TIPS does not increase mortality in patients undergoing TIPS



Do not contra-indicate TIPS in HE pts ? Discussion of LT …

Nardelli S et al., J Hepatol 2024

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Conclusion, in 2024 …

- Hepatic Encephalopathy is not a simple entity, as there are many confounders (differential or associated diagnosis ?)
- It is very important to precisely characterize the type of neurological impairment in order to propose an appropriate management of patients
- The bad prognostic value of HE, especially after TIPS,but probably not only, has to be revisited …

ARTICLE IN PRESS

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

EASL Clinical Practice Guidelines on the management of hepatic encephalopathy☆

European Association for the Study of the Liver*

Summary

The EASL Clinical Practice Guidelines (CPGs) on the management of hepatic encephalopathy (HE) present evidence-based answers to a set of relevant questions (where possible, formulated in PICO [patient/population, intervention, comparison and outcomes] format) on the definition, diagnosis, differential diagnosis and treatment of HE. The document does not cover the pathophysiology of HE and does not cover all available treatment options. The methods through which it was developed and any information relevant to its interpretation are also provided.

Introduction and methods

The Governing Board of the European Association for the Study of the Liver (EASL) selected a panel of experts to prepare these Clinical Practice Guideline (CPGs) with the purpose of providing the best available evidence on diagnosis and management of hepatic encephalopathy (HE). The EASL Governing Board and the CPG panel went on to identify a Delphi panel of 36 reviewers including 24 hepatologists/gastroenterologists/internists, 5 nurses, 2 methodologists, 1 neurologist, 1 neurophysiologist, 1 neuropsychologist, 1 neuroradiologist, 1 neuroscientist and 1 patient with a background in psychology, all with an interest in HE; 24 participated in all review steps. The CPG panel was first assigned the task of identifying the most relevant topics, in the form of PICO [P Patient, Population, or Problem; I Intervention, Prognostic Factor, or Exposure; C Comparison or Intervention (if appropriate), O Outcome] questions, which resulted in 29 questions; on first Delphi panel review, some of these questions were modified/removed and some added, resulting in the 31 final questions which are presented in the current document. While the panel agreed to the PICO format, for a number of topics the format was not applicable and/or the evidence insufficient. Therefore, intermediate format questions were accepted and treated as such.

Received 1 June 2022; accepted 1 June 2022; available online xxx

☆ Clinical Practice Guideline Panel: Chair: Sara Montagnese; EASL Governing Board representative: Pierre-Emmanuel Rautou; Panel members: Manuel Romero-Gómez, Fin Stolze Larsen, Debbie L. Shawcross, Dominique Thabut, Hendrik Vilstrup, Karin Weissenborn.

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E-mail address: easloffice@easloffice.eu.

https://doi.org/10.1016/j.jhep.2022.06.001

An extensive literature search of publications in English was performed by an experienced research librarian (Helene Sognstrup, Royal Danish Library Aarhus) using PubMed, Embase and the Cochrane Library.

Features and limits: Language: English (not possible in Cochrane); Publication year: All years; Publication type: Clinical, trials, Randomized controlled trials.

((“Hepatic Encephalopathy”[MeSH Terms] OR “Hepatic Encephalopathy”[Text Word] OR neuropsycholog*[Text Word] OR “Psychometrics”[Mesh] OR “Cognition Disorders”[MeSH Terms] OR “Cognition”[MeSH Terms]) AND (((“Liver Diseases”[MeSH Terms] OR “liver diseas*”[Text Word]) AND (“Chronic Disease”[MeSH Terms] OR “chronic disease*”[Text Word])) OR (“Liver Cirrhosis”[MeSH Terms] OR “Liver Cirrhosis”[Text Word])) AND (“clinical trial”[Title] OR “randomi*”[Title])) OR ((“Hepatic Encephalopathy”[MeSH Terms] OR “Hepatic Encephalopathy”[-Text Word] OR neuropsycholog*[Text Word] OR “Psychometrics”[Mesh] OR “Cognition Disorders”[MeSH Terms] OR "Cognition"[MeSH Terms]) AND (((“Liver Diseases”[MeSH Terms] OR “liver diseas*”[Text Word]) AND (“Chronic Disease”[MeSH Terms] OR “chronic disease*”[Text Word])) OR (“Liver Cirrhosis”[MeSH Terms] OR "Liver Cirrhosis"[Text Word])) AND (“clinical trial”[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH Terms] OR "Clinical Trials as Topic"[MeSH Terms]))

Four hundred and sixteen references were retrieved from PubMed, 326 from Embase and 257 from the Cochrane Library, for a total of 999 references, which were then reduced to 726 after deduplication. All panellists read the retrieved literature and searched for further literature, where appropriate. Each panellist chose a number of PICO questions based on their specific expertise; where overlap/disparities were present agreement was sought and easily reached.

