Malaga 2016

Hepatic Encephalopathy
A 2016 perspective

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Disclosures (Rajiv Jalan):

- **Inventor:** Ornithine phenyl acetate for the treatment of hepatic encephalopathy (licensed to Ocera Therapeutics)
- **Consultancy and Speaker Fees:** Ocera Therapeutics, Grifols, Norgine
- **Research Collaboration:** Ocera Therapeutics, Grifols, Gambro
- **Chief Investigator:** Sequana medical sponsored study of alfapump
- **Founder:** UCL spin-out company, Yaqrit Ltd

Questions

- Classification of Hepatic Encephalopathy
  - Covert vs Minimal
  - The brain in ACLF
- Pathogenesis of HE
  - Ammonia and Inflammation
    - New concepts of underlying mechanisms
  - Involvement of different inflammatory cell types in HE
- Why may HE increase the risk of death of cirrhotic patients?
- Is HE truly reversible?
- Interorgan ammonia metabolism: The basis of novel therapies of HE

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Classification of HE: Clarification or Confusion?

Underlying liver disease	Severity		Time course	Existence precipitating factor
Type	Grade		Time course	Spontaneous or precipitated
A	MHE 1	Covert	Episodic	Spontaneous
B	2	Overt	Recurrent	Precipitated (specify)
	3			
C	4		Persistent	

One disease or two?

Vilstrup et al. J Hepatol 2014

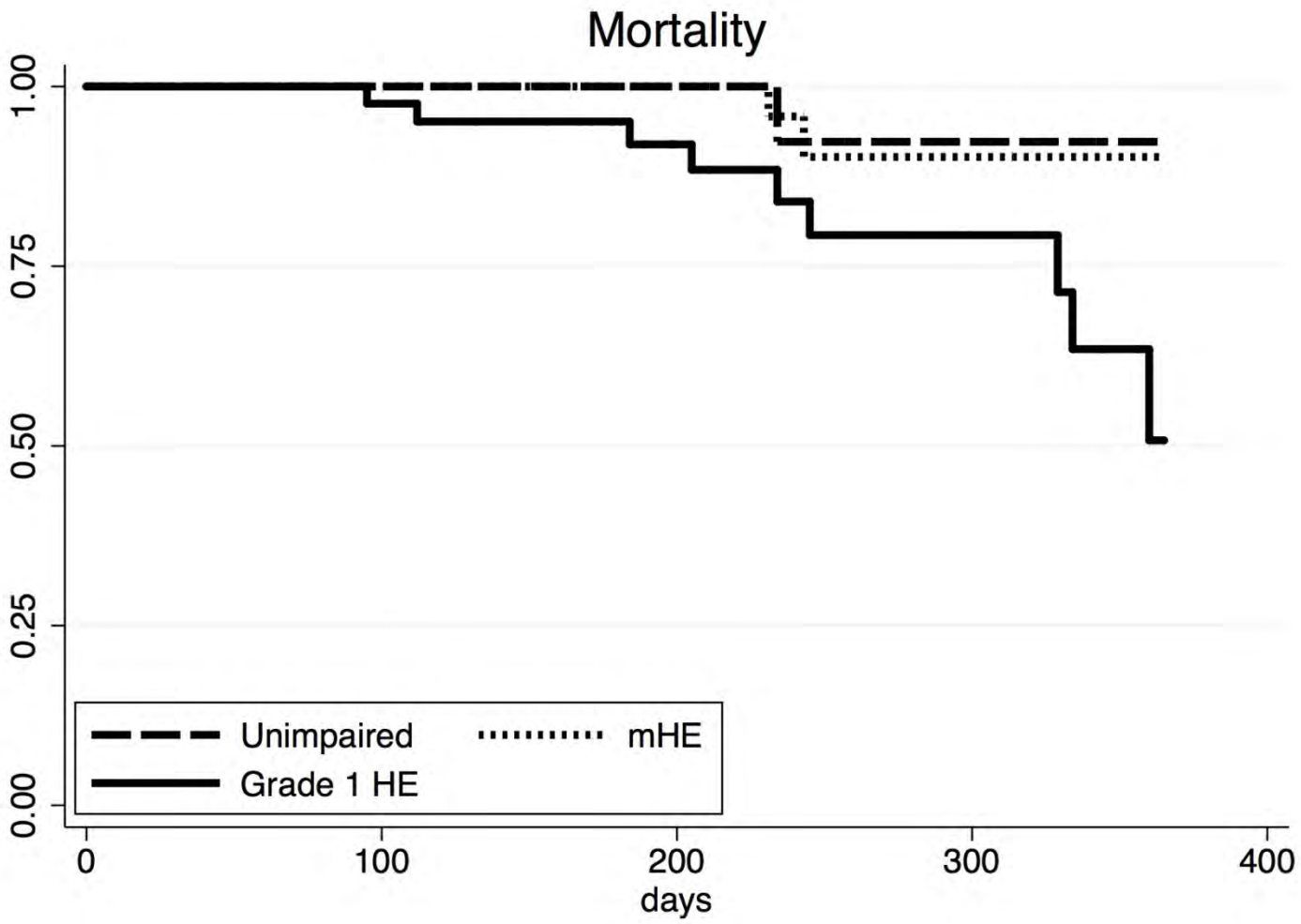
Patients

	Unimpaired n=23	mHE n=39	Grade 1 HE n=44
Age (year)	59 ± 6	58 ± 10	58 ± 12
MELD	15 ± 6	14 ± 6	16 ± 6
Albumin (g/dL)	2.8 ± 0.7	2.9 ± 0.5	2.9 ± 0.5
Ammonia (□mol/L)	48 ± 11	61 ± 14*	62 ± 12*
Sodium (mmol/L)	136 ± 5	136 ± 6	135 ± 5
Creatinine (□mol/L)	91 ± 60	69 ± 39	81 ± 43
WBC count (x 10^9/L)	5.0 ± 2.2	6.5 ± 3.1	7.4 ± 4.8

*p<0.05 compared with unimpaired

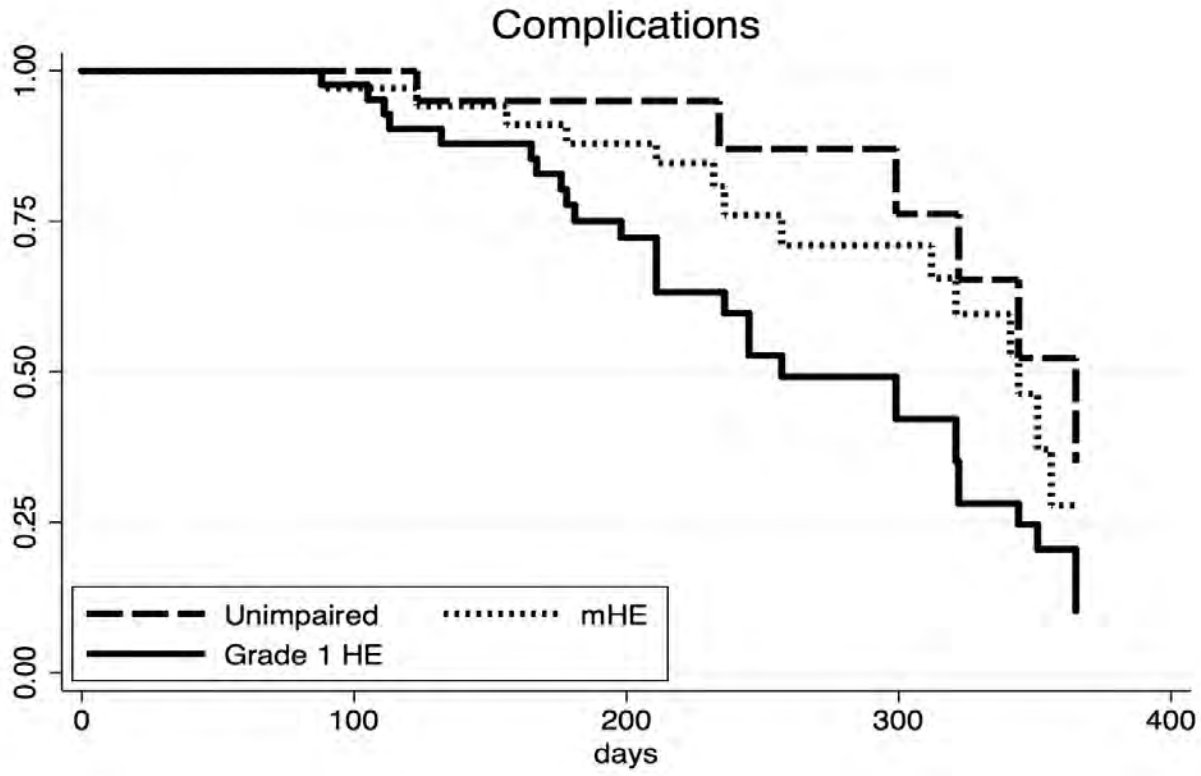
Thomsen et al. Plosone 2016

Mortality



Thomsen et al. Plosone 2016

Complications requiring hospitalisations



	Unimpaired n=23	mHE n=39	Grade 1 HE n=44
Infections n (%)	2 (9)	7 (18)	15 (34)
HE n (%)	1 (4)	3 (8)	8 (18)

Thomsen et al. Plosone 2016

Grade 1 HE patients have more immune dysfunction

	Unimpaired n=23	mHE n=39	Grade 1 HE n=44	P-value
Bacterial DNA n (%)	5 (22)	14 (36)	25 (57)	P=0.01
Neut. resp. burst (%)	13 ± 11	13 ± 14	22 ± 22	P=0.03
Phagocytosis (GMFI)	84 ± 15	81 ± 13	78 ± 10	P=0.16

Cause or Effect?

Thomsen et al. Plosone 2016

Overt Hepatic Encephalopathy

Is there need for a Type D

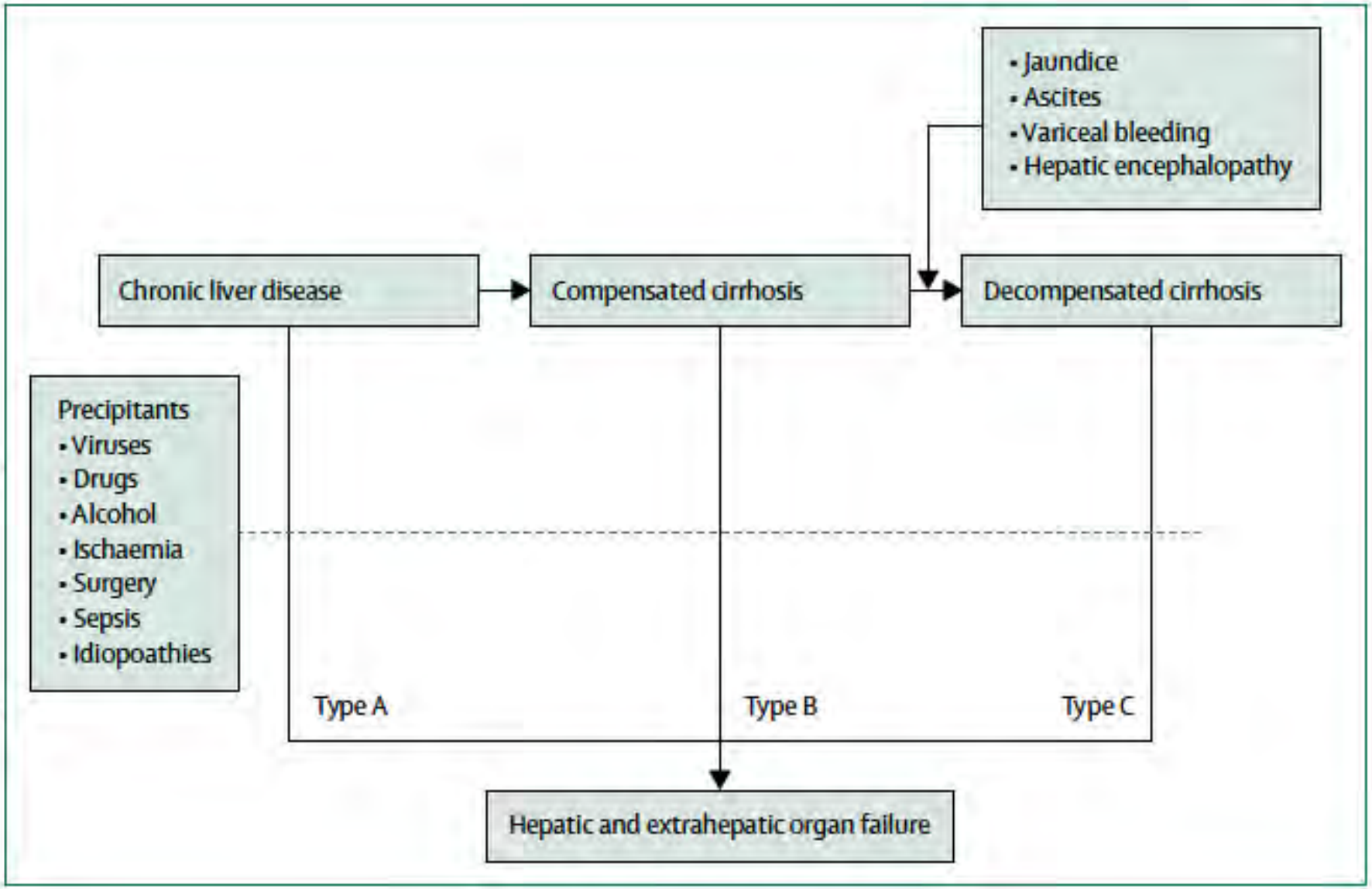
Underlying liver disease	Severity		Time course	Existence precipitating factor
Type	Grade		Time course	Spontaneous or precipitated
A	MHE	Covert	Episodic	Spontaneous
	1			
B	2	Overt	Recurrent	Precipitated (specify)
	3			
C	4		Persistent	

EASL/AASLD Concensus. JHEP 2014

Acute-on-chronic liver failure

William Bernal, Rajiv Jalan, Alberto Quaglia, Kenneth Simpson, Julia Wendon, Andrew Burroughs

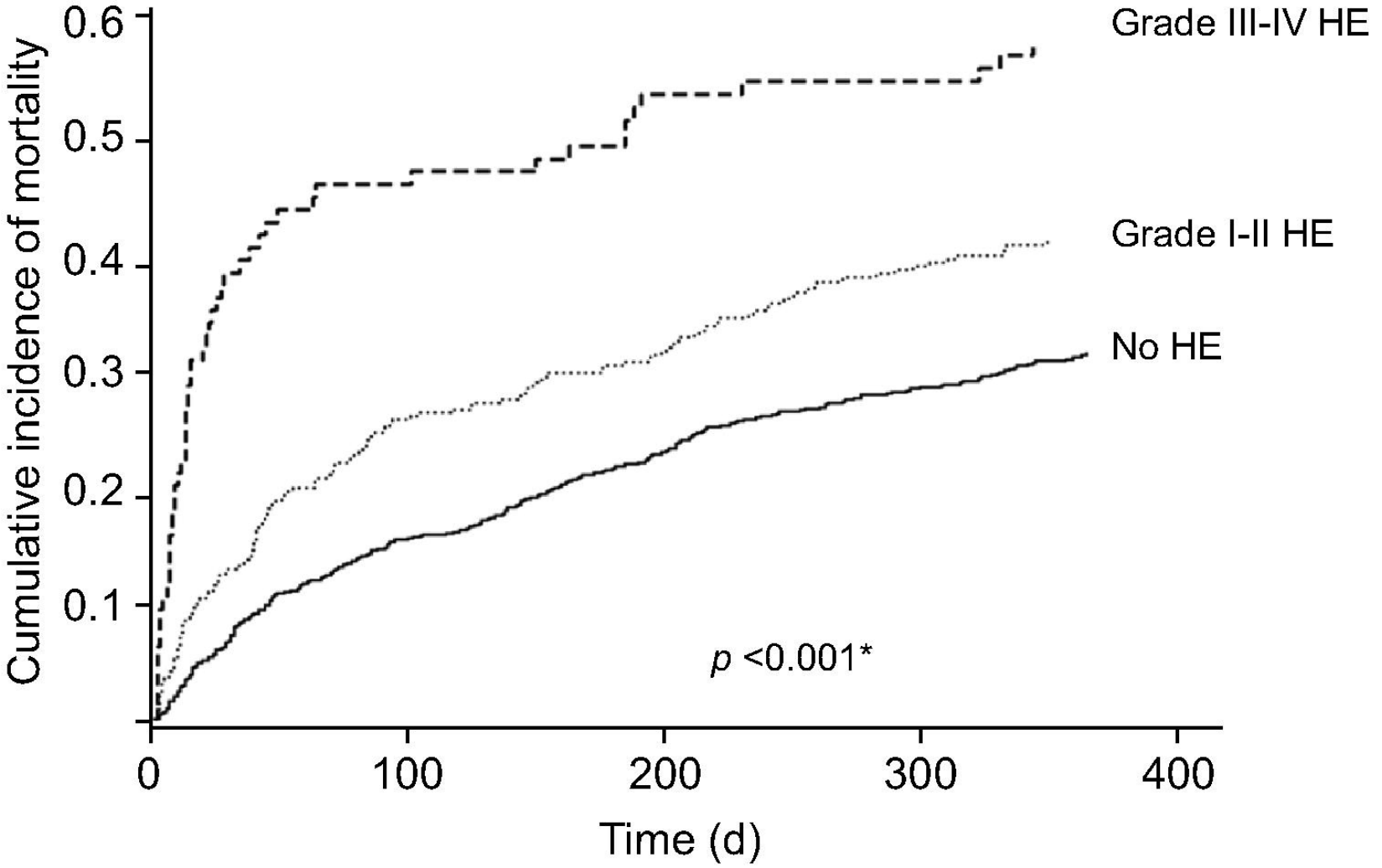
THE LANCET



Adapted from Jalan et al. Gastro 2014

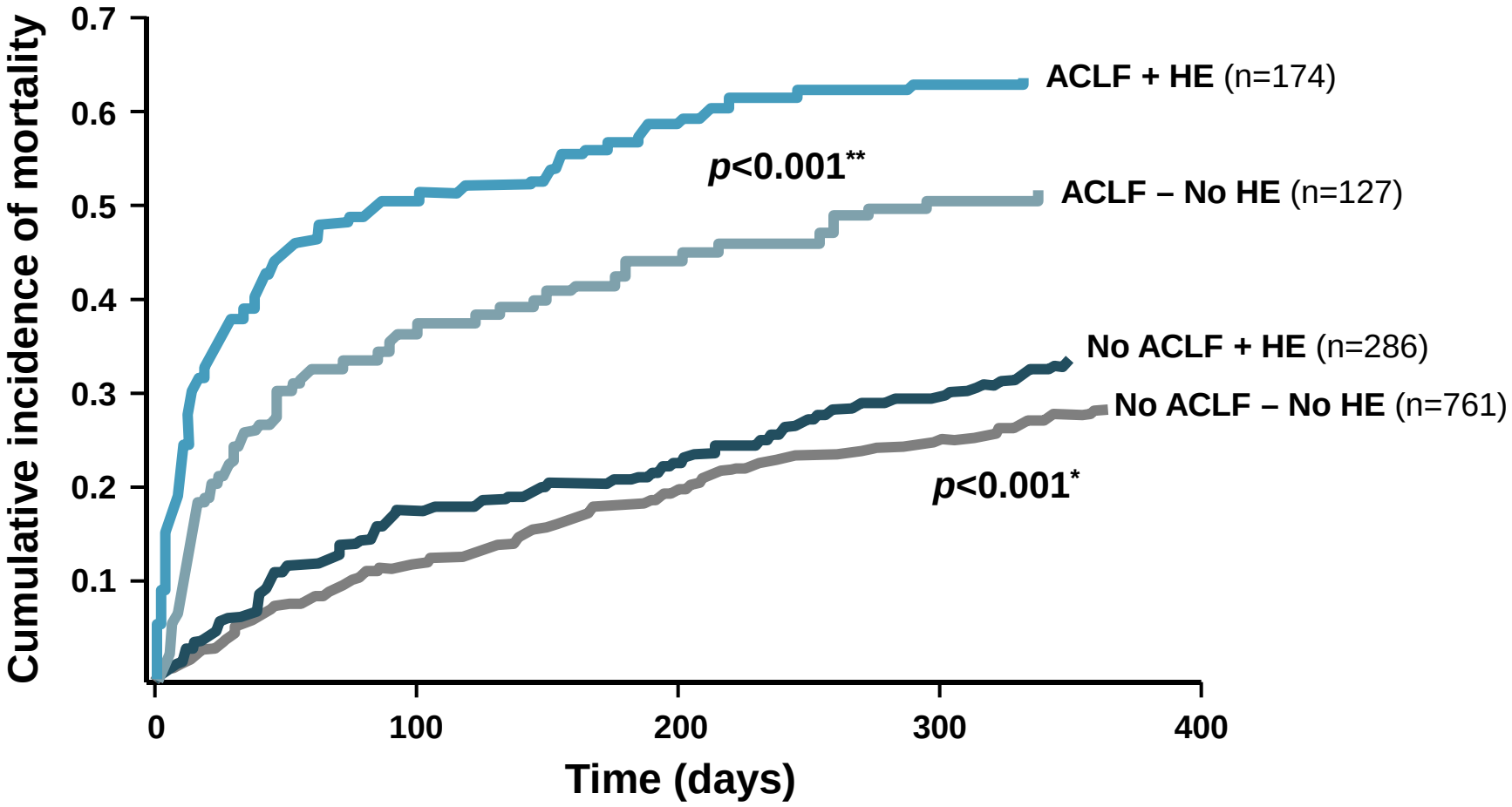
2015

The severity of HE is associated with different short and medium term mortality



Adapted from Cordoba J *et al. J Hepatol* 2014;60:275–81

The presence of ACLF alters the natural history of Hepatic Encephalopathy



Competing risk assessment

***p-value comparing presence vs absence of HE in patients without ACLF**

****p-value comparing presence vs absence of HE in patients with ACLF**

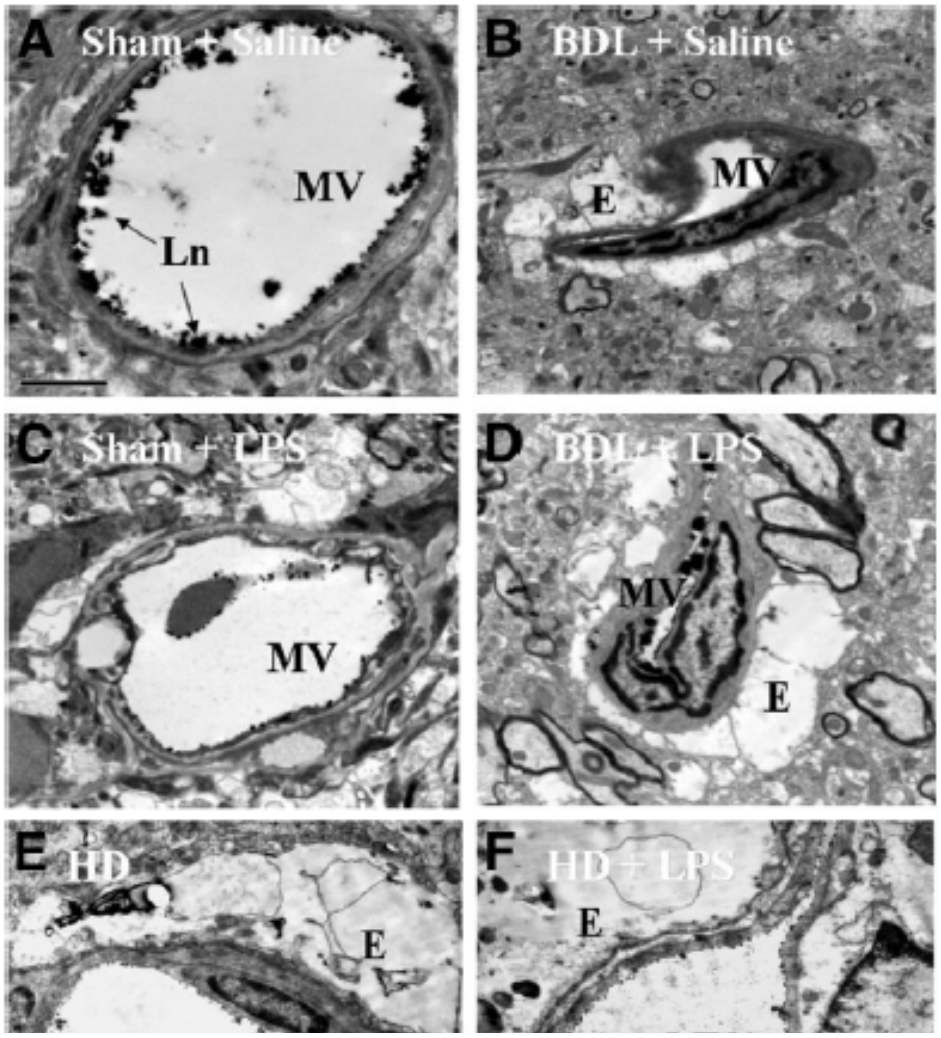
Adapted from Cordoba J *et al. J Hepatol* 2014;60:275–81

Inflammation is a key factor distinguishing HE with ACLF vs HE without ACLF?