The evidence was evaluated and scored, and the recommendations produced following EASL’s methodological recommendations for CPGs (Tables 1 and 2)[1]; definitions and statements were not graded. After a first in-person meeting, due to the COVID-19 pandemic, all subsequent meetings were held by teleconference. All recommendations were discussed and approved by all panellists. The Delphi panel examined the recommendations. Returning scores were graded as follows: less than 50% approval: re-write recommendation and resubmit to the Delphi panel; 50%-75% approval: re-write/improve the recommendation, but no resubmission to the Delphi panel; 75-90% approval: no need to re-write the recommendation but the document will take into account the comments; ≥90% approval: assumed as consensus, no change needed but small corrections possible. To consider a question approved, an

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International Society for Hepatic Encephalopathy and Nitrogen Metabolism

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Pr Louis Puybasset
Dr Vincent Perlbarg

Neurophysiologie
Pr Vincent Navarro
Dr Bertrand Hermann

Neuropsychologie
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Pr Dominique Bonnefont-Rousselot

Transplantation hépatique
Pr Olivier Scatton
Pr Yvon Calmus
Pr Filomena Conti
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Dr Maxime Mallet

Sommeil
Pr Thomas Similowski
Pr Isabelle Arnulf
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Ophtalmologie
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CHU Toulouse
Pr Christophe Bureau

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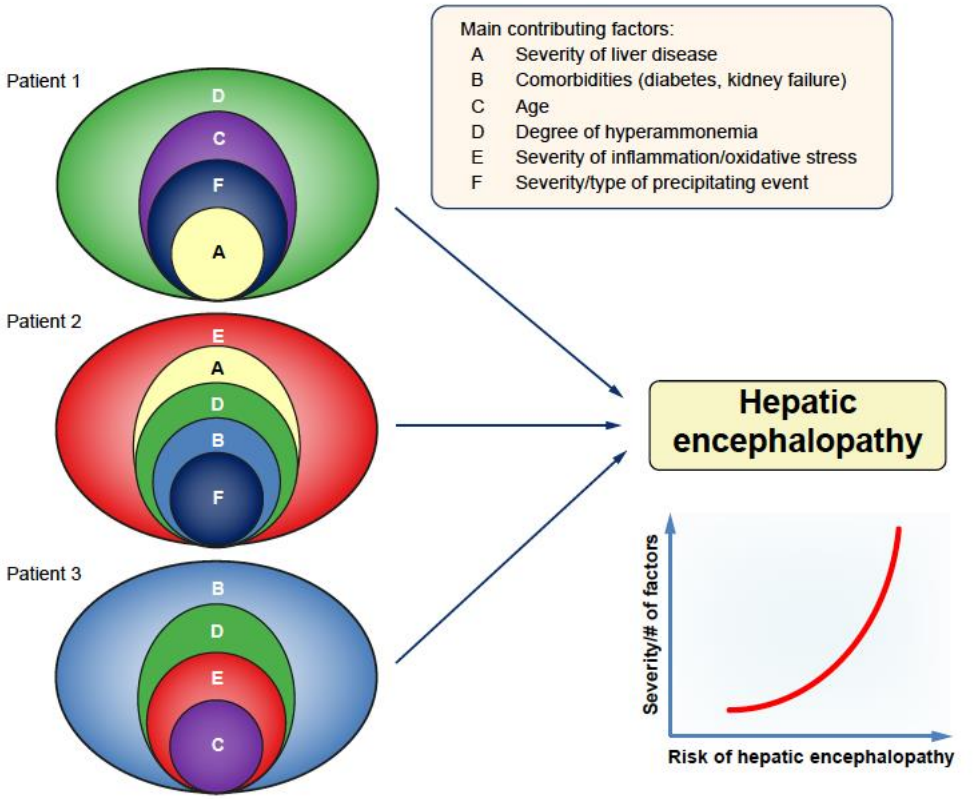
Pr Rajiv Jalan

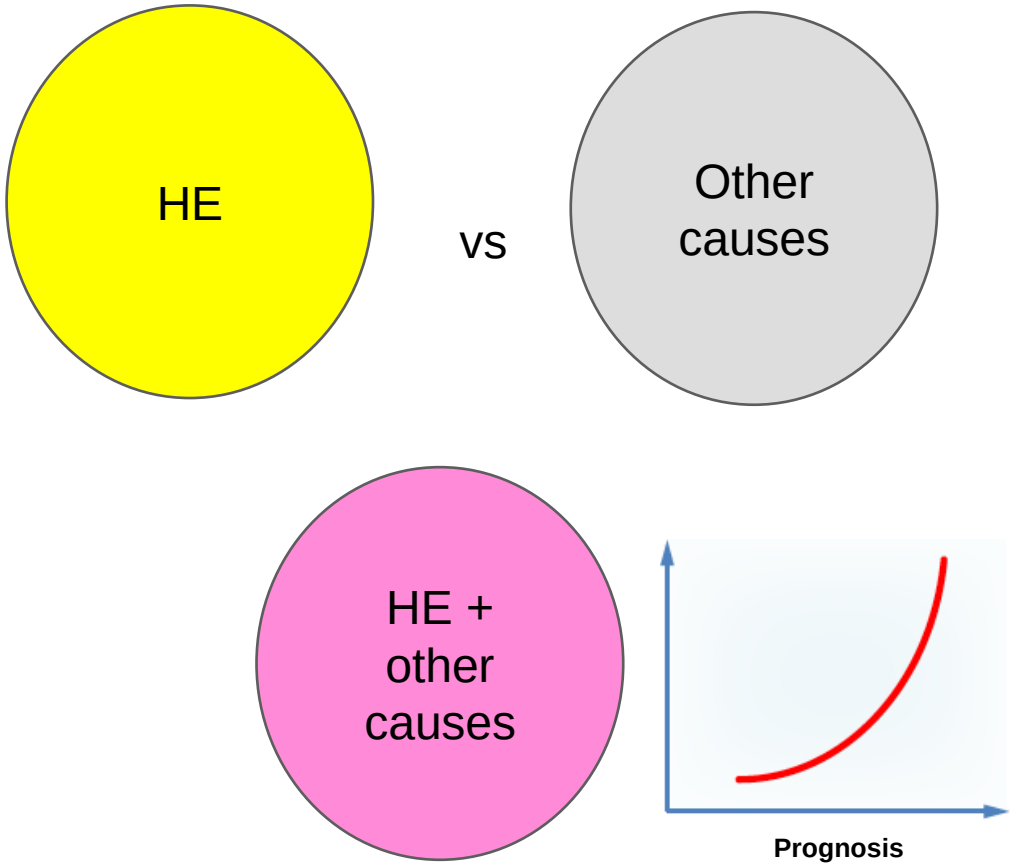
Univ. of Padova, Padoue
Pr Sarah Montagnese
Dr Chiara Formentin

McGuire VA Medical center, Richmond, USA
Pr Jasmohan Bajaj

Inst. of Liver and Biliary Sciences, Delhi
Pr Shiv Sarin
Dr Rakhi Maiwall

Encephalopathy, Other Causes of Neurological Impairment (acute or chronic) or both ?





Rose C et al., J Hepatol 2020

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Simple Tools for diagnosis

Clinical examination

« Atypical clinical examination ?

➢ Seek for differential diagnosis of HE and Call a Friend ! »

Blood tests

- Ammonia

In patients with delirium, is ammonia measurement useful for purposes of diagnosis, differential diagnosis, treatment and prognosis?

Recommendation

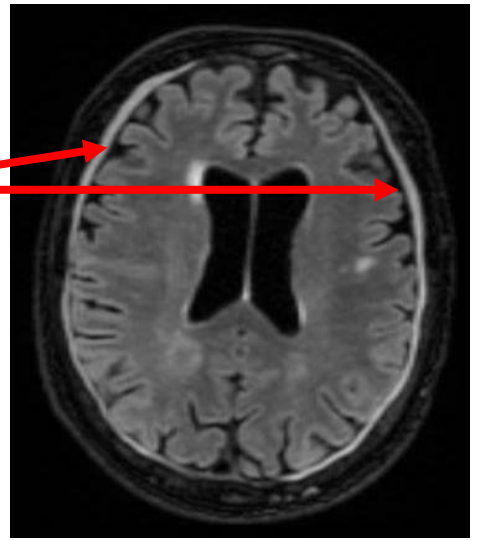
- In patients with delirium/encephalopathy and liver disease, plasma ammonia measurement should be performed, as a normal value brings the diagnosis of HE into question (**LoE 4, strong recommendation, 95% consensus**).