Variable	HE [No ACLF] [n=286]	HE [ACLF] [n=174]
Inflammatory Markers		
White Cell count	5.7 (4.2-8)	8.9 (5.8-13.7)***
CRP	13 (5-31)	32 (16-60)***

Adapted from Cordoba J *et al. J Hepatol* 2014;60:275–81

Are they neuropathologically different?



Inflammation worsens Brain Swelling during Hyperammonemia but anatomical break down of Blood-Brain Barrier was NOT observed

What is the pathophysiological basis of HE in ACLF in humans?

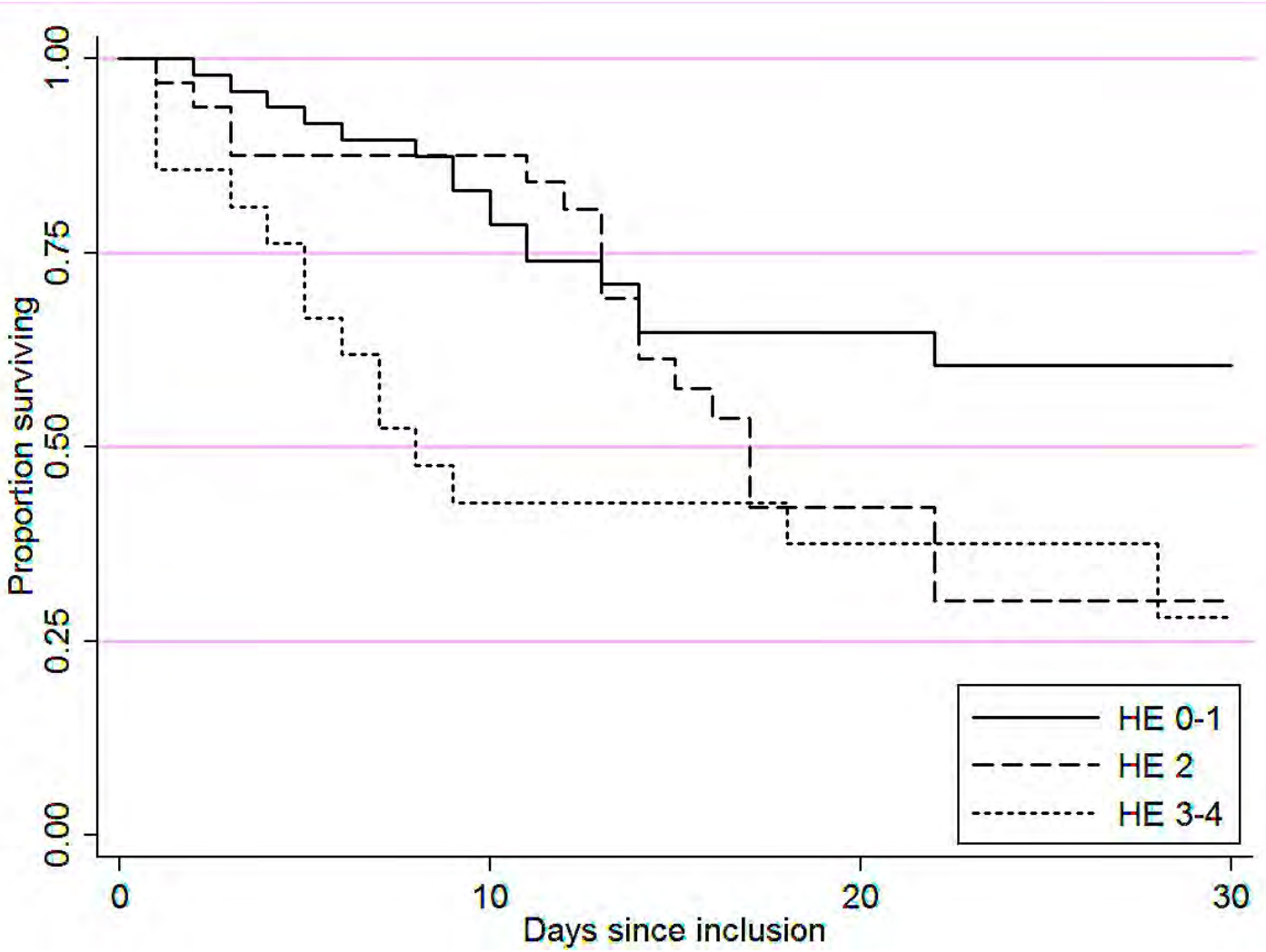
Prospective Study in ICU admitted patients with ACLF with an without HE

- N=101
- HE graded using West Haven cirteria
- Overt HE: Defined as Grade 2 or more

- Patients monitored
  - Sequential arterial ammonia
  - Inflammatory markers
  - Reverse jugular catheter to monitor oxygen saturation
- Standard of care defined

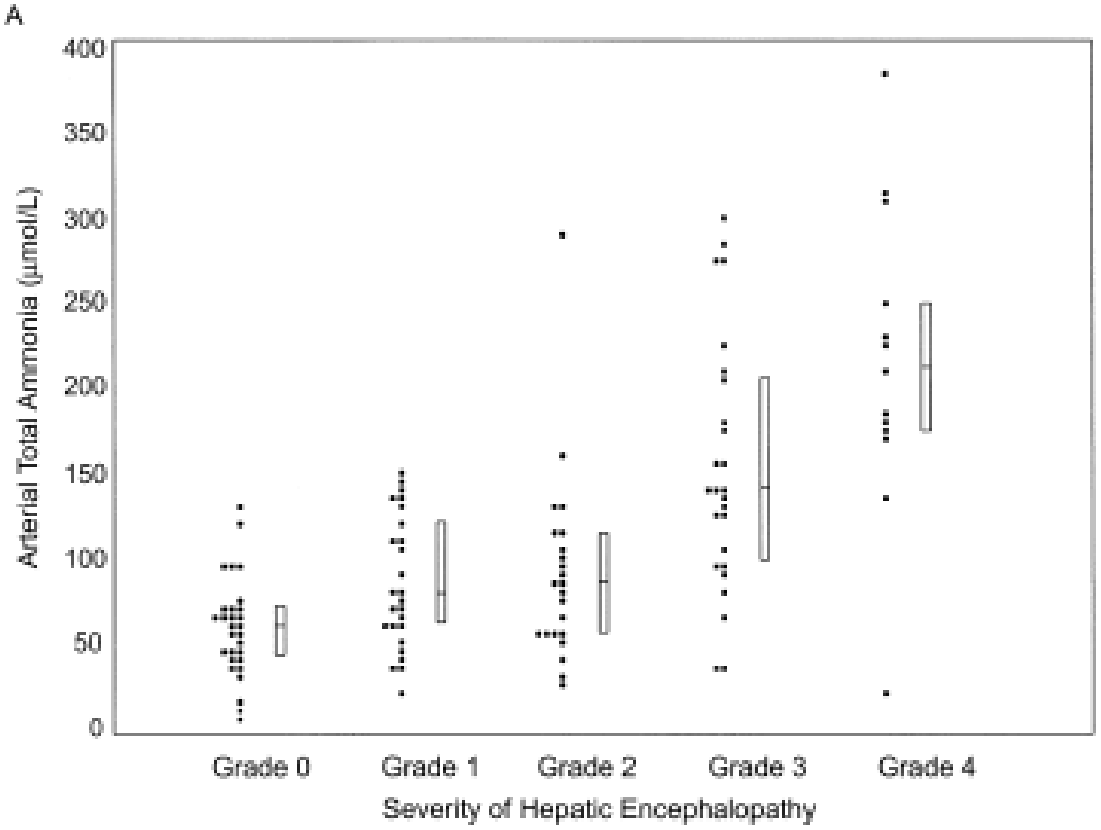
Sawhney et al. Liver Transplantation 2016

The presence of HE determines the risk of death in ACLF patients studied prospectively (n=101)



Sawhney et al. Liver Transplantation 2016

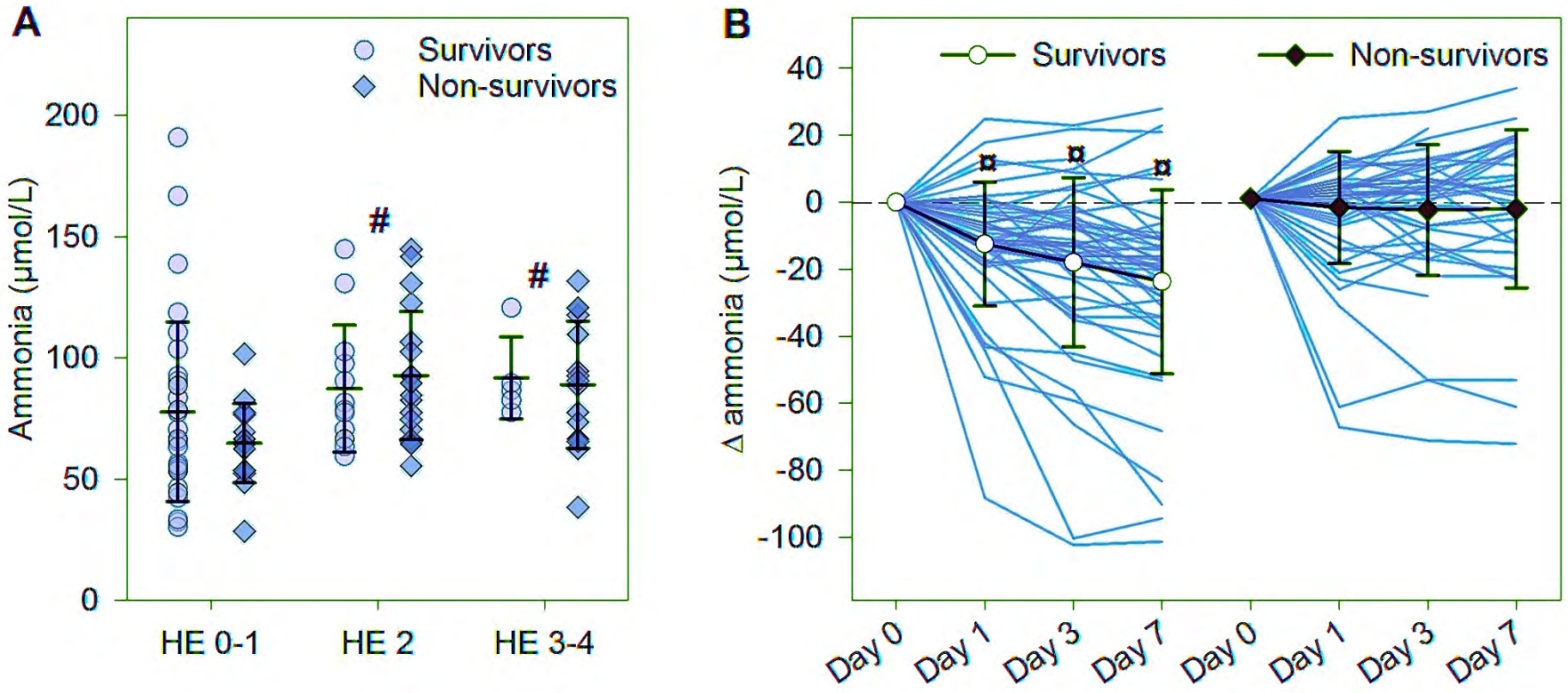
Ammonia levels in overt HE (likely no ACLF)



Ammonia levels were an independent predictor of severity of HE

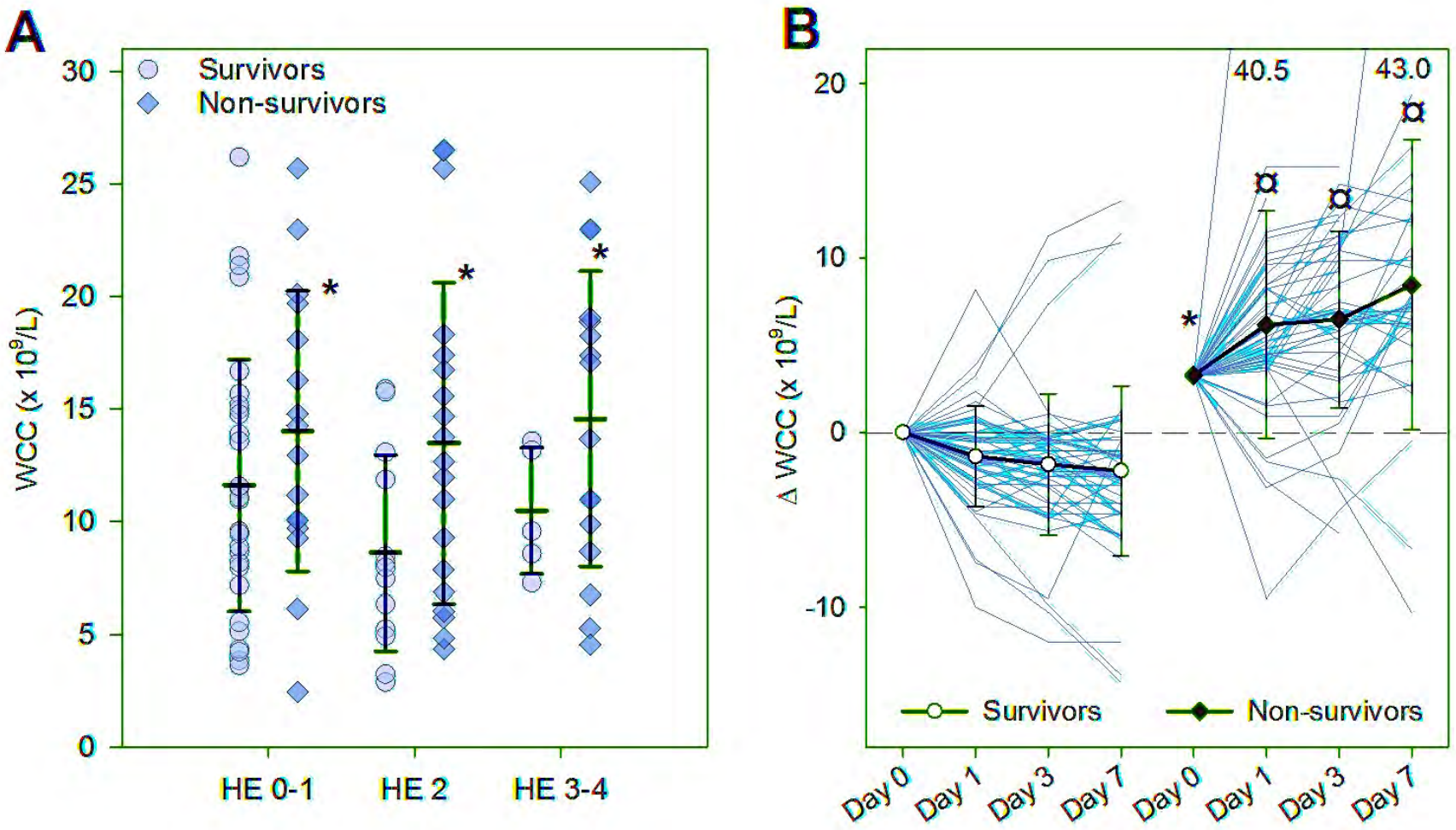
Ong et al. Am J Med 2003

What about patients with ACLF?



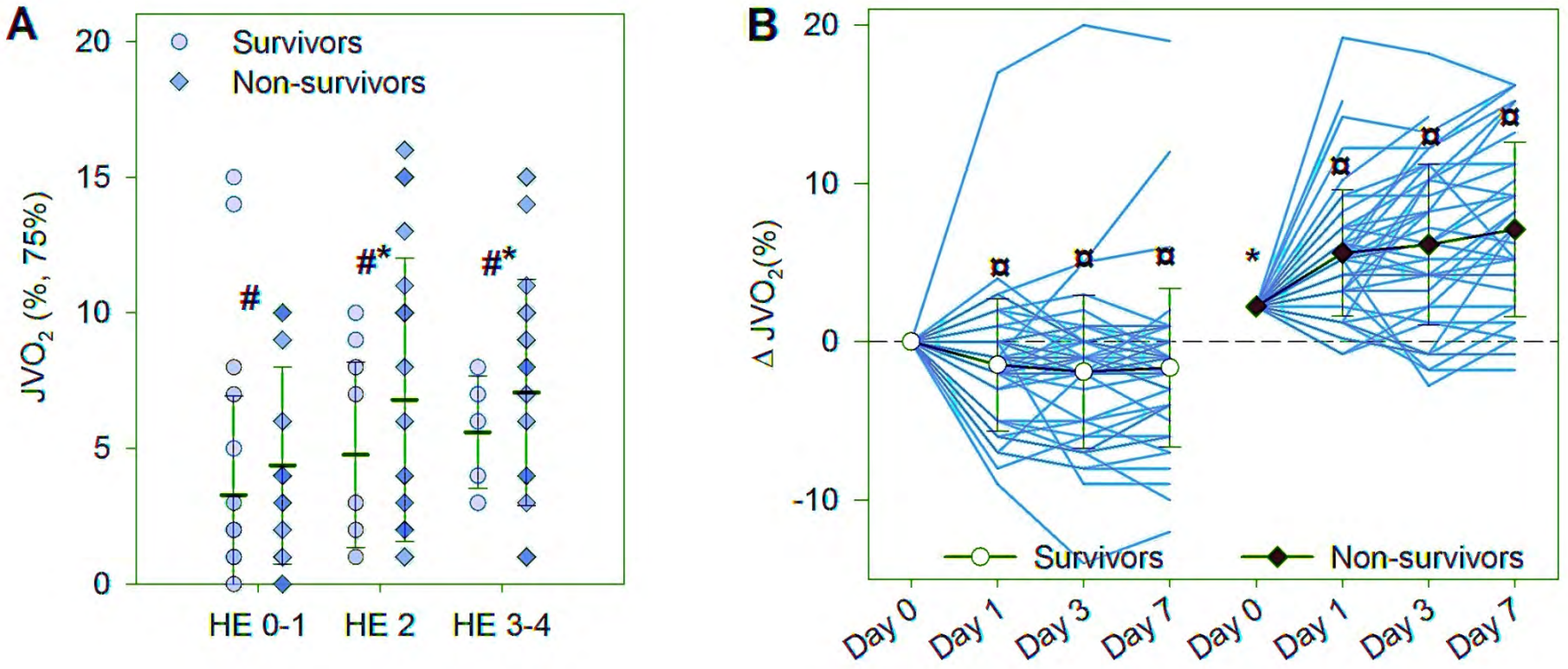
Sawhney et al. Liver Transplantation 2016

Inflammation (WCC)



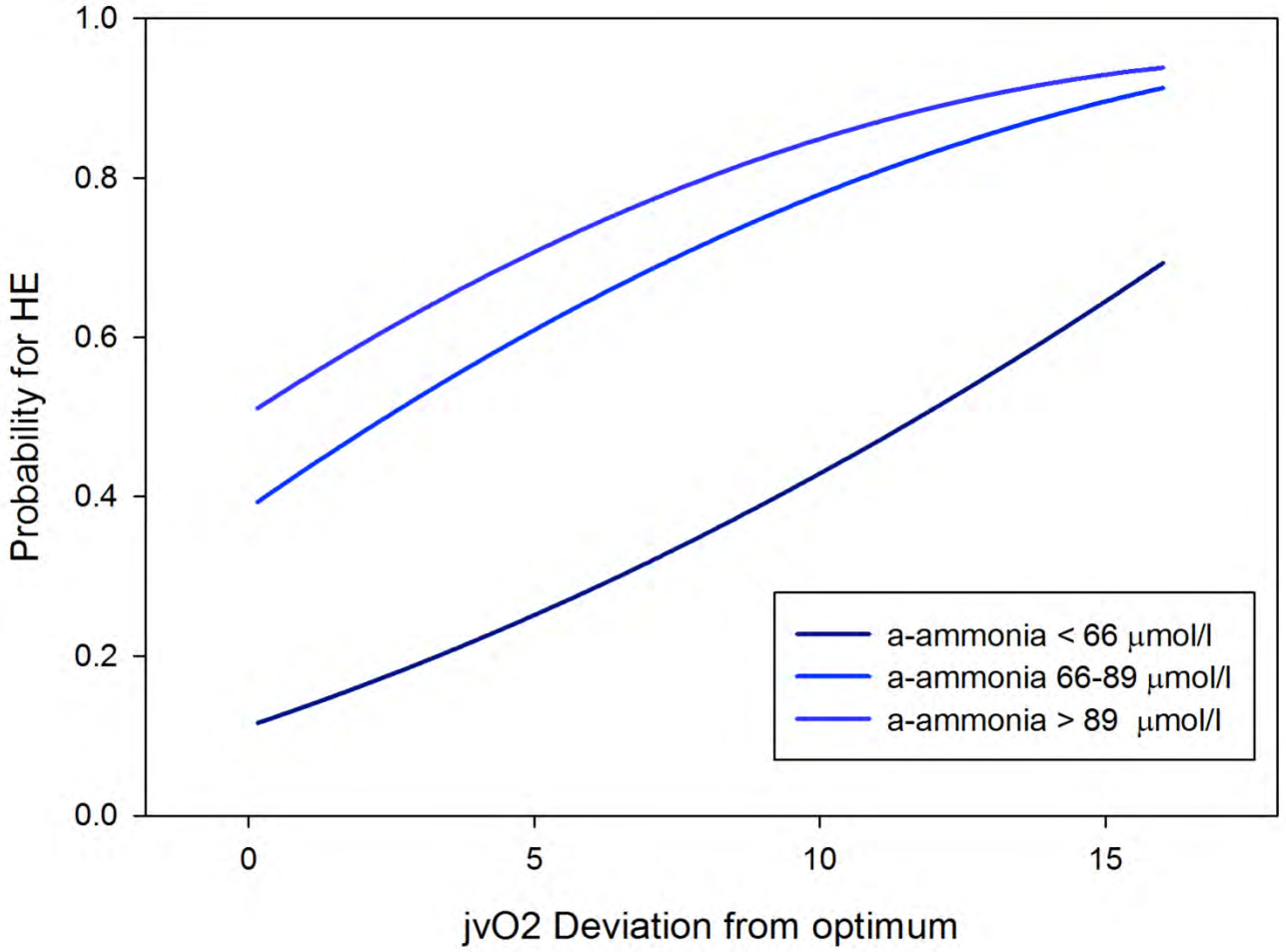
Sawhney et al. Liver Transplantation 2016

In ACLF and Brain oxygenation



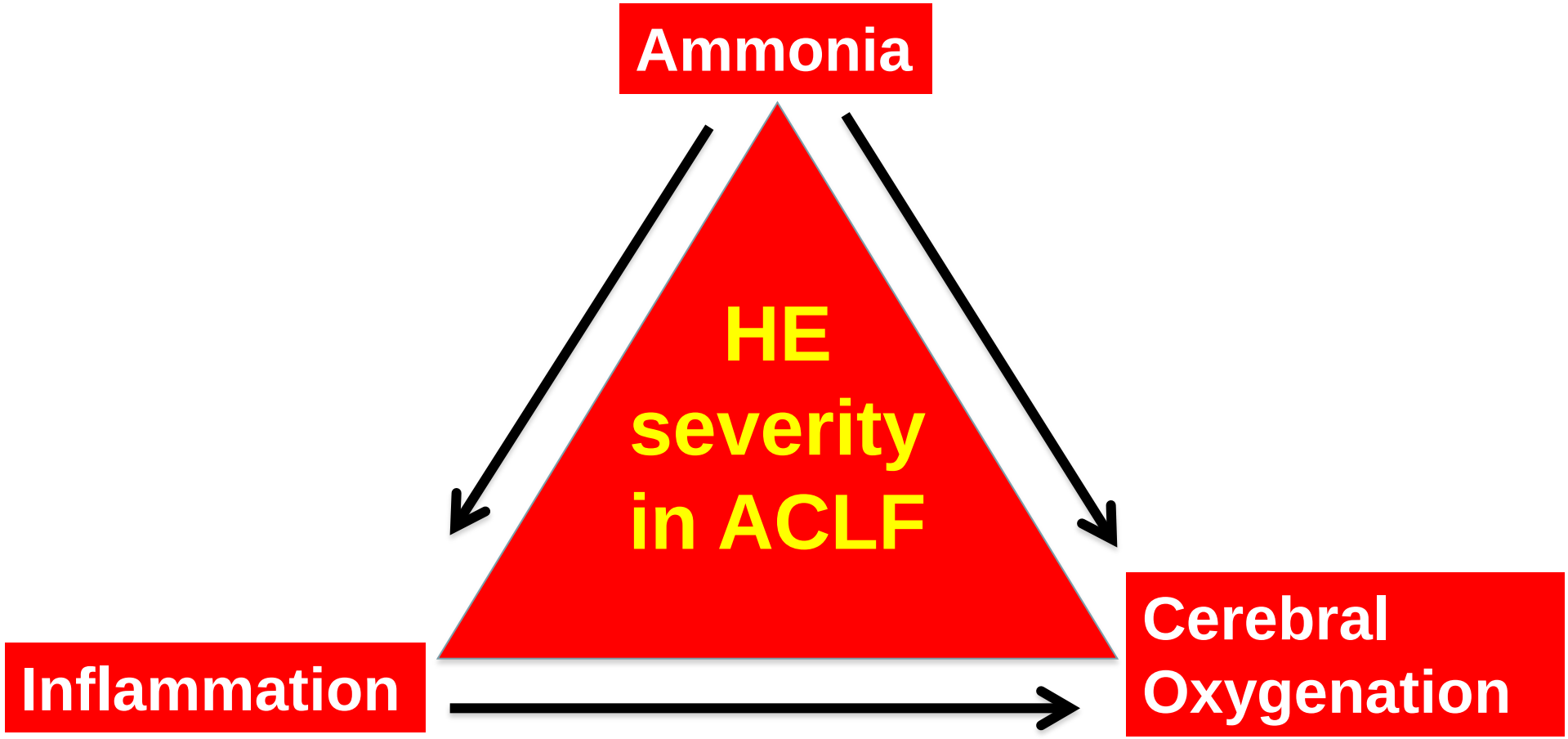
Sawhney et al. Liver Transplantation 2016

The severity of hyperammonemia and jugular venous oxygen saturation determines risk of HE



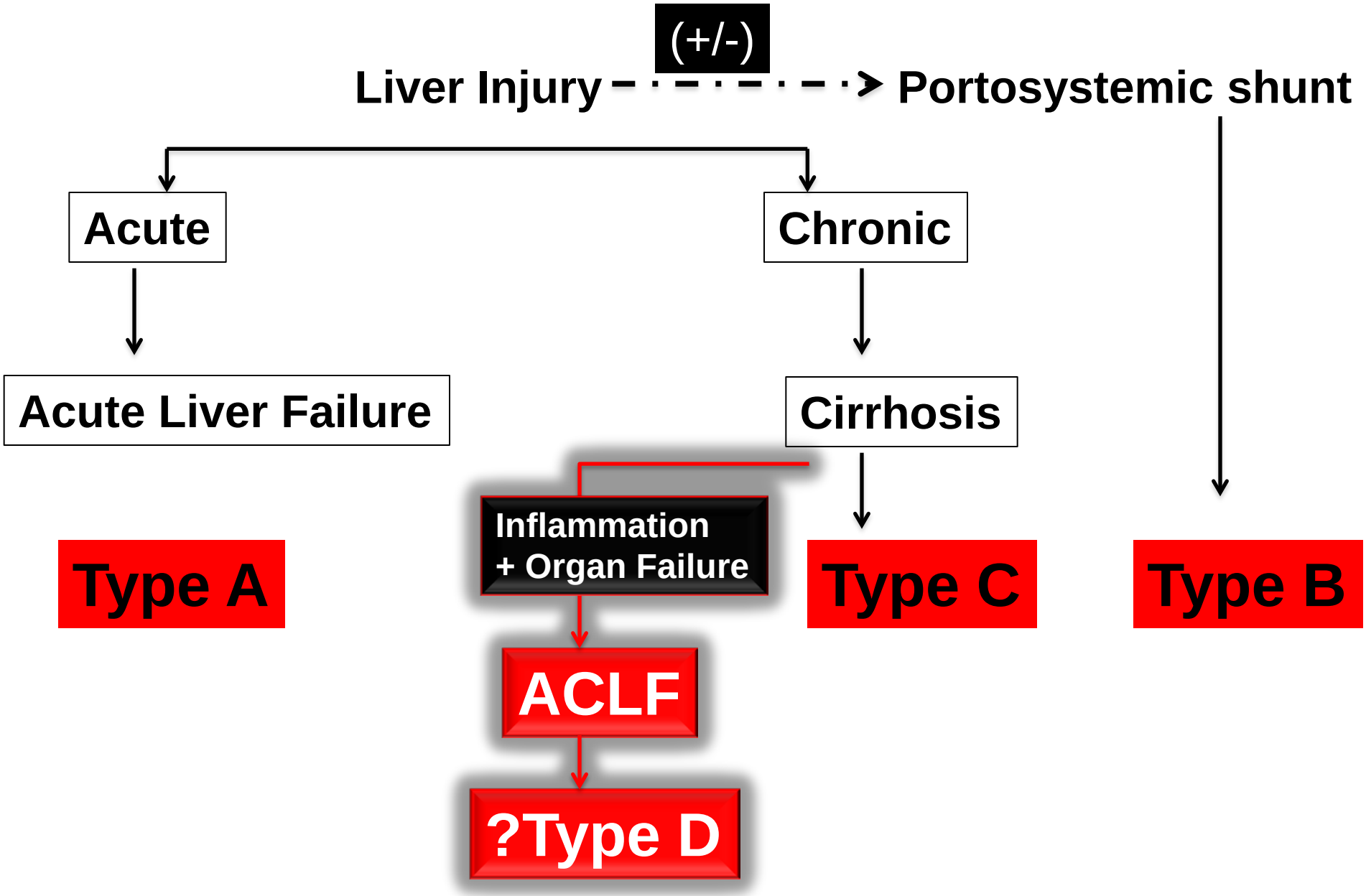
Sawhney and Holland-Fischer et al. AASLD 2014

Pathophysiology of HE in ACLF



Sawhney et al. Liver Transplantation 2016

Where would the Type D fit in?



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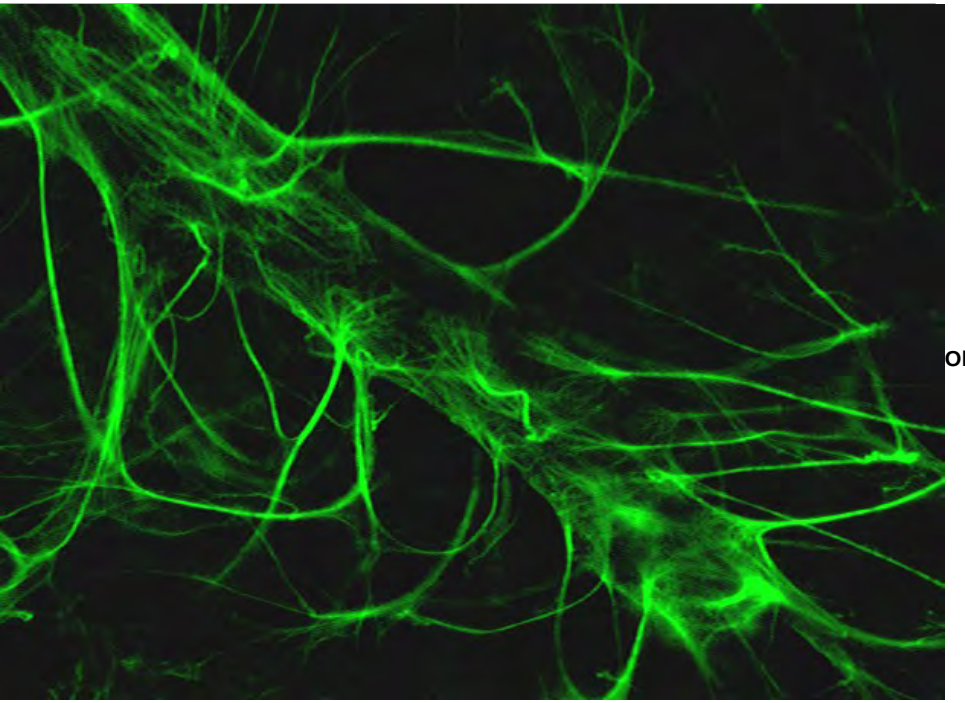
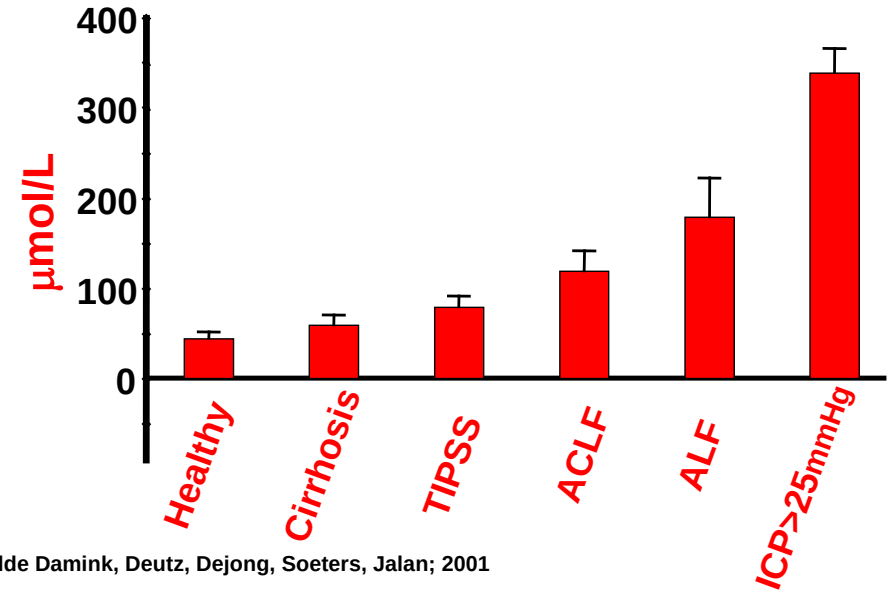
The Ammonia Story of Hepatic Encephalopathy

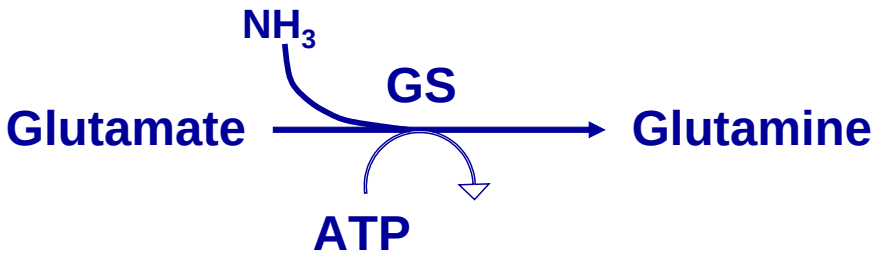
Neuropathology

Astrocyte Dysfunction and swelling





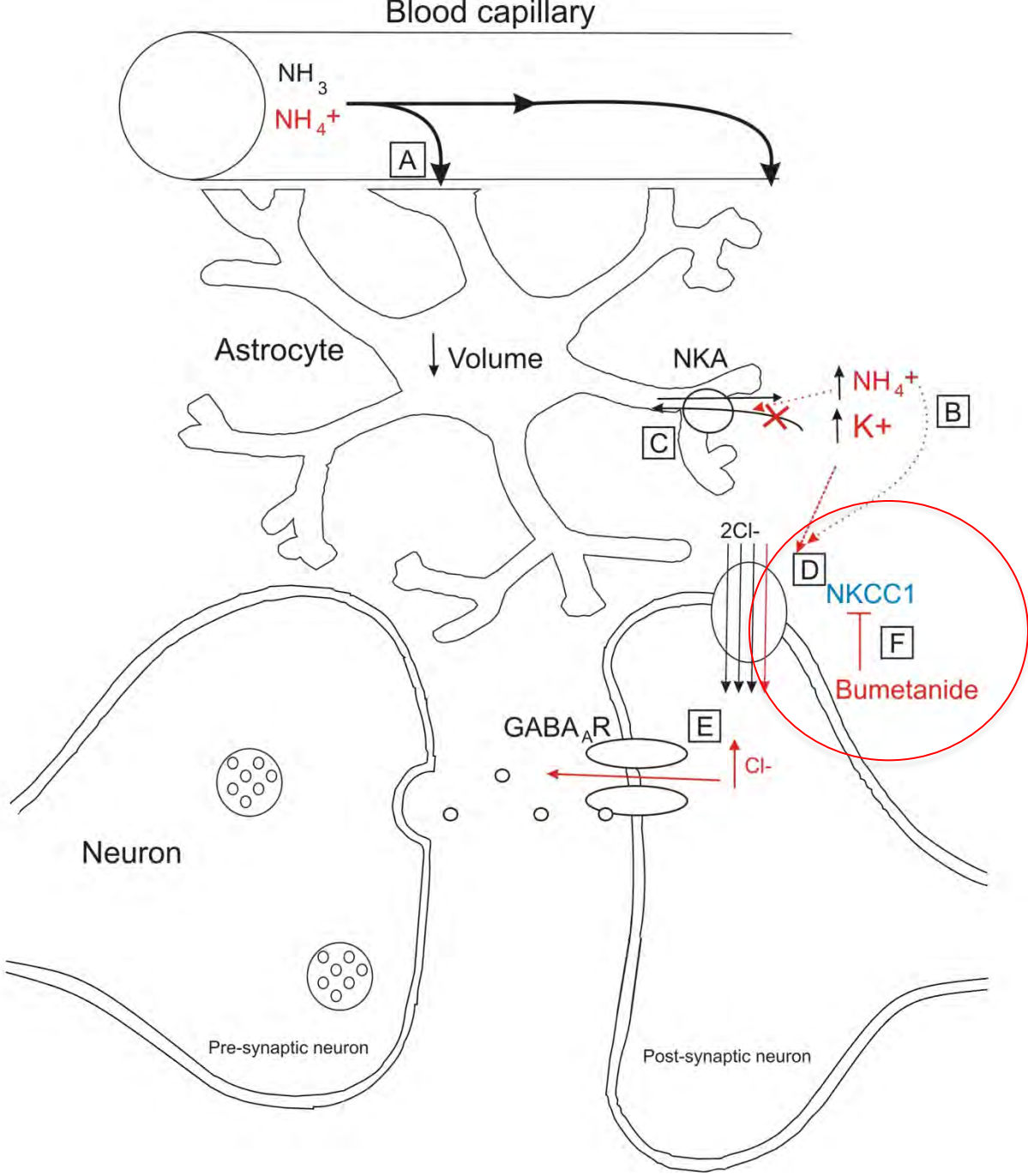
Olde Damink, Deutz, Dejong, Soeters, Jalan; 2001



Astrocyte Swelling vs Shrinkage

Involvement of the Ammonia transporter NKCC1 (Thrane et al. *Nature Medicin 19, 1643–1648)*

- **>98% of ammonia present as NH_4^+**
- **NH_4^+ is capable crossing all phospholipid cell membranes through K^+ channels**



Hadjihambi, Rose and Jalan
Hepatology 2014

Inflammation and Encephalopathy

* On admission

SIRS* score	Maximum Coma Grade				
	I	II	III	IV	ICP
0	42	29	29	47	17
I	66	34	28	46	30
II	0	40	20	56	35
III	0	0	47	100	72
IV	0	0	0	84	65

VAQUERO ET AL.