➢ **If n**

Other causes of encephalopathy : septic, drug-induced …

Brain imaging

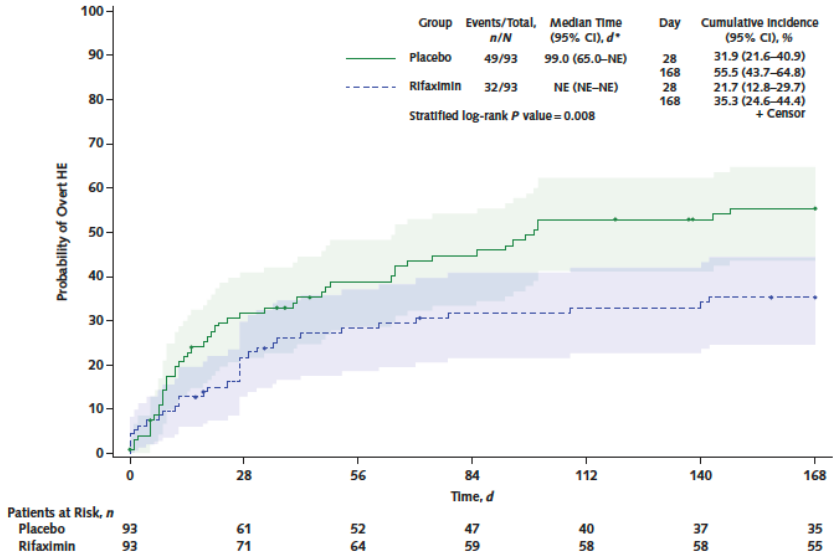
Subdural hematomas



Vilstrup et al., J Hepatol 2014
Bajaj et al., AJG 2020
Mouri et al., Neurocritical care 2014
Rudler M et al., Clin Liver Dis 2021
Weiss N et al., J Hepatol 2017
Bajaj JS et al., APT 2019
Imbert-Bismut F, Clin Chim Acta 2020
Shalimar KD et al., Hepatology 2019
Reuter B et al., APT 2018
Weiss N et al., J Hepatol 2016

Prevention of HE in elective situations: pharmacology

- TIPS indication: ascites 81%
- RFX 14 days before TIPS



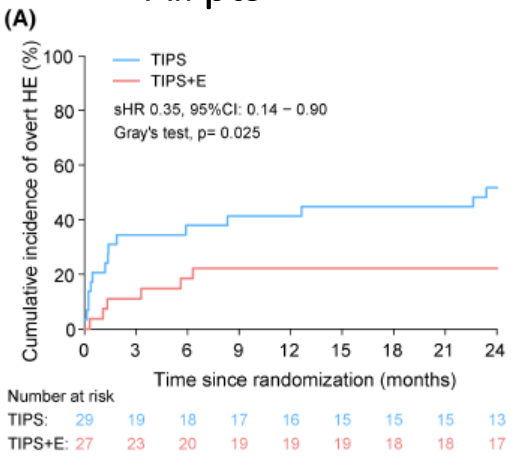
Recommendation

- In patients with cirrhosis and previous episodes of overt HE, rifaximin can be considered for prophylaxis of HE prior to non-urgent TIPS placement. Non-absorbable disaccharides, as a stand-alone or in combination, are worthy of further study in this context **(LoE 2, strong recommendation, 82% consensus).**

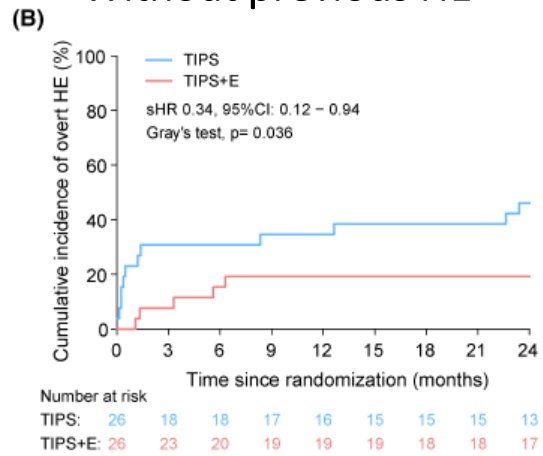
Bureau C et al., Ann Int Med 2021

- TIPS indication: prophylaxis of VB
- Embolisation before TIPS

All pts



Without previous HE



- Embolisation before TIPS, shunts>8 mm
- No HE prophylaxis

Thabut D et al., Liv Int 2023
EASL CPG, J Hepatol 2022

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TIPS and Hepatic Encephalopathy

Risk of HE after TIPS

	Nb of studies	HE after TIPS
Salvage TIPS	7	6-84%
Preemptive TIPS	4 RCT	19-41%
Elective TIPS	5	38-77%

Large heterogeneity in

- Pts selection (previous HE or not)
- TIPS technique/diameter
- Ways of seeking for/diagnosing HE