Infection and the Progression of Hepatic Encephalopathy in Acute Liver Failure

GASTROENTEROLOGY 2003;125:755–764

Rolando et al, Hepatology 32, 734, 2000

Systemic inflammatory response exacerbates the neuropsychological effects of induced hyperammonemia in cirrhosis☆

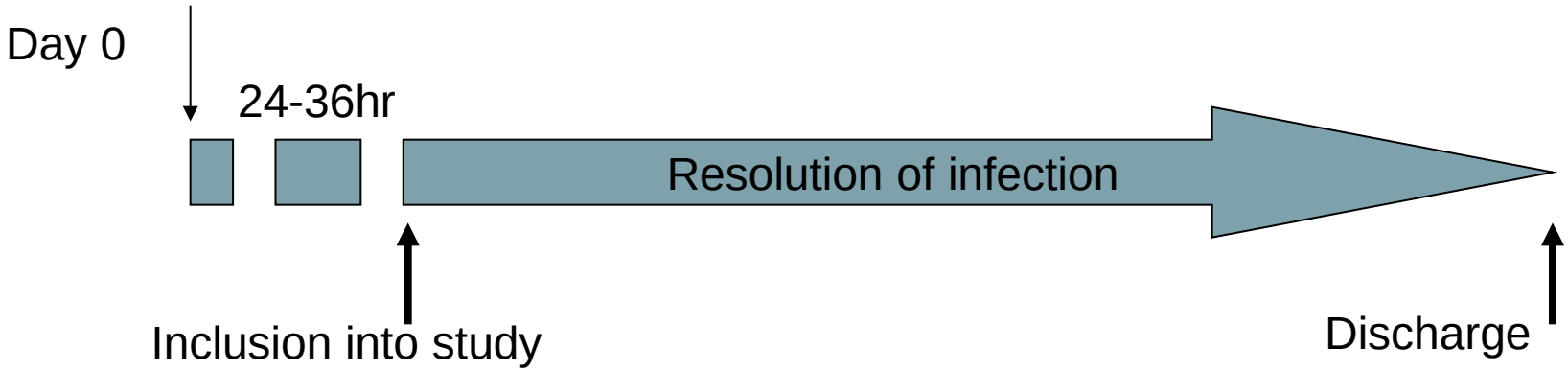
Debbie L. Shawcross, Nathan A. Davies, Roger Williams, Rajiv Jalan*

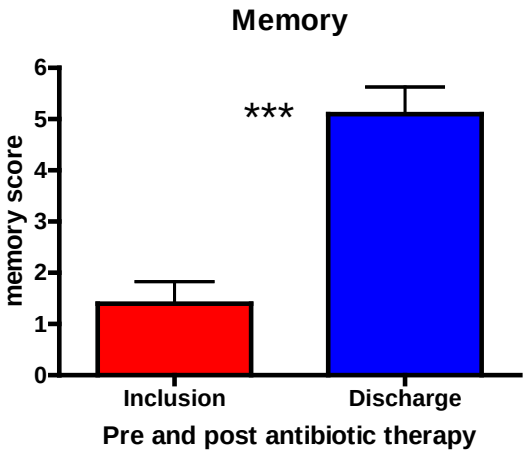
Liver Failure Group, Institute of Hepatology, University College London Medical School, 69-75, Chenies Mews, London WC1E 6HX, UK

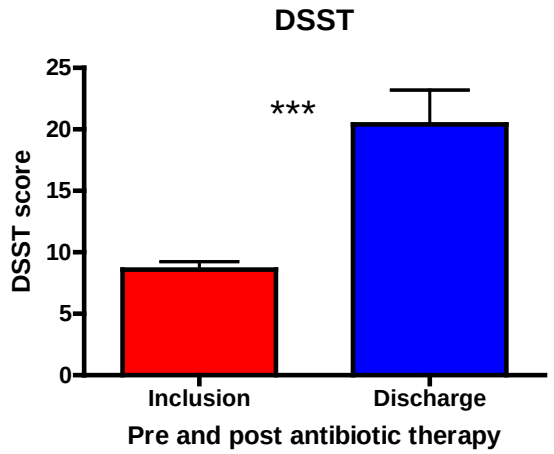
Admission with infection
- Resuscitate
- Start antibiotics
- Induce hyperammonemia

Measure changes in neuropsychometry

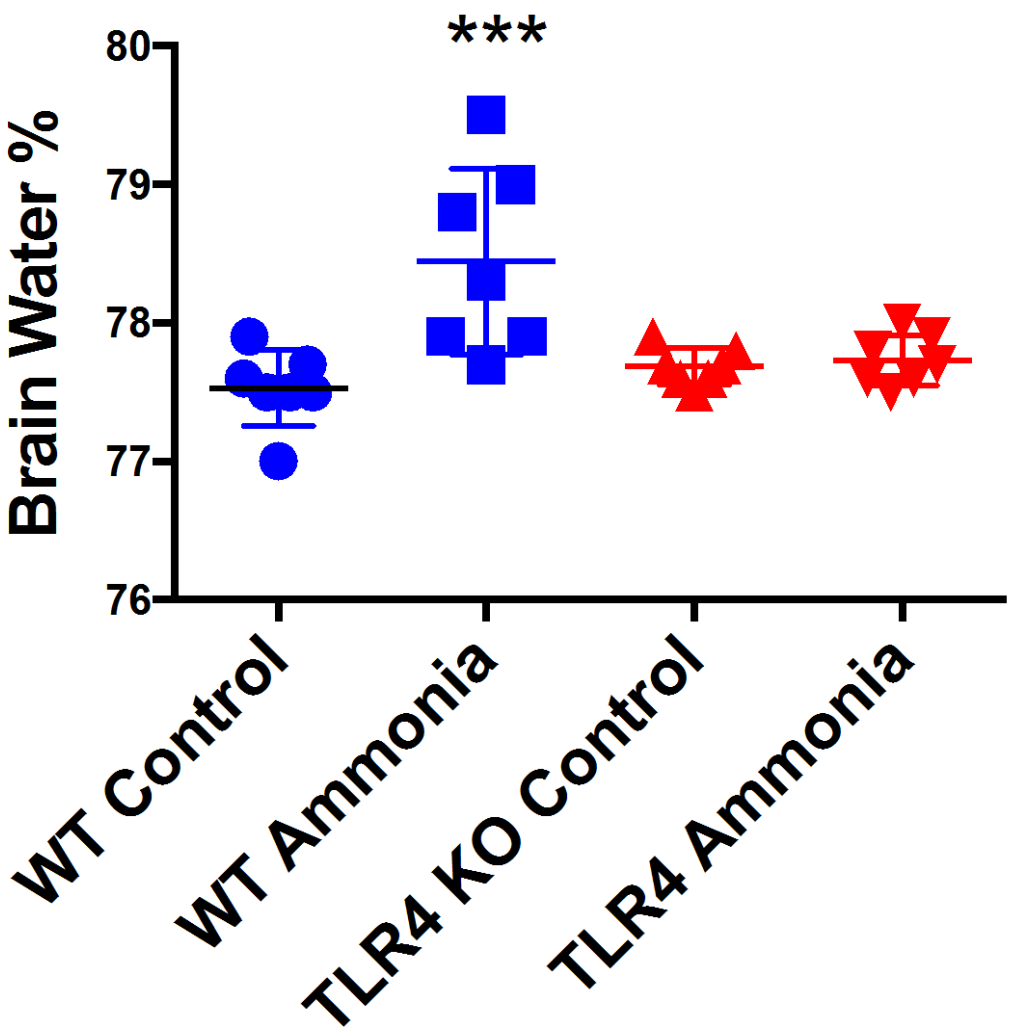
Journal of Hepatology 40 (2004) 247–254

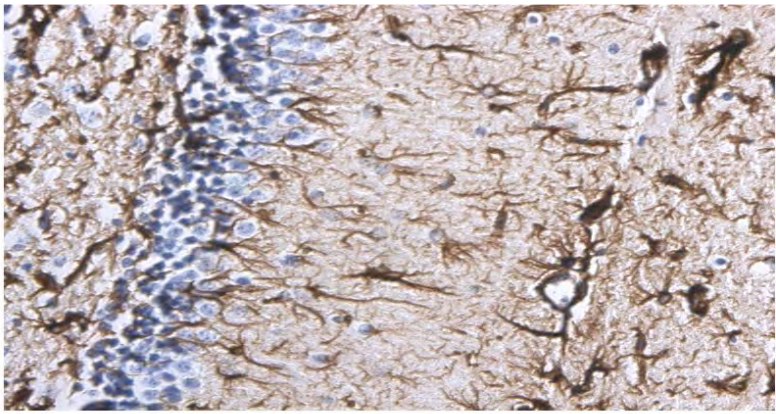




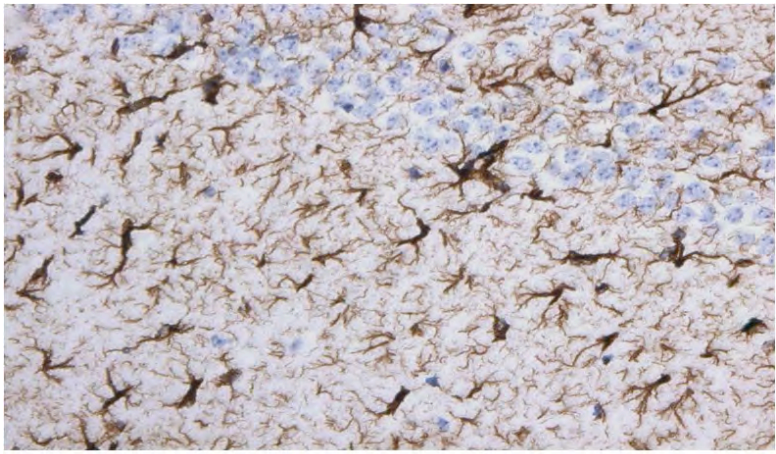


Ammonia and Inflammation:
Ammonia induced Brain edema is reduced in TLRKO





C57 NH_4CL , GFAP x40

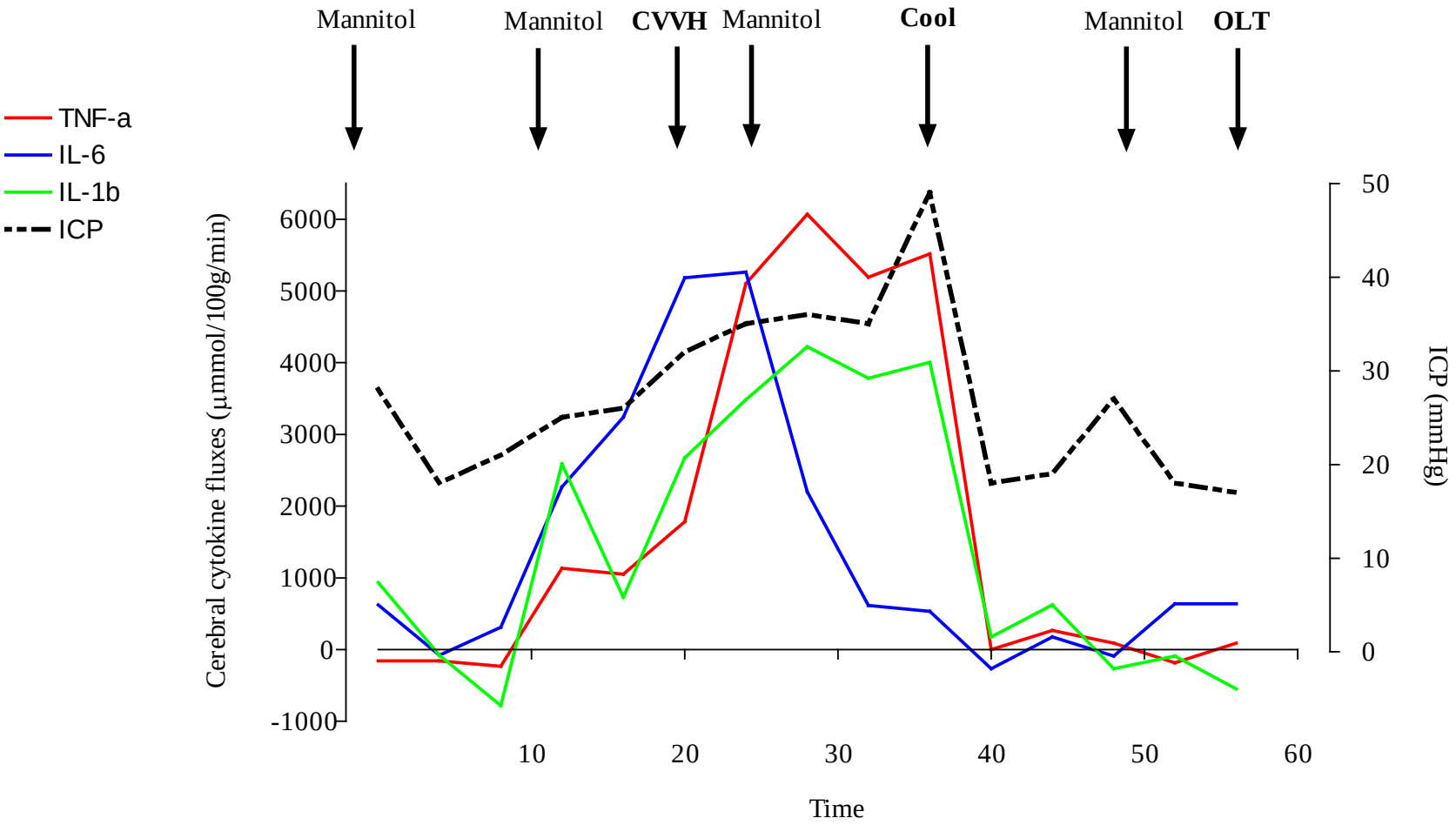


TLR4 NH_4CL , GFAP

Sharifi et al. AASLD 2014

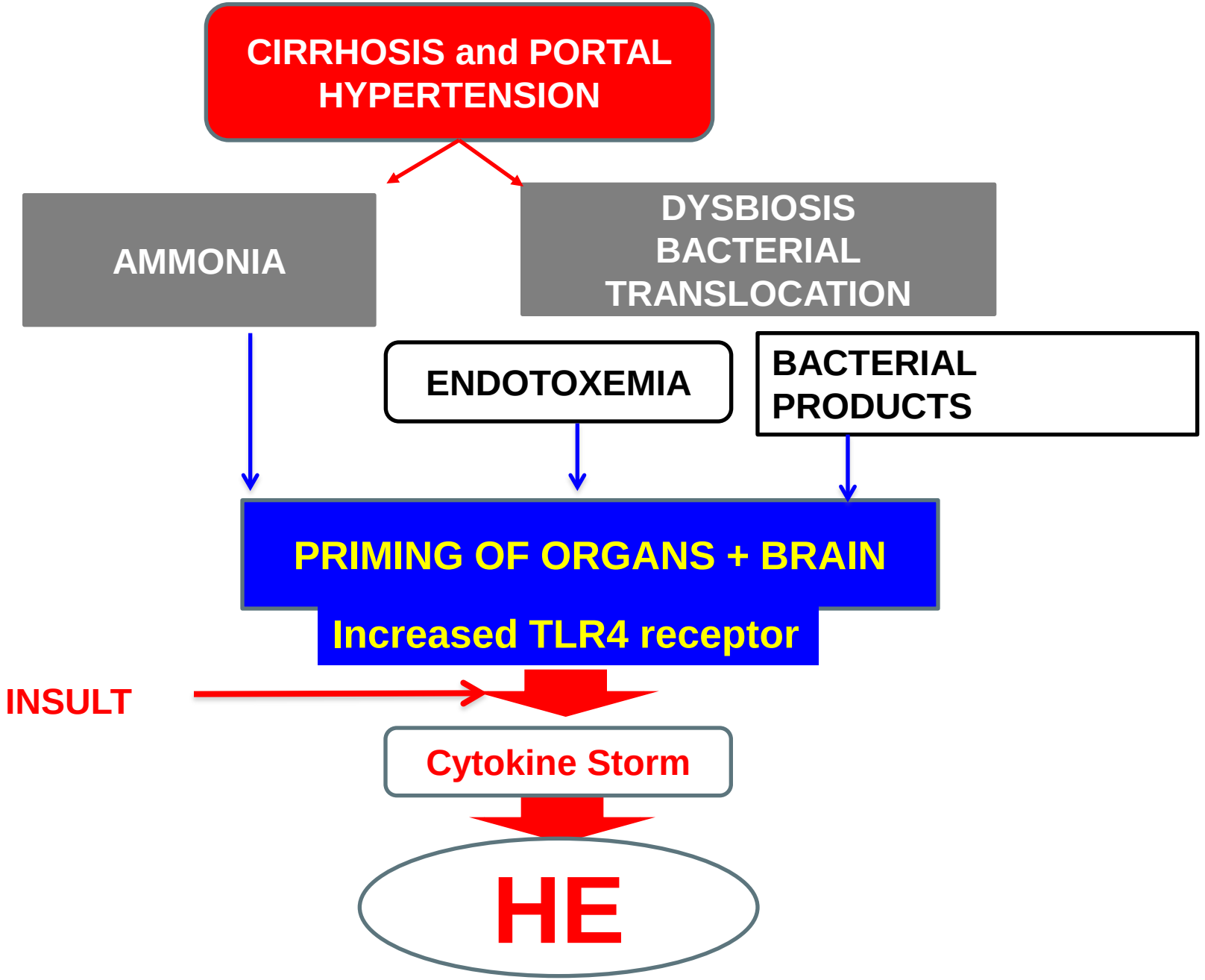
Brain Flux of Pro-Inflammatory Cytokines

ICP: Uncontrolled during patient FU



Wright et al. Metab Brain Dis, 2007

Unifying Hypothesis



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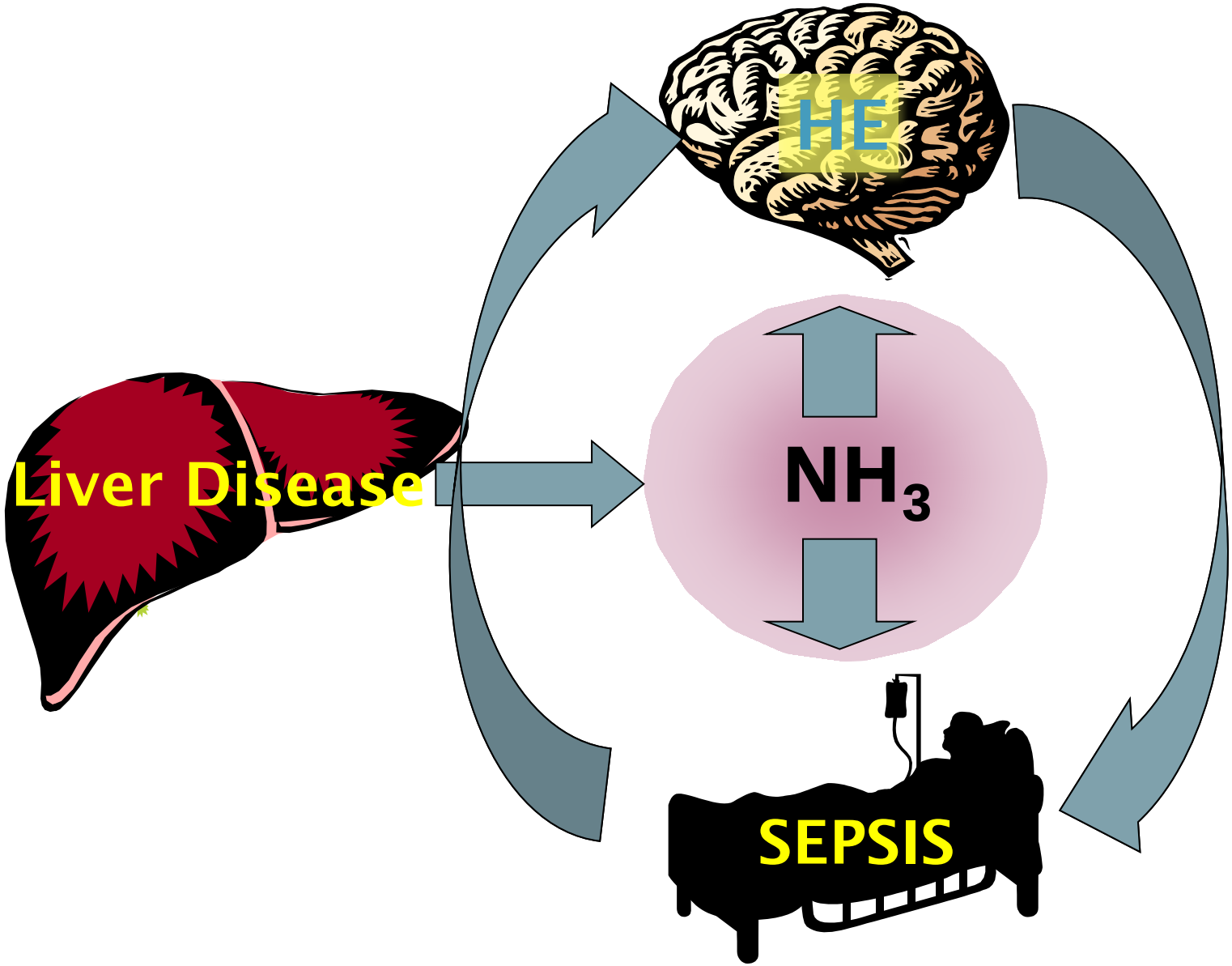
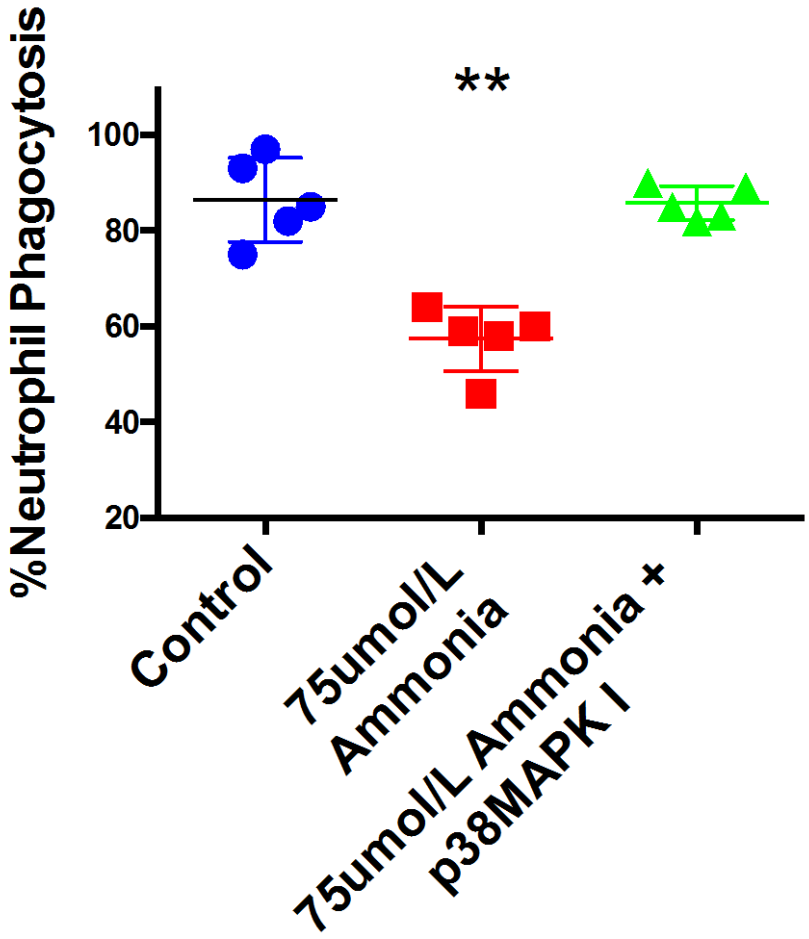
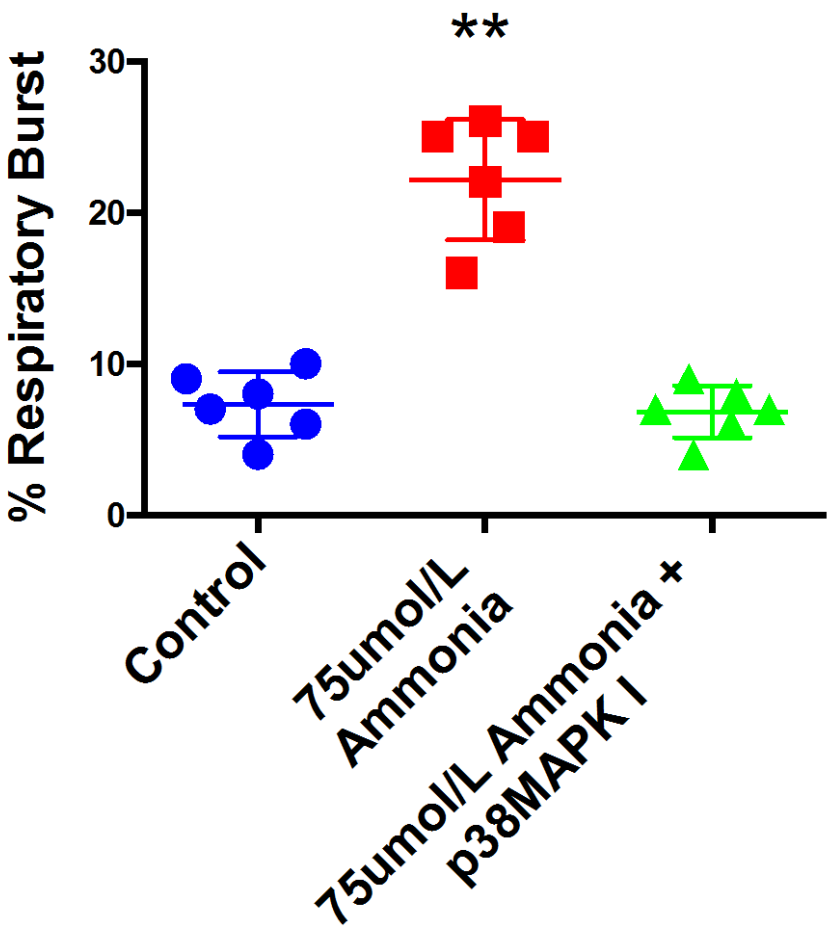
Hypothesis



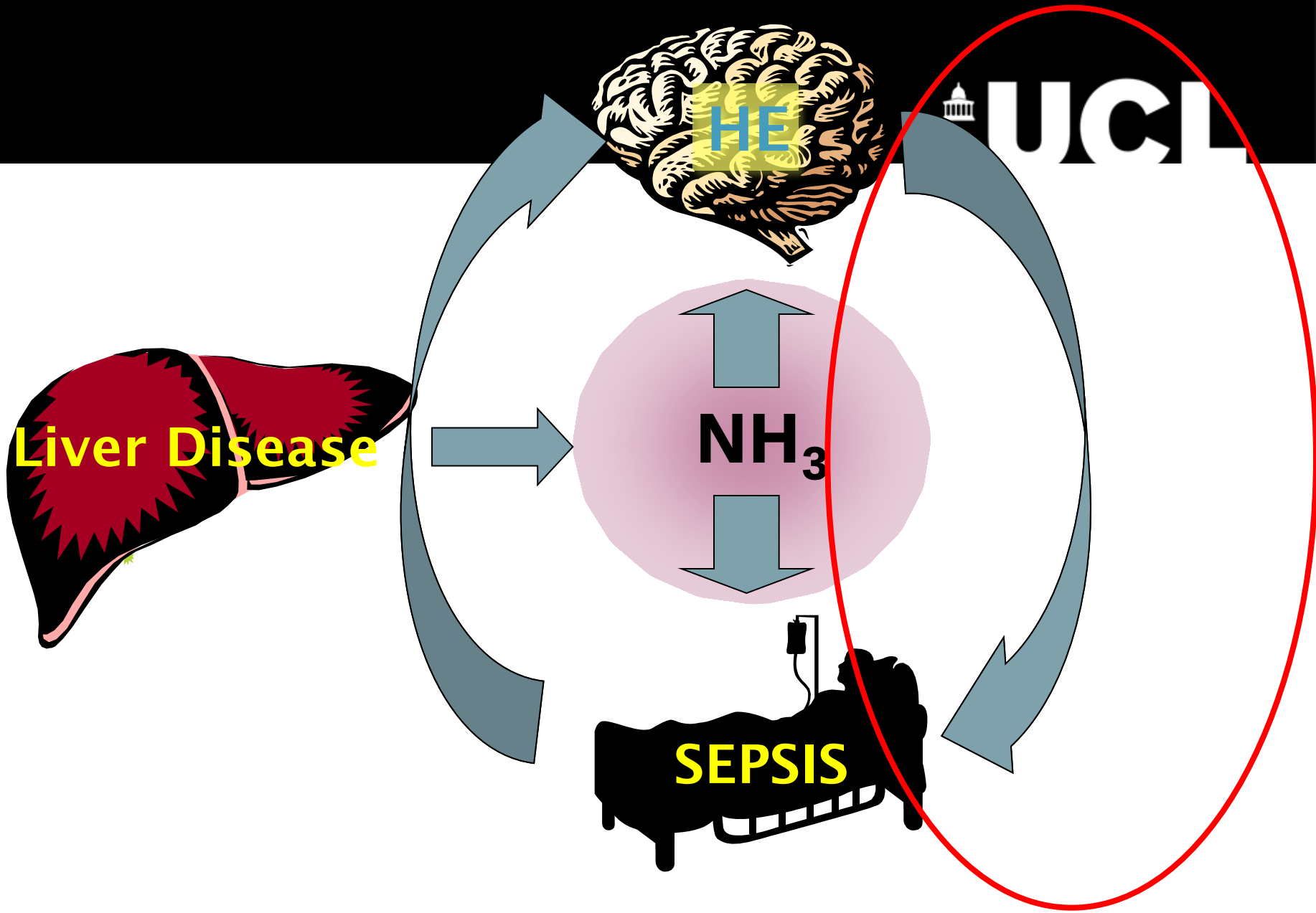
Ammonia induces spontaneous respiratory burst through effects on p38 MAP kinase pathway

p38 antagonist: 10 µM SB203580

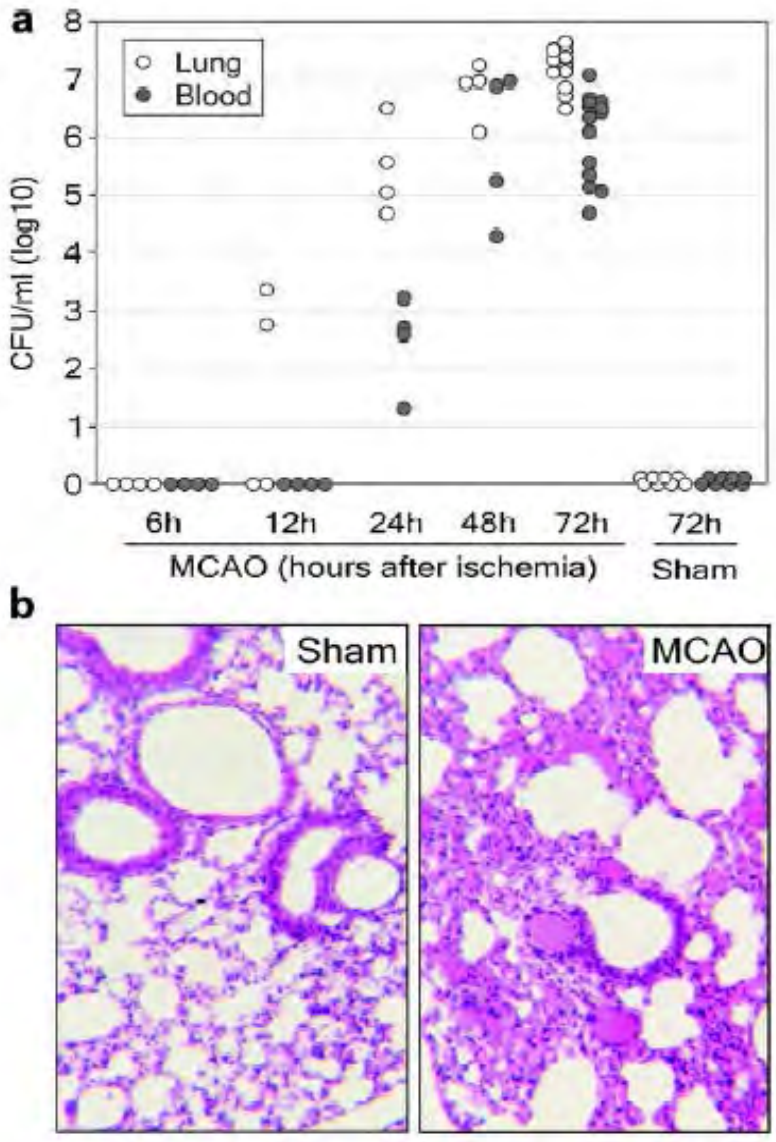




Shawcross and Jalan et al. Hepatology 2007


HE
Liver Disease
NH_3
SEPSIS

Can Hepatic Encephalopathy produce Immune Failure?



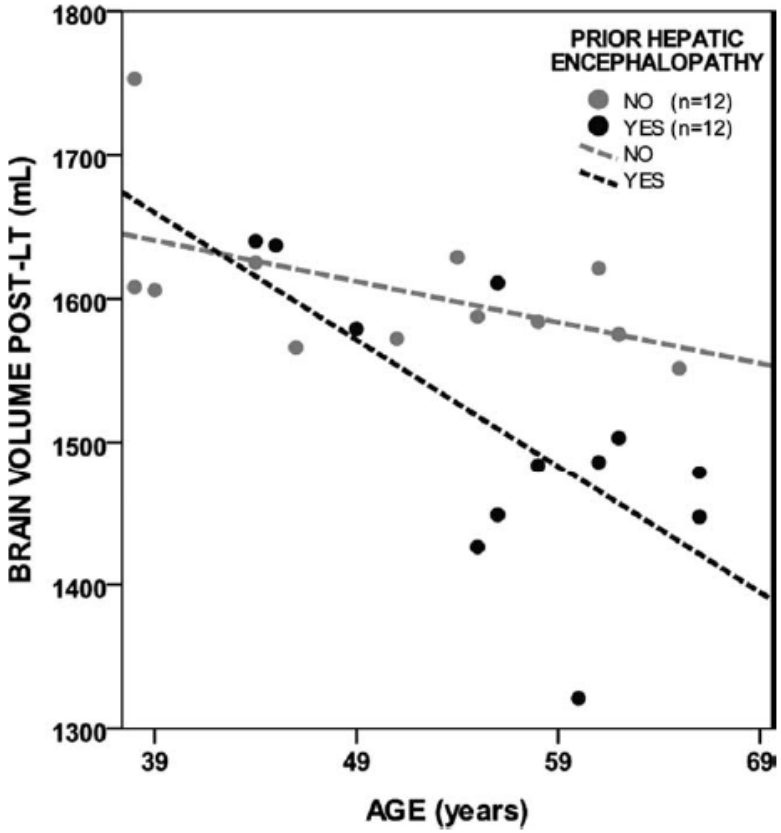
Due to apoptotic loss of Lymphocytes

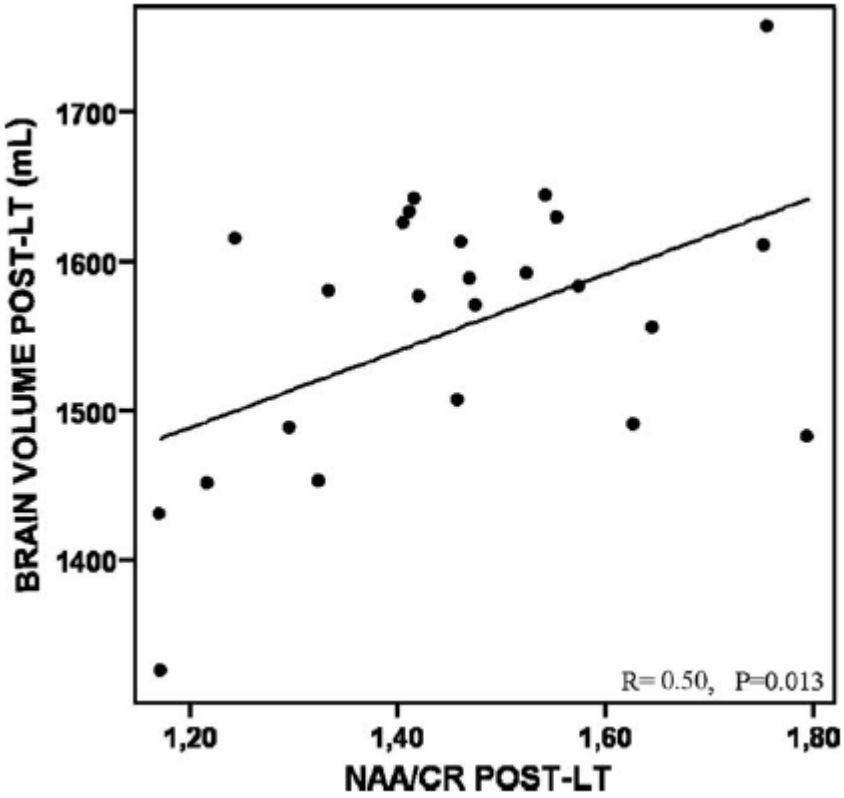
Shift from Th-1 to Th-2 Phenotype

Reversed by inhibition of Sympathetic System

Prass et al. J Exp Med. 2009 Sep 1;198(5):725-36.

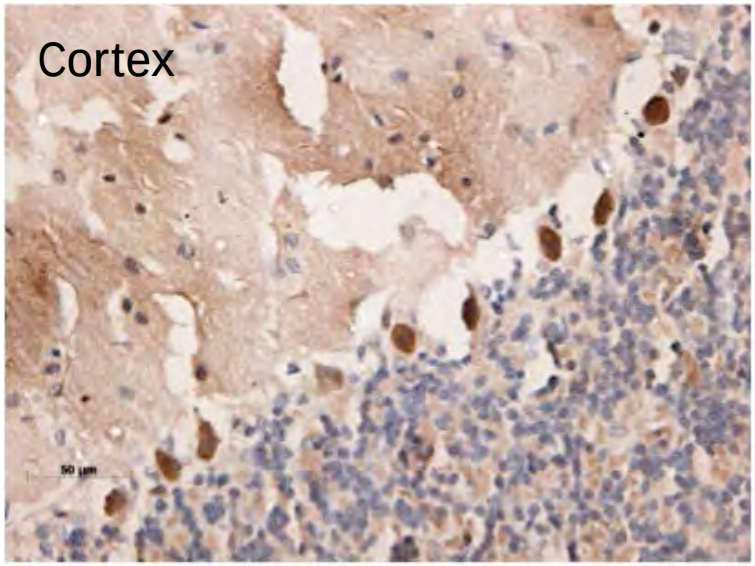
Episodes of HE lead to neurodegeneration

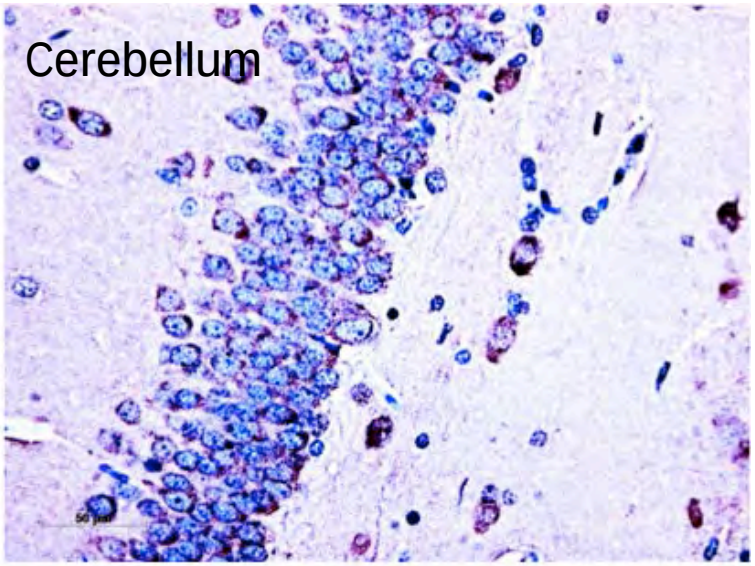


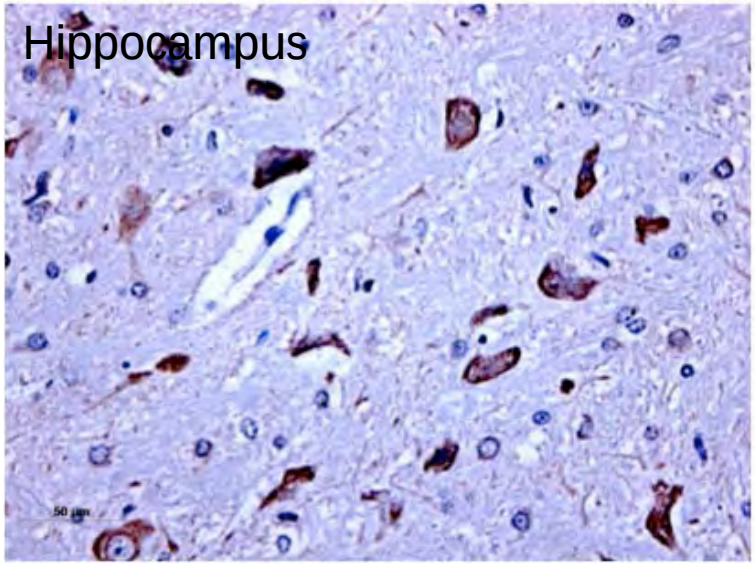


García-Martinez R. et al 2011

What is the mechanism?