Recommendation

- In patients scheduled for non-urgent TIPS, the presence and/or history of overt and covert HE should be thoroughly assessed. One single episode of HE is not an absolute contraindication, especially if precipitated by bleeding **(LoE 5, strong recommendation, 89% consensus).**

EASL CPG, J Hepatol 2022

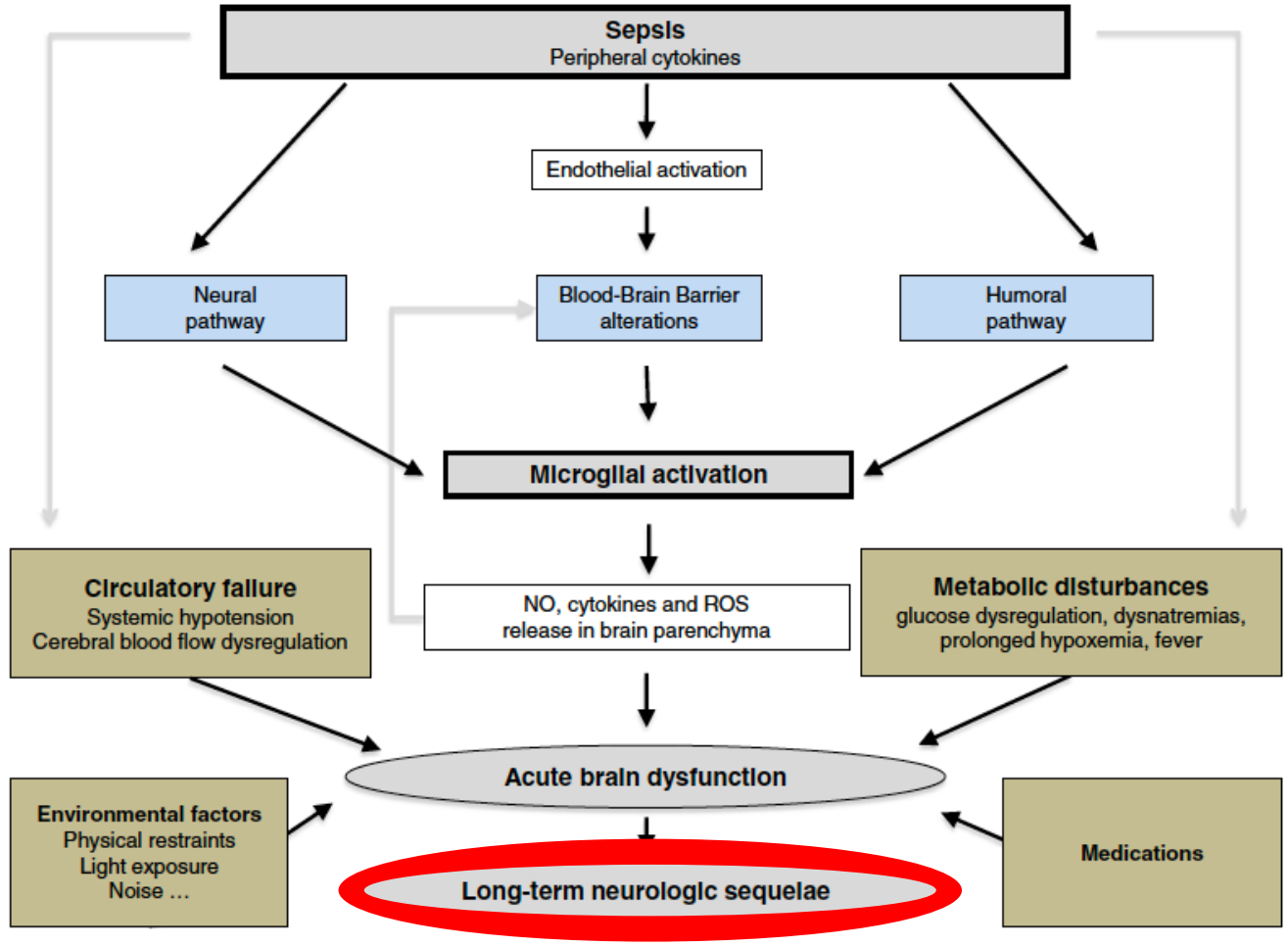
Cerebral consequences of systemic inflammation

How to look at consequences of systemic inflammation ?

Take a medical condition associated with systemic inflammation:

- ✓ Septic shock (sepsis)
- ✓ Acute Respiratory Distress syndrome (ARDS)
- ✓ **Cirrhosis**
- ✓ Pancreatitis
- ✓ Surgery
- ✓ Covid-19 ?
- ✓ …

Septic encephalopathy (up to 75%)



Sonneville et al., Ann Int Care 2013

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