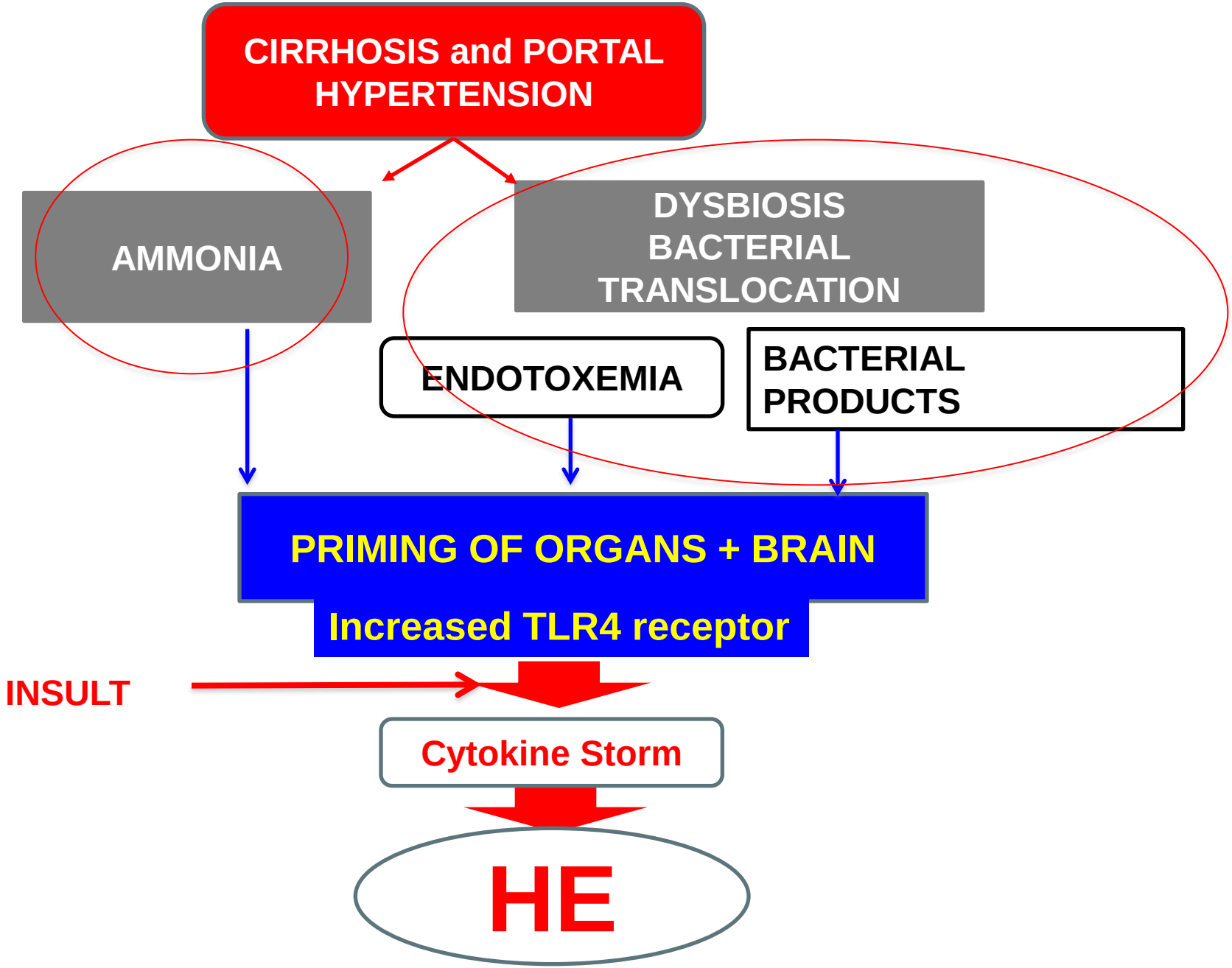


Expression of Serpin-1, a marker of senescence is increased in HE

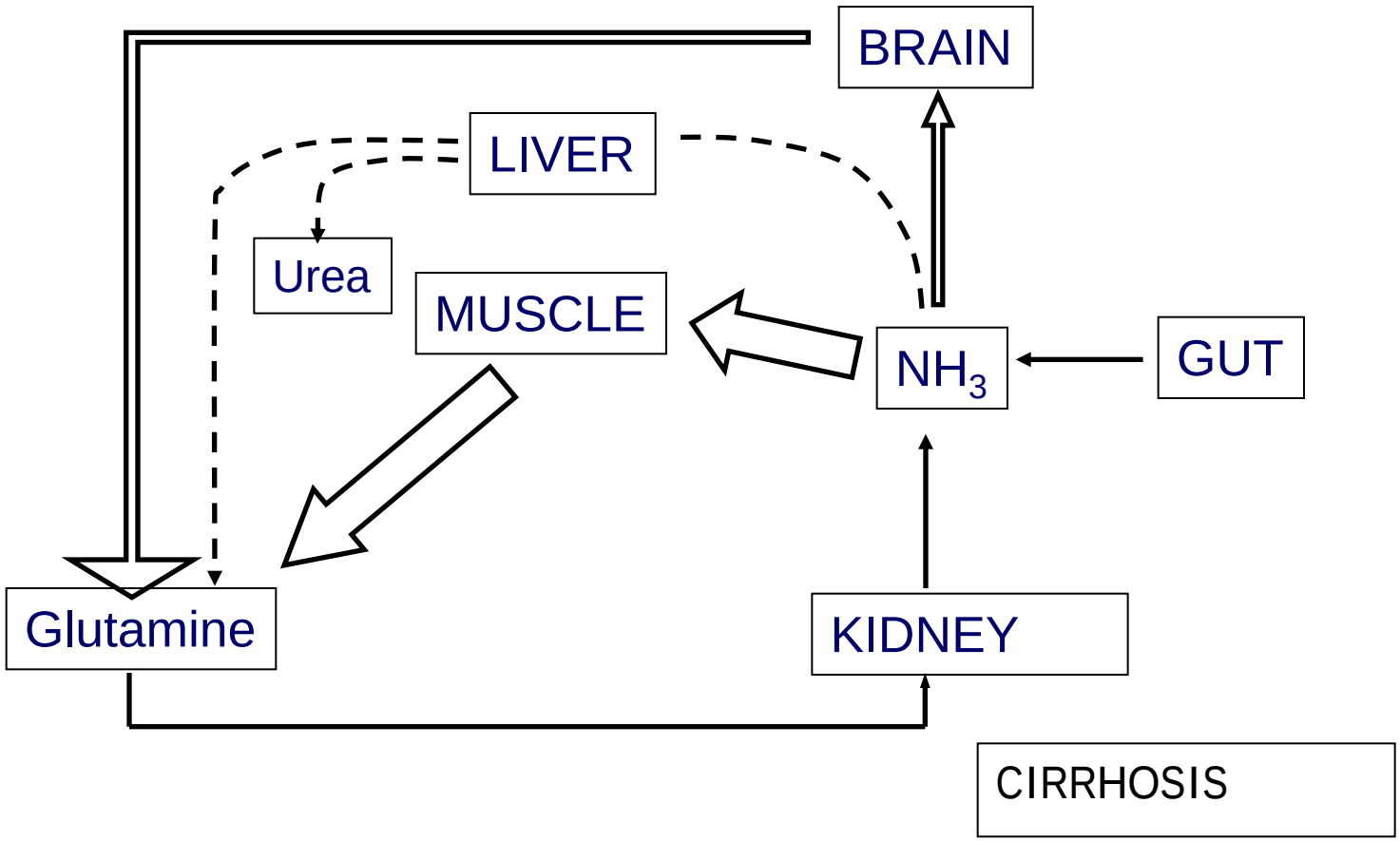
Oria et al. EASL 2014

Therapeutic Approaches

Unifying Hypothesis



Where is Ammonia metabolised in *Liver Failure* patients

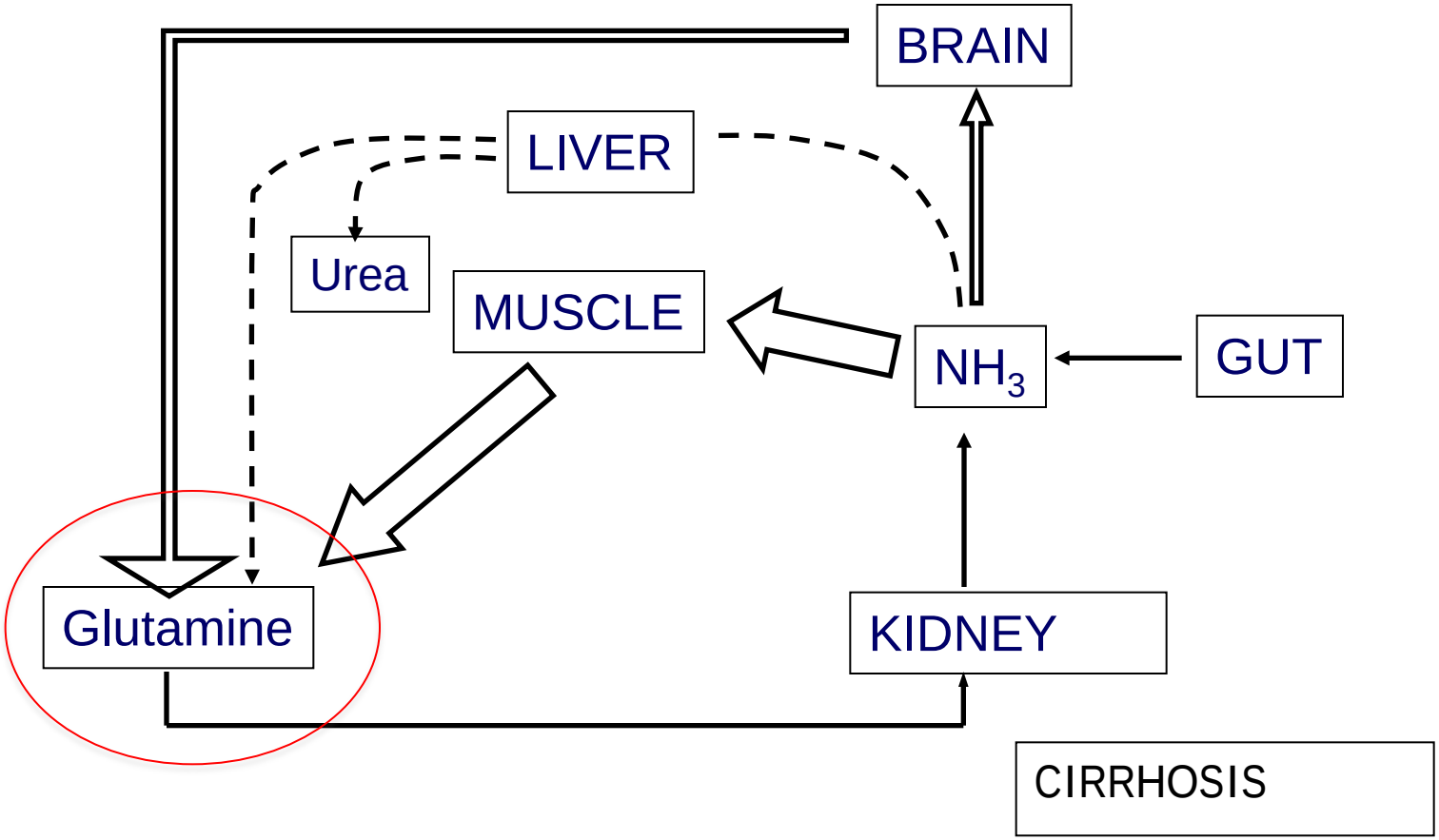


Shawcross and Jalan, Lancet 2005

Therefore, *new target organs* for reducing ammonia

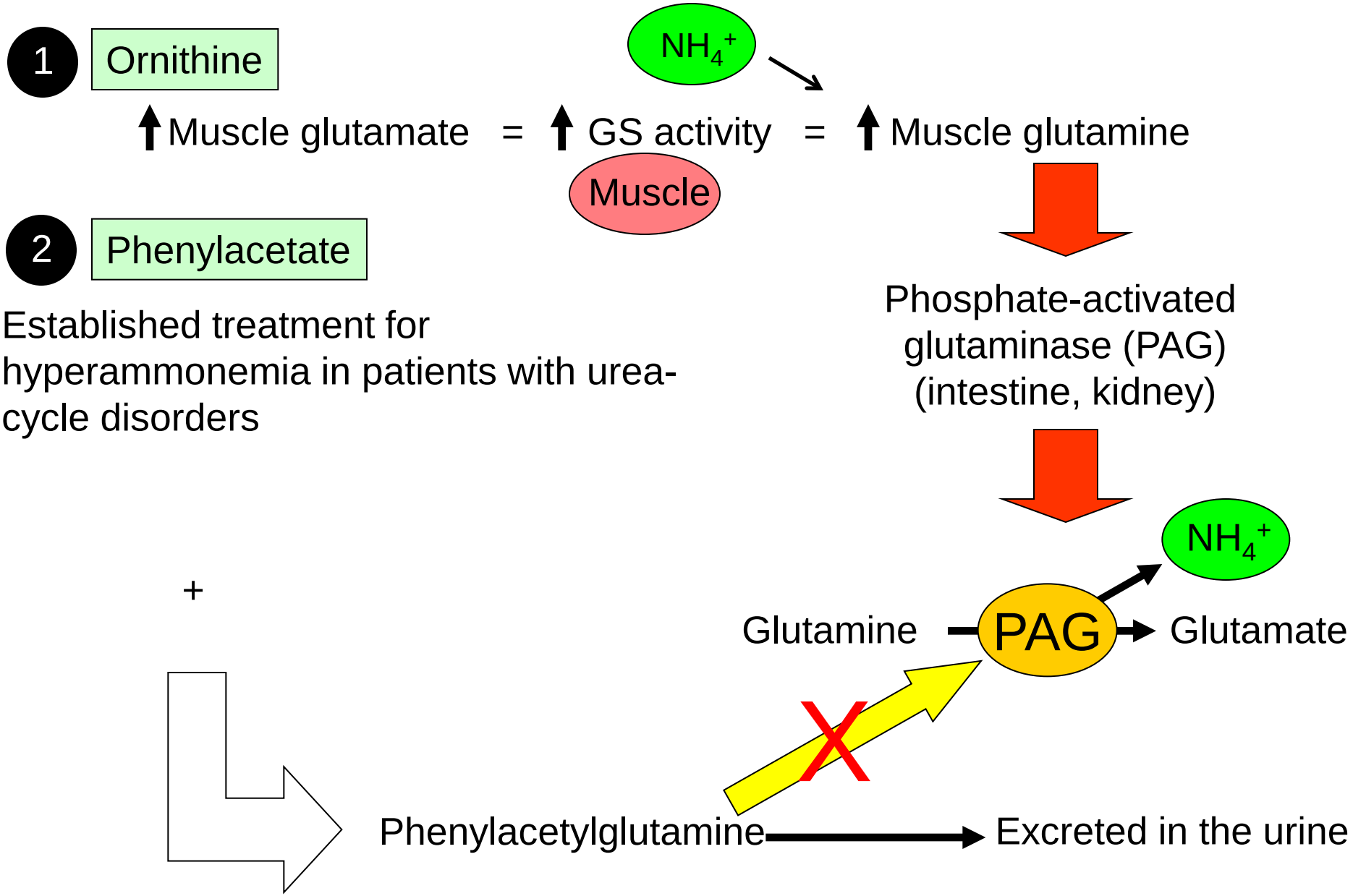
- GUT
- Kidneys
- Muscle

Glycerol Phenylbutyrate works by removing Glutamine



Shawcross and Jalan, Lancet 2005

How does Ornithine Phenylacetate work?



Treatment of hepatic encephalopathy

- **Primary Prophylaxis**
- **Secondary Prophylaxis**
- **Treatment of the Acute episode**

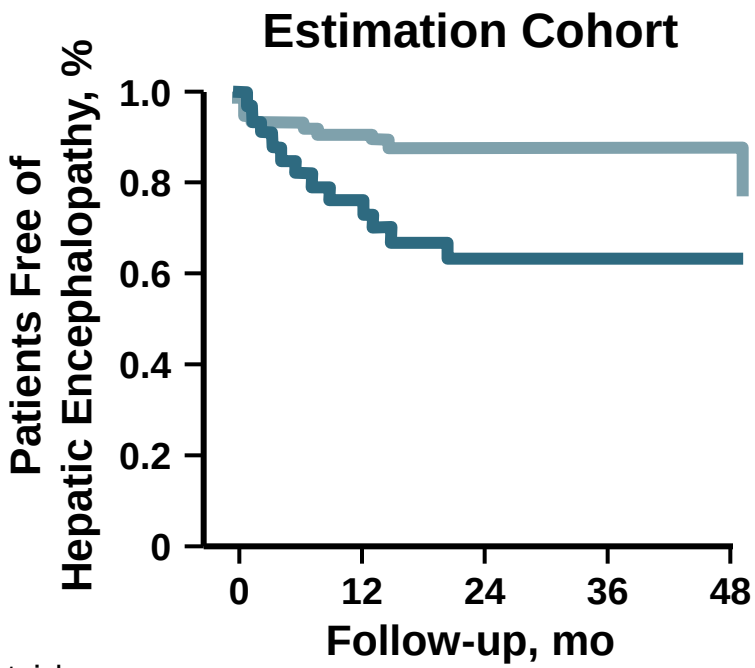
Can we predict which patients with cirrhosis will develop HE and can the first episode be prevented?

Annals of Internal Medicine | ARTICLE

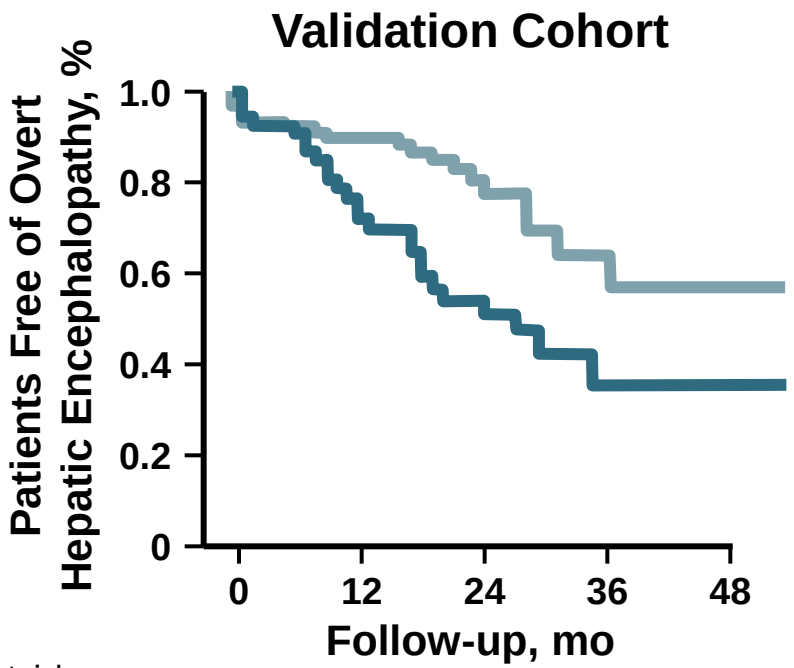
Variations in the Promoter Region of the Glutaminase Gene and the Development of Hepatic Encephalopathy in Patients With Cirrhosis

A Cohort Study

Manuel Romero-Gómez, MD, PhD; María Jover, PhD; José A. Del Campo, PhD; José L. Royo, PhD; Elena Hoyas, MD; José J. Galán, PhD; Carmina Montoliu, PhD; Eugenia Baccaro, MD; Mónica Guevara, MD, PhD; Juan Córdoba, MD, PhD; Germán Soriano, MD, PhD; José M. Navarro, MD; Carmen Martínez-Sierra, MD, PhD; Lourdes Grande, MD, PhD; Antonio Galindo, MD, PhD; Emilia Mira, PhD; Santos Mañes, PhD; and Agustín Ruiz, MD, PhD



Patients at risk, n					
Short-short or short-long	75	66	46	22	19
Long-long	34	26	17	6	6

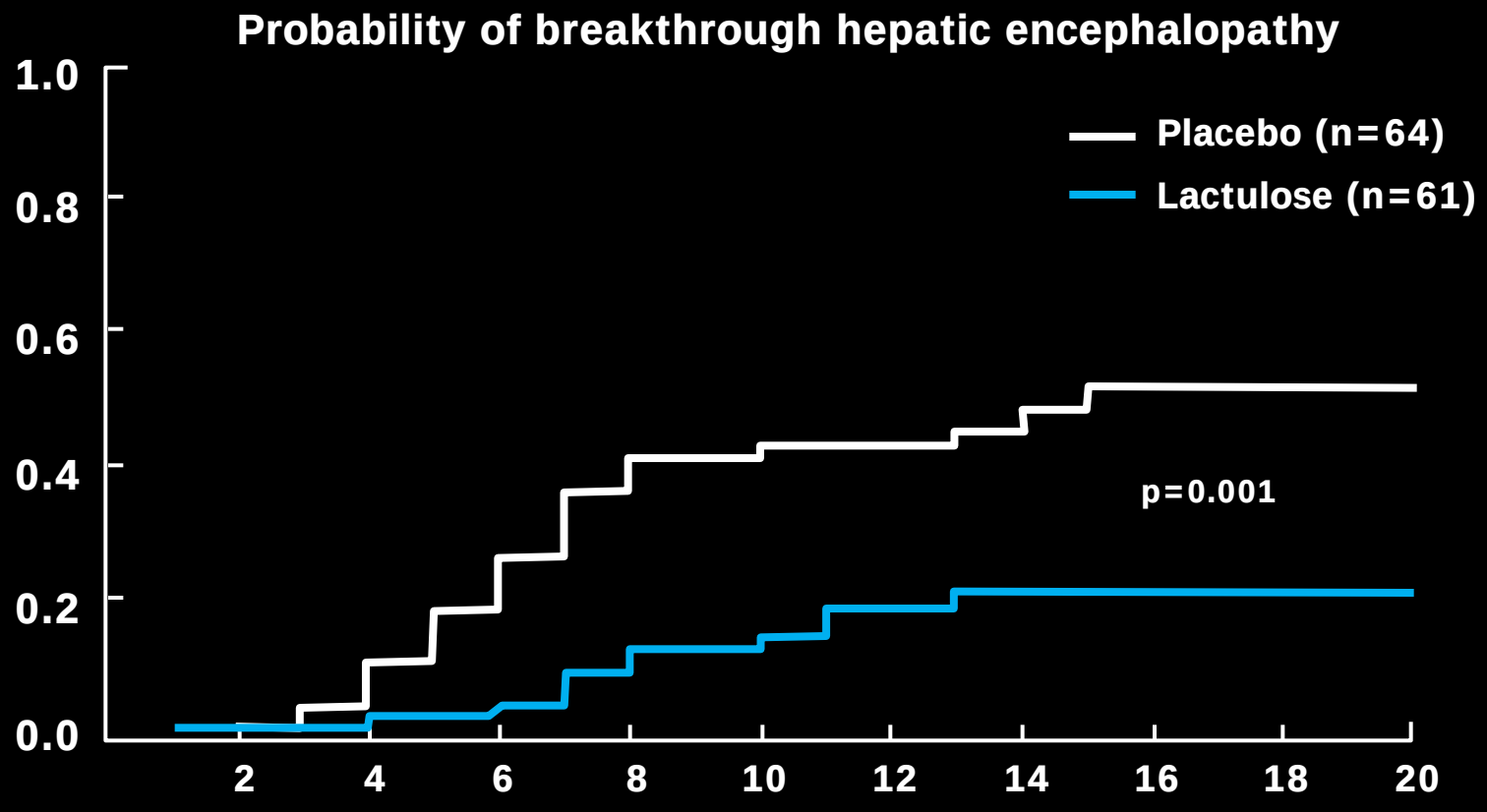


Patients at risk, n					
Short-short or short-long	121	78	29	9	7
Long-long	56	34	18	4	2

Romero-Gomez M *et al. Ann Intern Med* 2010;153:281–88

Secondary Prophylaxis

Lactulose for Secondary Prophylaxis

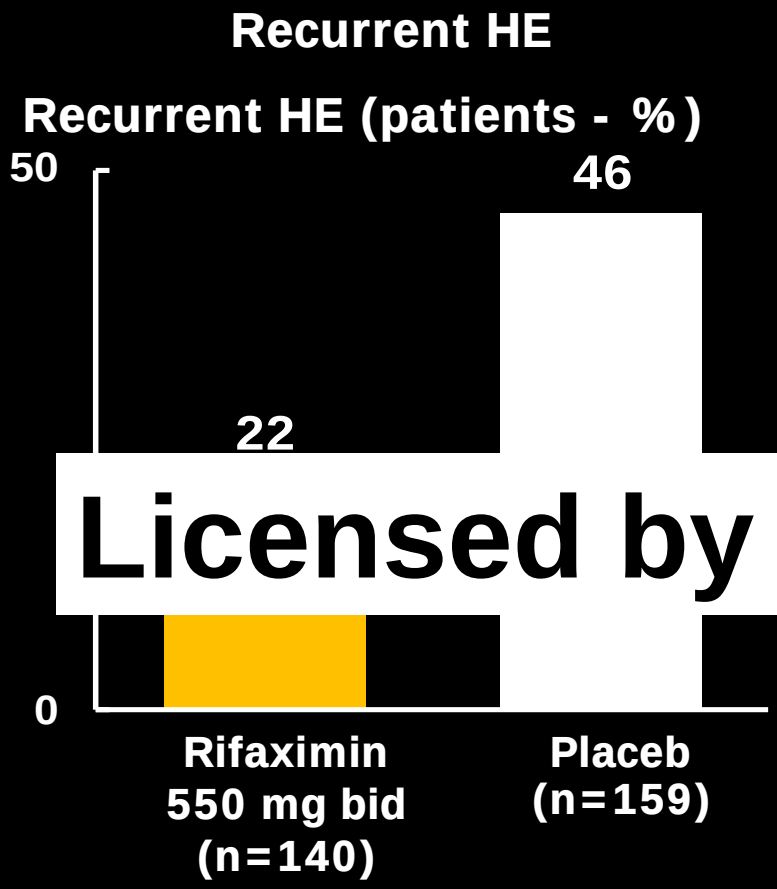


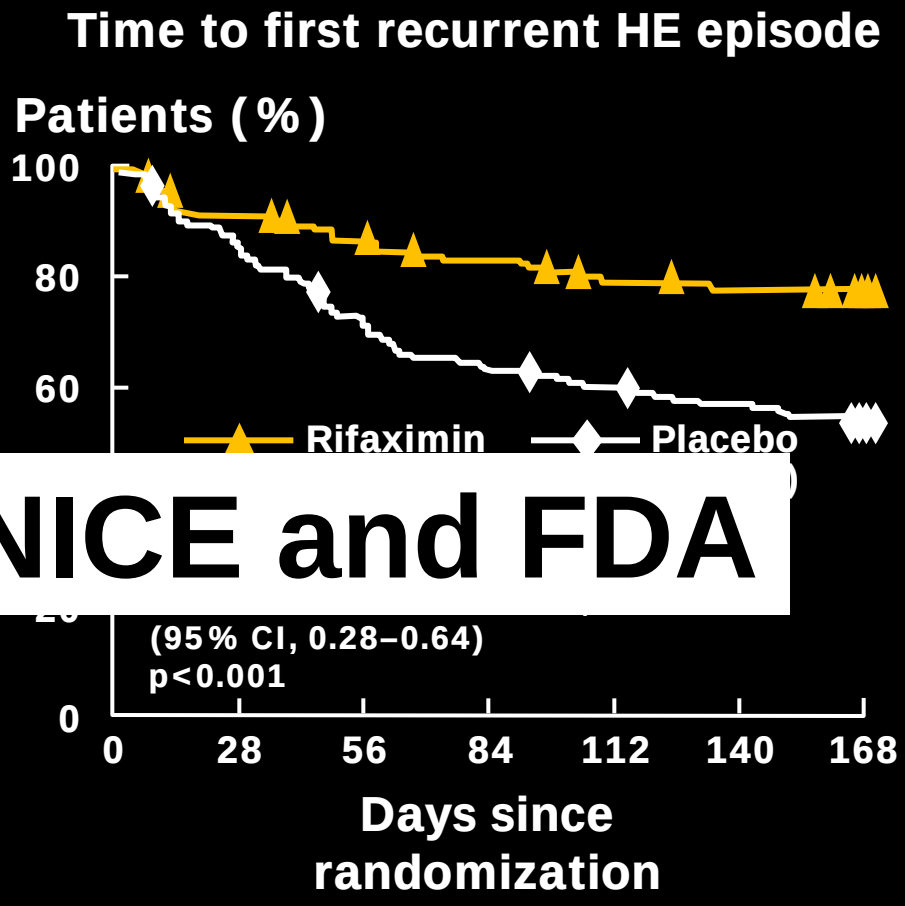
Patients at risk

Lactulose	61	60	59	58	51	45	38	28	10	7	1
Placebo	64	62	59	50	37	33	28	19	13	8	4

Gastroenterology, 2009;137:885–91.

Rifaximin for Secondary Prophylaxis of HE: Recurrence





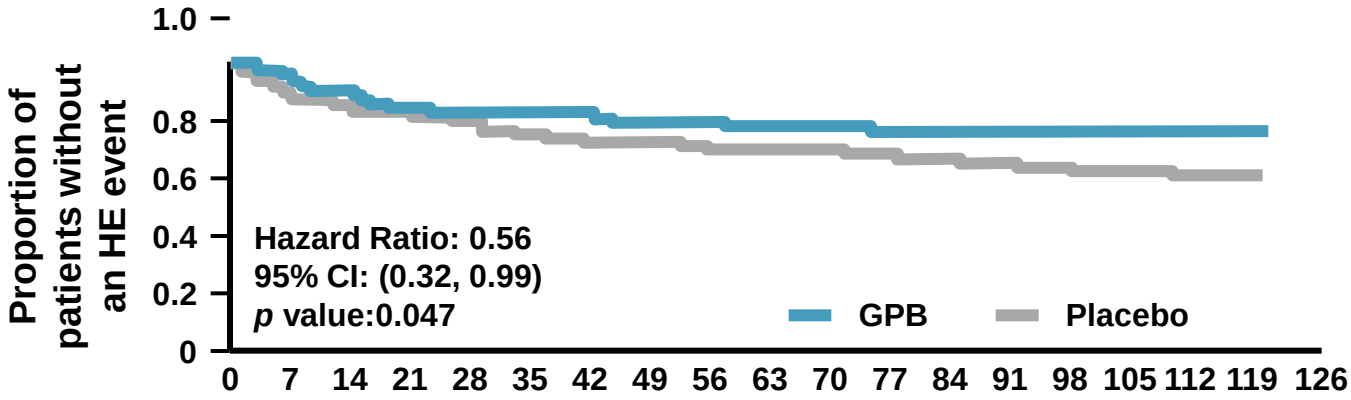
Licensed by NICE and FDA

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

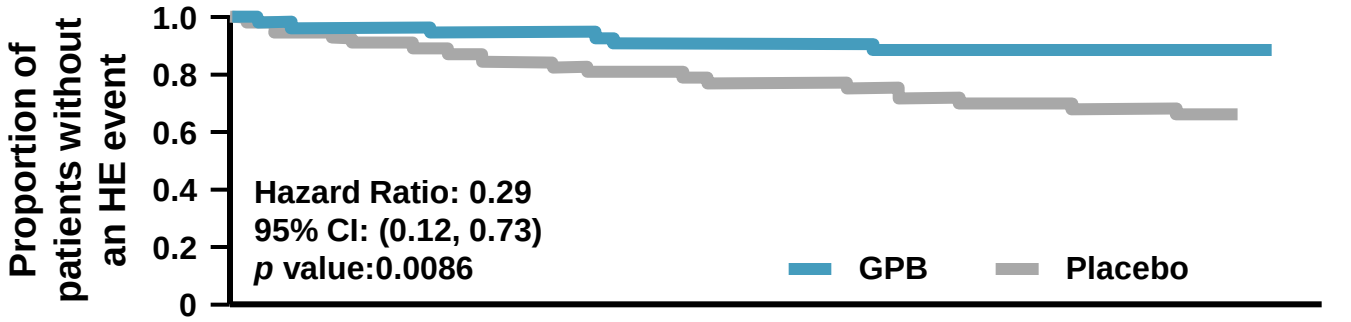
Glycerol phenylbutyrate reduces ammonia and prevents HE

AMMONIA	Baseline	Treatment*
Placebo	54 (34) umol/L	58 umol/L/wk
GPB	48 (35) umol/L	46 umol/L/wk

All patients



Non-rifaximin patients



Time to HE event. The time to the first HE event over time is depicted for all patients (top panel; n=178), in patients not on rifaximin at baseline (middle panel; n=119), and in patients on rifaximin at baseline (bottom panel; n=59)

Rockey D *et al. Hepatology* 2014;59:1073–83

Treatment of the Acute Episode

- Treat precipitating event
- Nutrition
- Clean Bowel
- Treat precipitating factors
- Reduce ammonia: GPB; OP

- In patients in whom there is no response?
  - Albumin Dialysis

Low protein diet?

Normal protein diet for episodic HE: results of a randomised study

Cordoba et al. J of Hepatol

- **Outcome of HE was no different.**
- **Protein synthesis was similar.**
- ***Those on the low-protein diet group showed higher protein breakdown.***

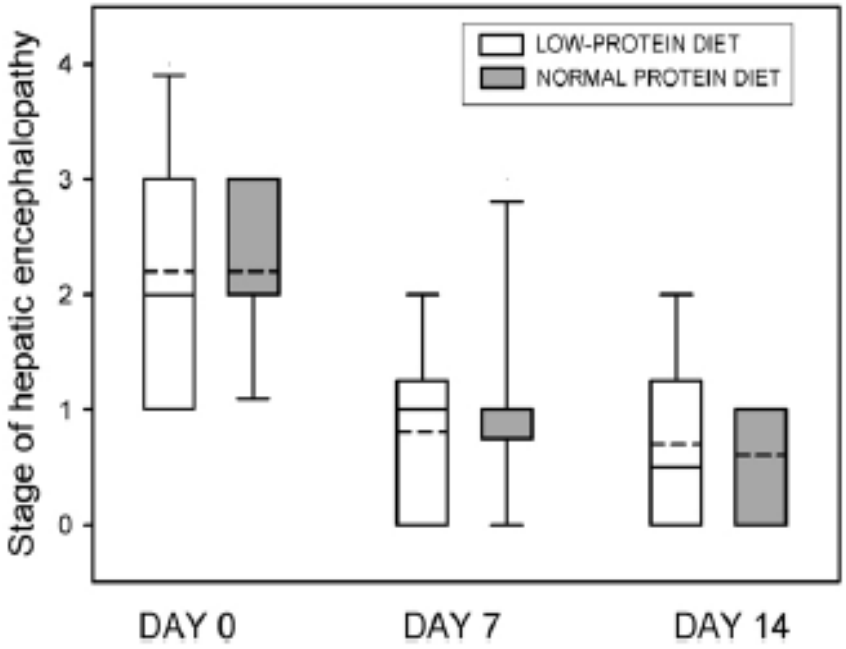
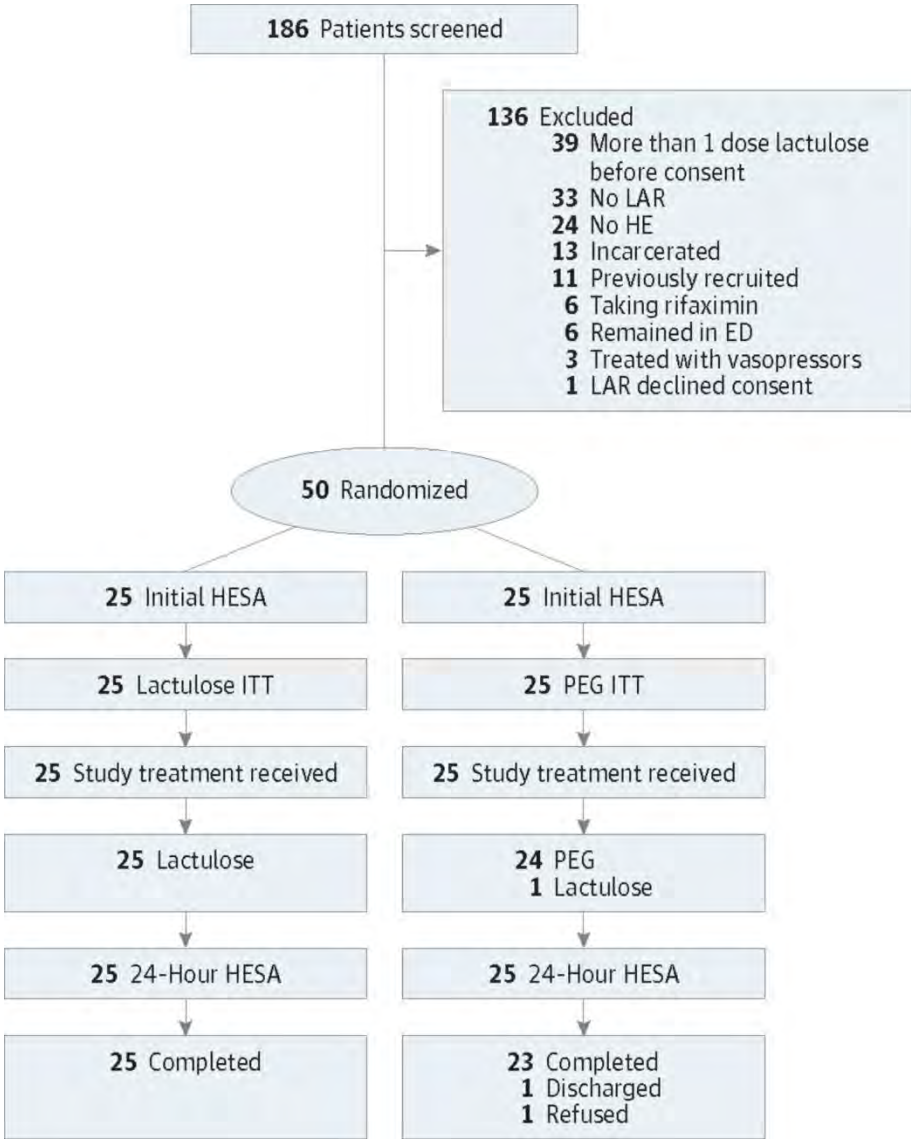


Fig. 3. Stage of hepatic encephalopathy (box plot: median, 10th–90th percentile, 25th–75th percentile, dashed line: mean) at inclusion (day 0), day 7 and end of the study (day 14) in the patients that finished the study (per-protocol analysis), grouped according to treatment. There were no statistical differences between the low-protein diet (white boxes) and the normal protein diet (gray boxes).

Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution for Treatment of Overt Hepatic Encephalopathy: The HELP Randomized Clinical Trial



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

Table 2. Study Outcomes

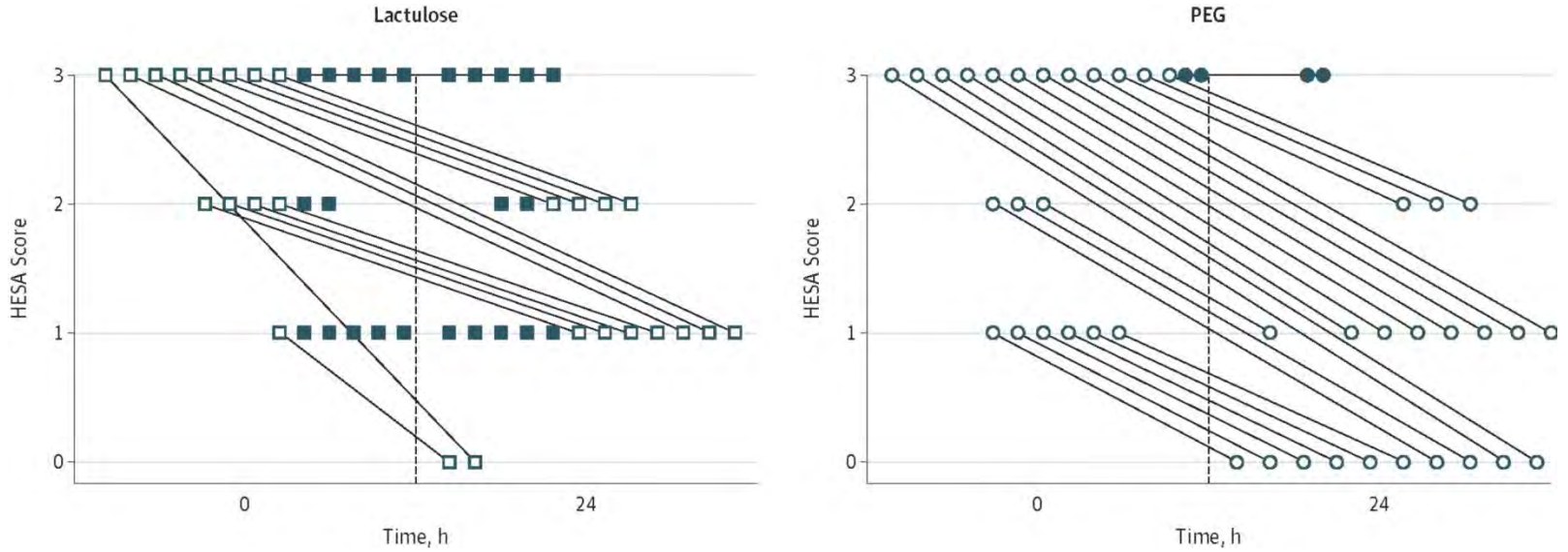
Characteristic	Total (N = 50)	Lactulose (n = 25)	PEG (n = 25)	*P* Value[a]
24-h HESA score change, mean (SD)	1.1 (0.8)	0.7 (0.8)	1.5 (0.8)[b]	.002
Length of stay, d	6 (9)	8 (12)	4 (3)	.07
6- to 24-h Ammonia, mean (SD), μmol/L[c]	(n = 33)	(n = 15)	(n = 18)	
Baseline	159 (73)	175 (70)	146 (75)	.19
After study	103 (51)	82 (29)	120 (60)	.049
Difference	56 (88)	93 (71)	26 (90)	.03

Abbreviations: HESA, hepatic encephalopathy scoring algorithm; PEG, polyethylene glycol 3350–electrolyte solution.

[a] Control (lactulose) and experimental (PEG) groups were compared using Wilcoxon (Mann-Whitney) rank-sum tests for ammonia and HESA score, Kaplan-Meier analysis for length of stay, and Fisher exact test for categorical variables.

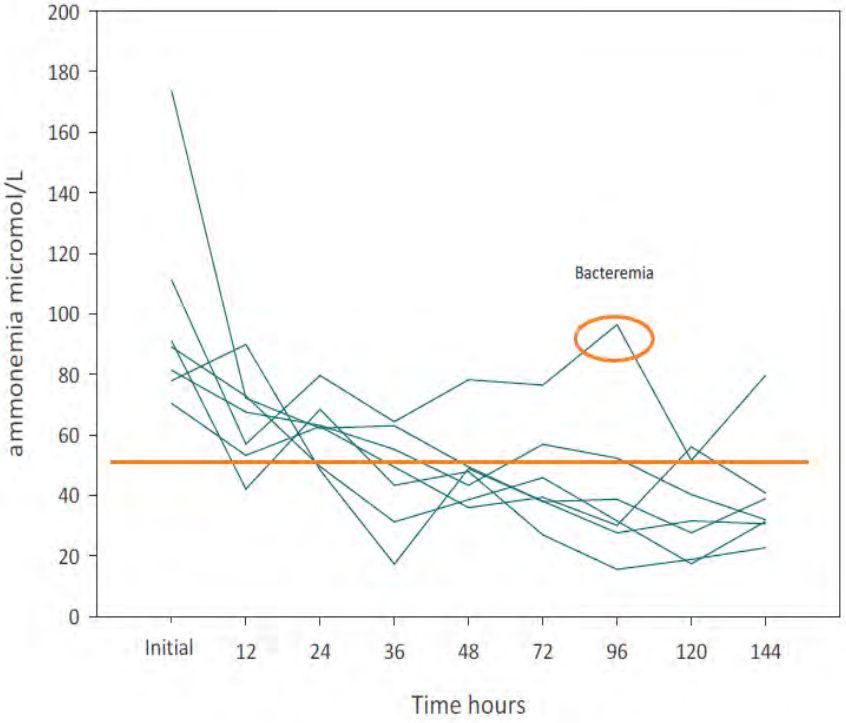
[b] Twenty-four hour HESA score was missing from 2 patients in the PEG group: one was competent and refused testing, the other was discharged in less than 24 h; thus, the 24-h HESA score change was calculated for 23 patients.

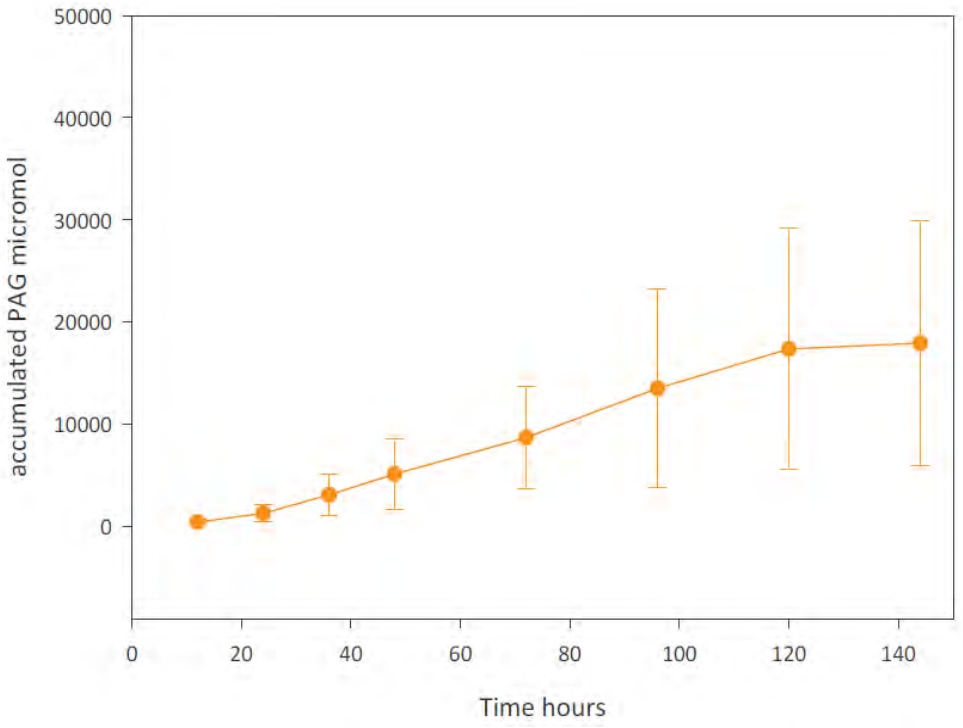
[c] Ammonia levels at 6 to 24 hours were not available for all patients.



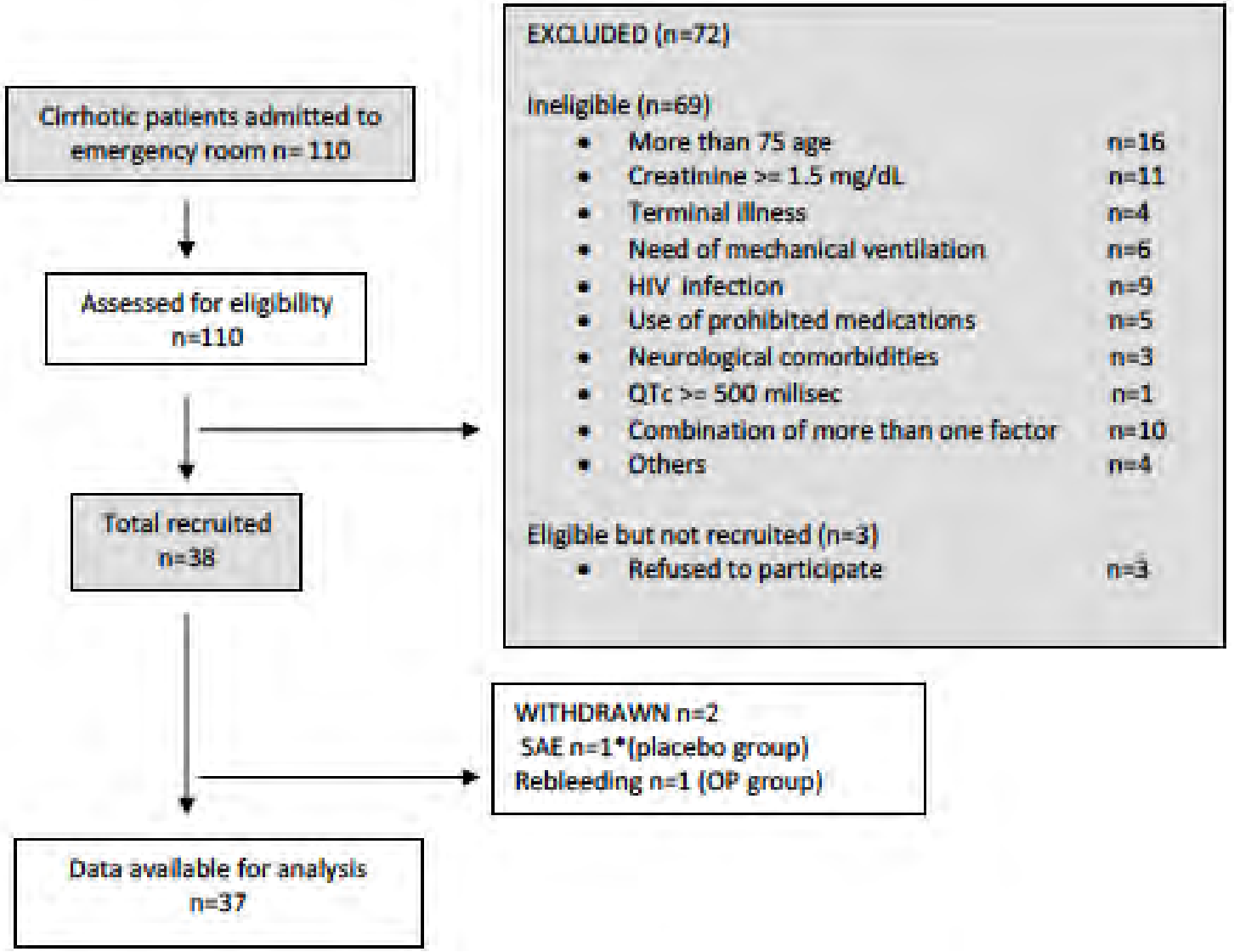
Open-label, dose-escalating single cohort study about safety and effects of ornithine-phenylacetate in patients with cirrhosis and upper gastrointestinal bleeding.

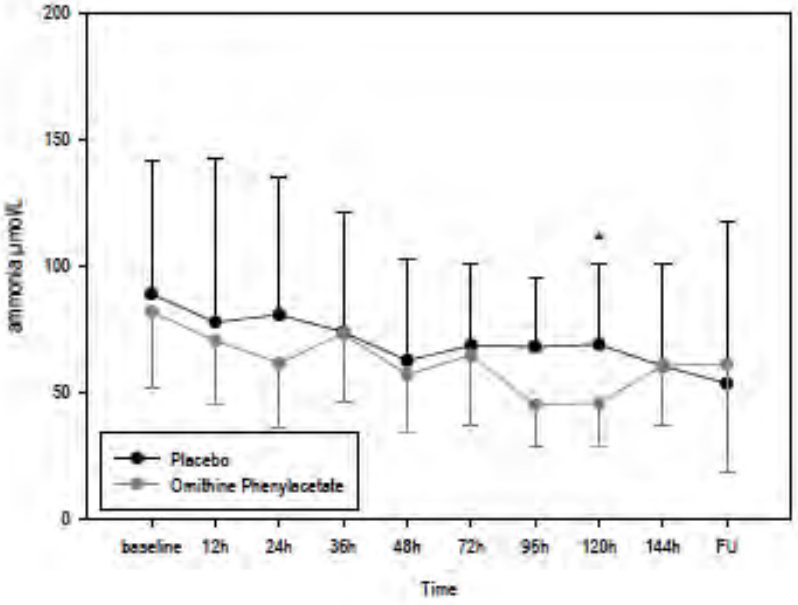
Meritxell Ventura-Cots (1), Macarena Simón-Talero (1), Maria Torrens (1) , Antonio Arranz (2), Albert Blanco (2) Encarnació Riudor (2) , Juan Córdoba (1), (3).
(1) Internal Medicine and Hepatology department Hospital Vall d'Hebron, Barcelona. (2) Clinical analysis department Hospital Vall d'Hebron, Barcelona. (3) CIBEREHD, Barcelona.



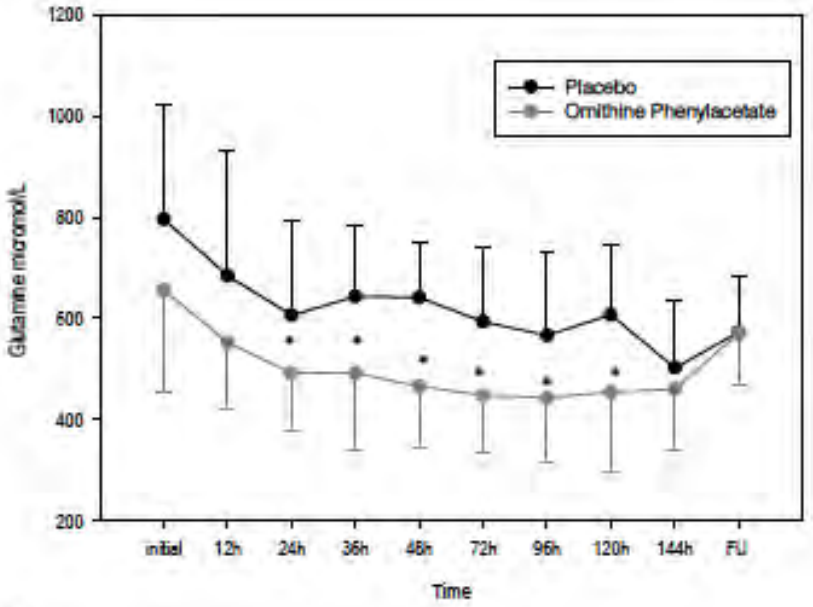


OCR-002 vs Standard of Care

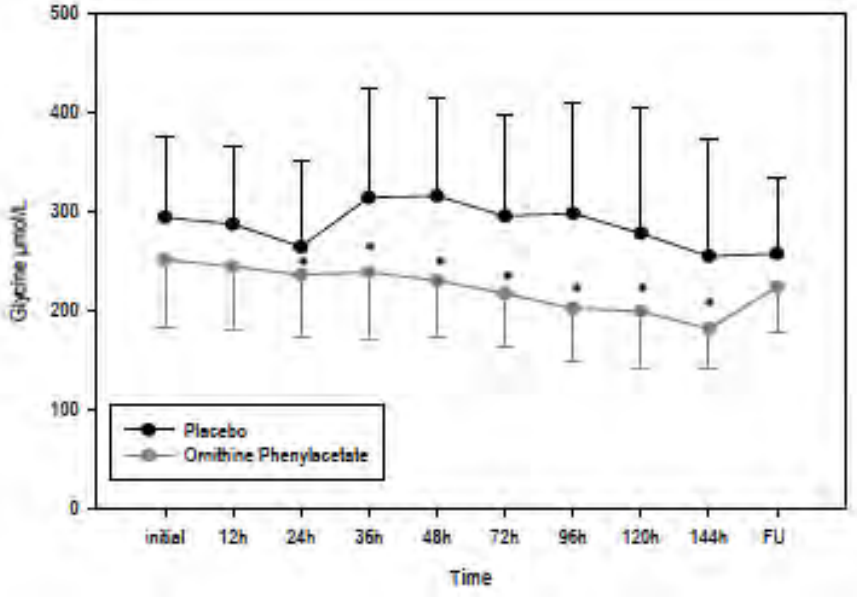




A

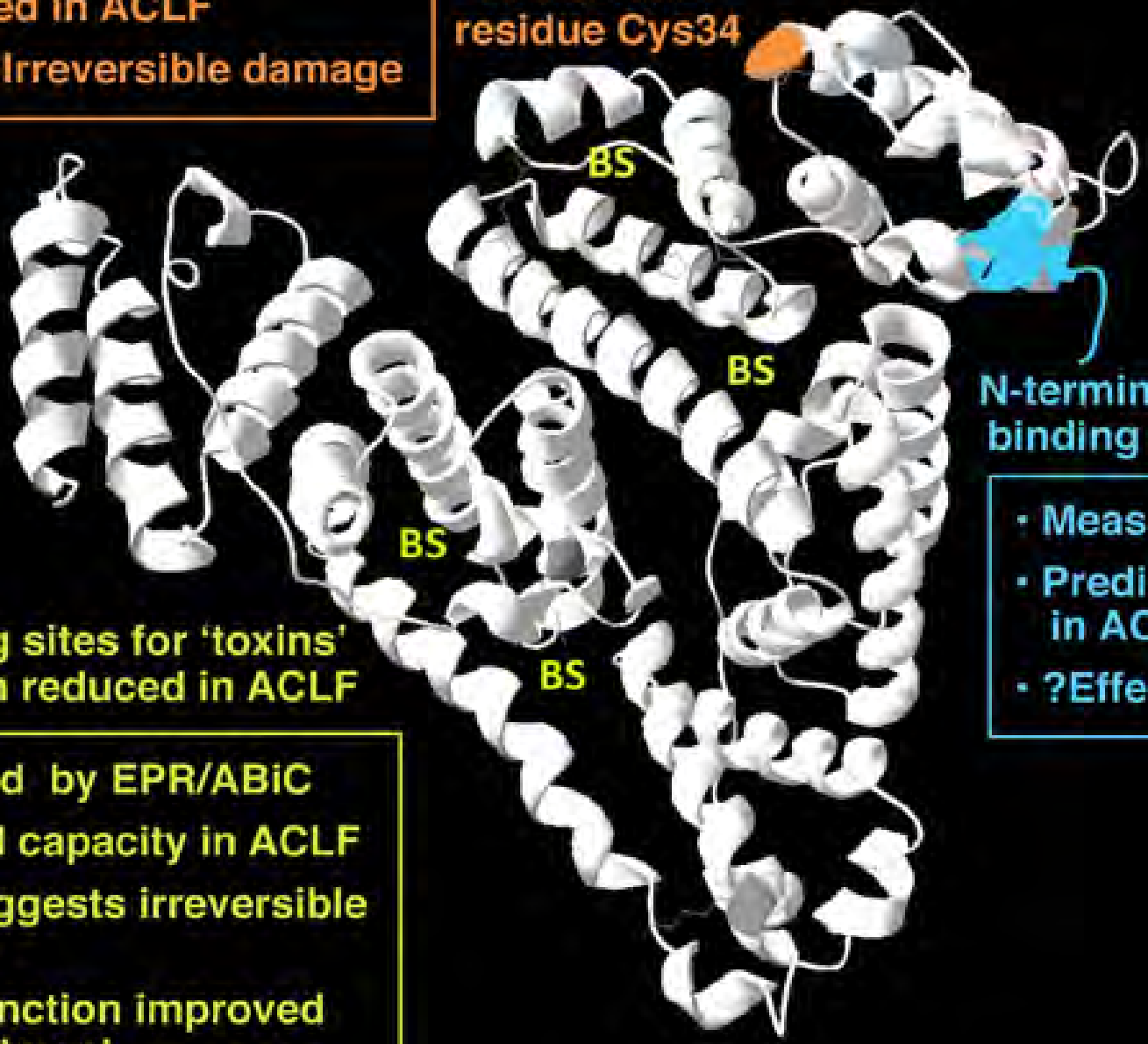


B



Courtesy: Genesca et al.

- Measured as HMA: HNA ratio
- Reduced in ACLF
- HNA2: Irreversible damage



- Measured as IMAR
- Predicts mortality in ACLF
- ?Effect of therapy

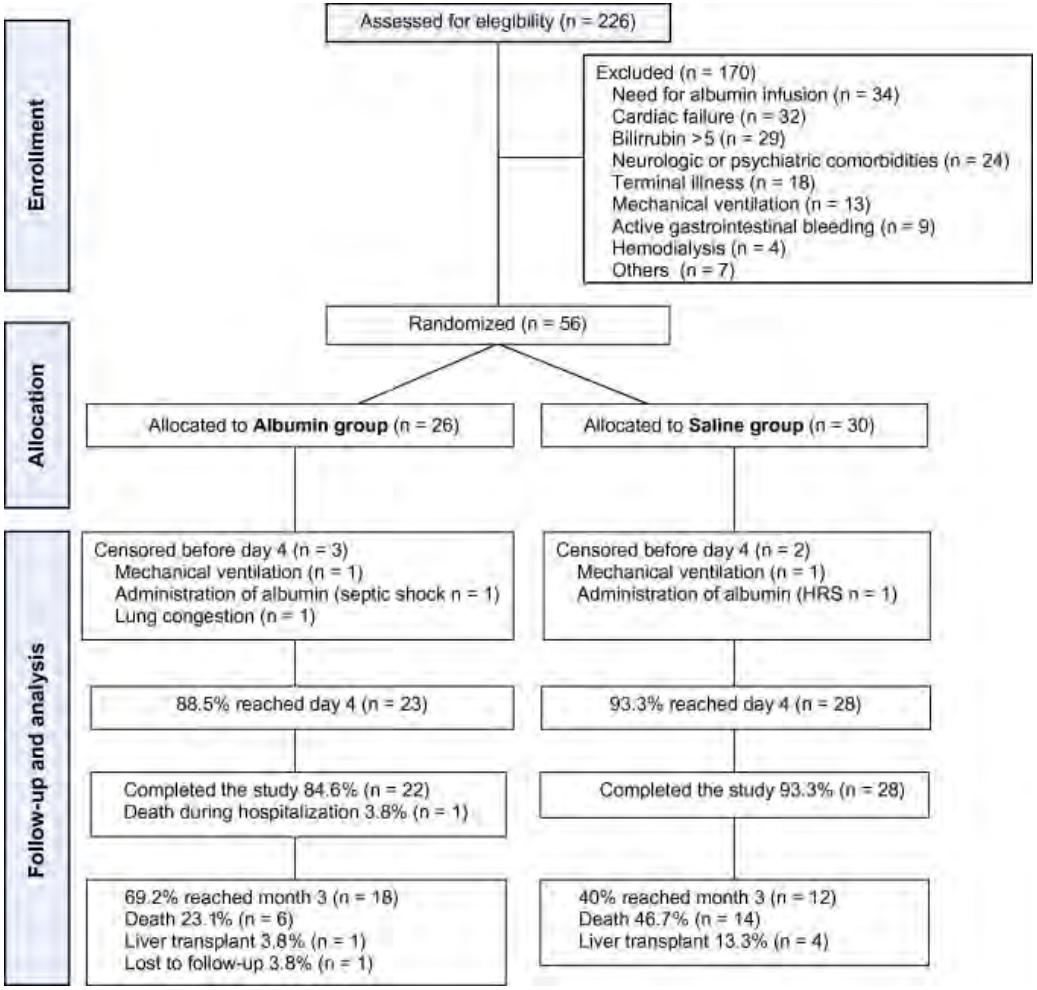
Binding sites for 'toxins' function reduced in ACLF

- Measured by EPR/ABiC
- Reduced capacity in ACLF
- EPR: suggests irreversible damage
- ABiC: function improved with treatment

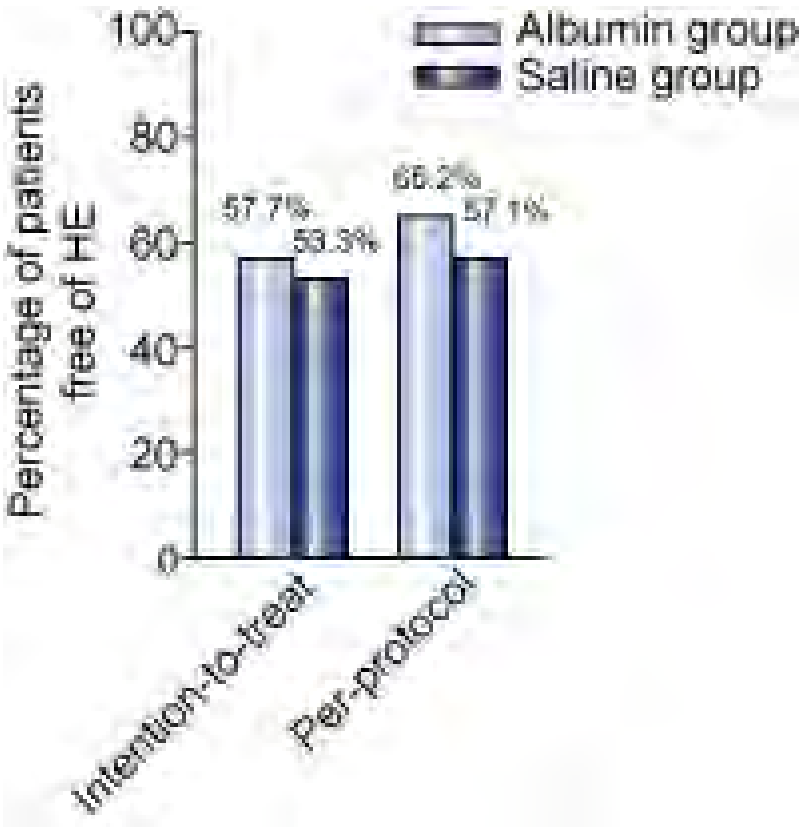
Leckie, Davies and Jalan GASTROENTEROLOGY 2012;142:690–699

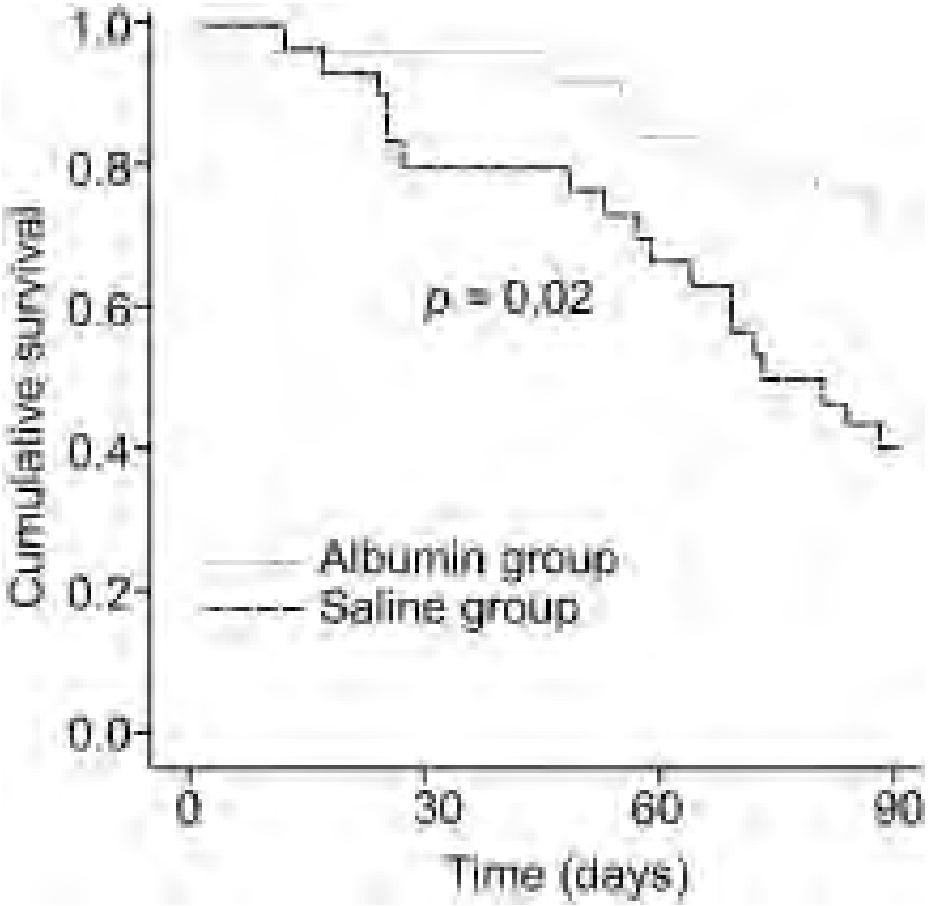
Effects of intravenous albumin in patients with cirrhosis and episodic hepatic encephalopathy: A randomized double-blind study☆

Macarena Simón-Talero[1], Rita García-Martínez[1], Maria Torrens[1], Salvador Augustin[1], Susana Gómez[2], Gustavo Pereira[3], Mónica Guevara[3,4,5], Pere Ginés[3,4,5], Germán Soriano[4,6], Eva Román[4,6], Jordi Sánchez-Delgado[4,7], Roser Ferrer[8], Juan C. Nieto[9], Pilar Sunyé[10], Inma Fuentes[11], Rafael Esteban[1,4], Juan Córdoba[1,4,*]

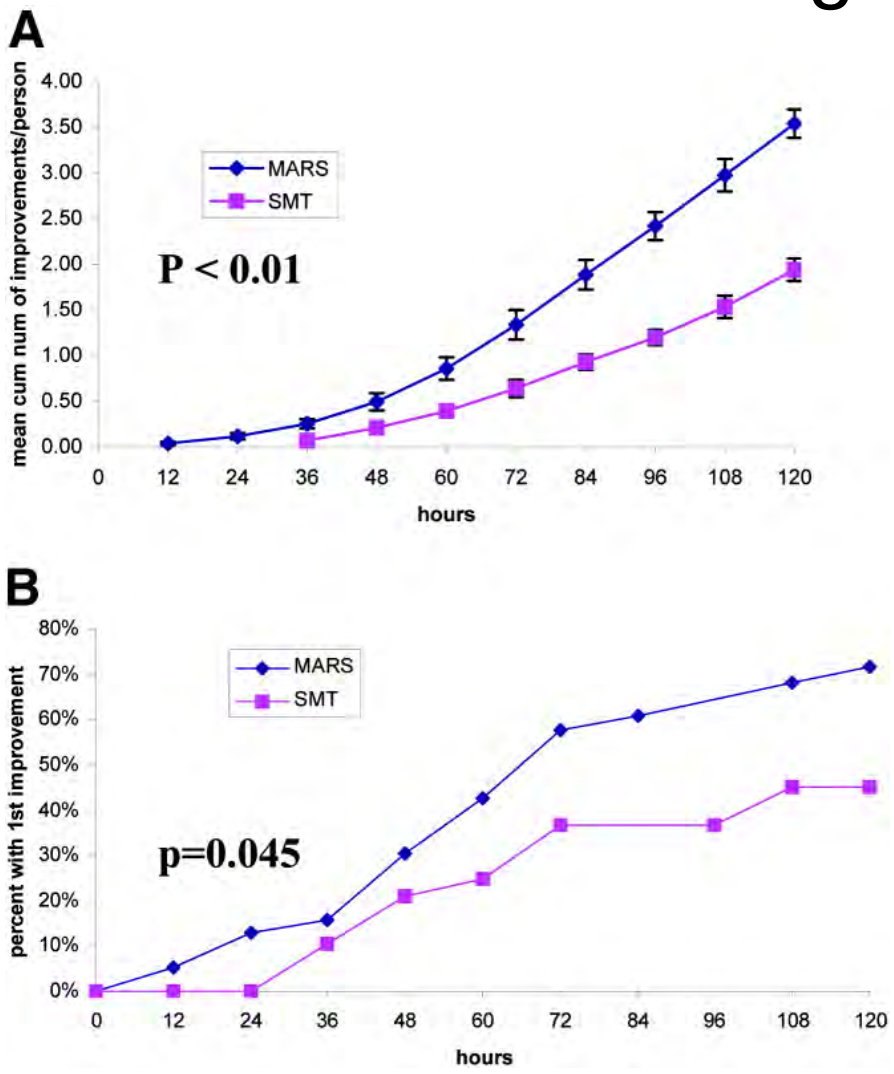


J Hepatol 2013


Albumin group
Saline group
Percentage of patients free of HE
100
80
60
40
20
0
57.7%
53.3%
65.2%
57.1%
Intention-to-treat
Per-protocol


Cumulative survival
1.0
0.8
0.6
0.4
0.2
0.0
p = 0,02
Albumin group
Saline group
0
30
60
90
Time (days)

MARS Rx was significantly better



Survival

2 and 4 week survival were significantly greater in the responders compared with non-responders

Hassanein et al. Hepatology 2007

Summary

Hepatic Encephalopathy

Minimal

Current
Lactulose

Future
Rifaximin
GPB
OP

Overt

Primary Prophylaxis

Probiotics

Future
Rifaximin
GPB
OP

Secondary Prophylaxis

Lactulose
Rifaximin

Future
GPB
OP

Acute Episode

Lactulose
Rifaximin

Future
PEG
GPB
OP
Albumin
MARS

Summary

- Classification of HE
  - Covert HE is a heterogenous entity
  - HE in ACLF should be classified separately
- The mechanisms of the deleterious effects of ammonia are being redefined
  - Ammonia and inflammation are synergistic in causing HE
  - Both are targets of therapy
- HE is not reversible and efforts to prevent 1st and recurrent episodes is urgently needed
- New therapeutic strategies for HE are emerging
  - More clinical trial data are needed

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Andrew Proven
Yalda Sharifi
Vikram Sharma

Giovanni Tritto
Montse De Oca
Maria Jover
Fausto Andreola
Luisa Baker
Karla Lee
Jane Macnaughtan
Gautam Mehta
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