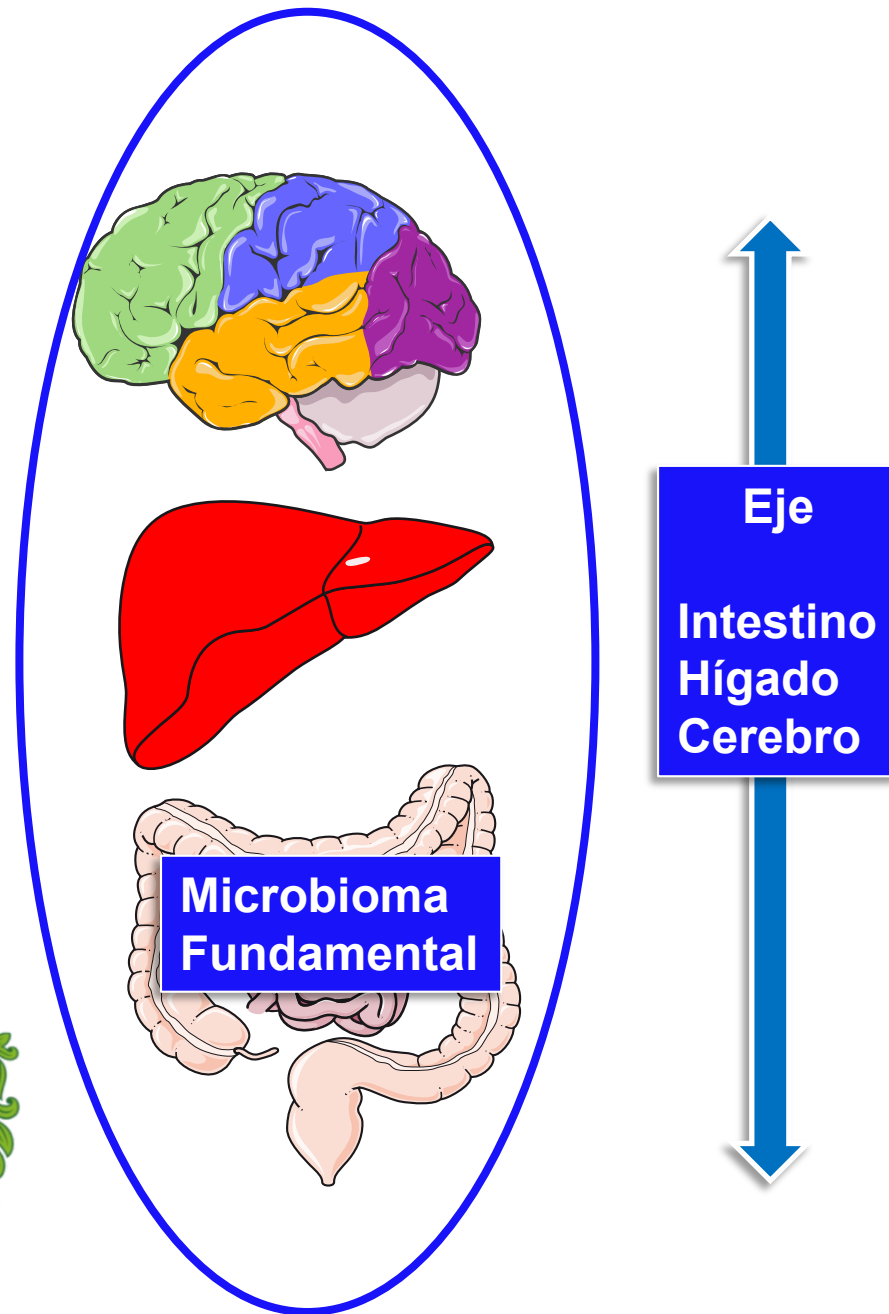




Papel de la microbiota en la encefalopatía hepática



William Otero R MD, FAGA, FASGE, FACP
Profesor Titular de Medicina,
Universidad Nacional de Colombia
Hospital Universitario Nacional de Colombia



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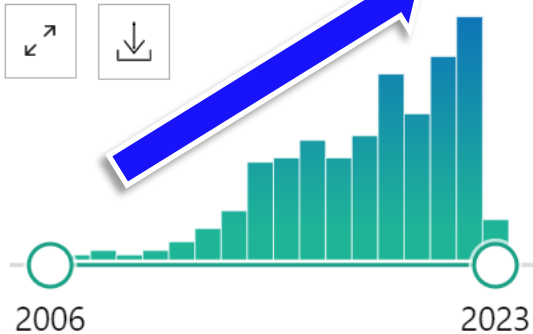
MY NCBI FILTERS ↗

274 results

Marzo 19, 2023

⏪ < Page 1 of 28 > ⏩

RESULTS BY YEAR



1 Integrated Analysis of Gut **Microbiome** and Liver Metabolome to Evaluate the Effects of Fecal **Microbiota** Transplantation on Lipopolysaccharide/D-galactosamine-Induced Acute Liver Injury in Mice.

1

Cite

Yuan C, Fan J, Jiang L, Ye W, Chen Z, Wu W, Huang Q, Qian L.

Share

Nutrients. 2023 Feb 24;15(5):1149. doi: 10.3390/nu15051149.

PMID: 36904149 [Free PMC article.](#)

There exists a relationship between the human intestinal **microbiota** and liver, so intestinal **microbiota** modulation may be a strategy for therapy of **hepatic** diseases. ...Metabolomics analysis revealed that FMT significantly altered LPS/D-gal induced disordered ...

TEXT AVAILABILITY

Abstract

Free full text

Full text

2 Gut **microbiome**-brain-cirrhosis axis.

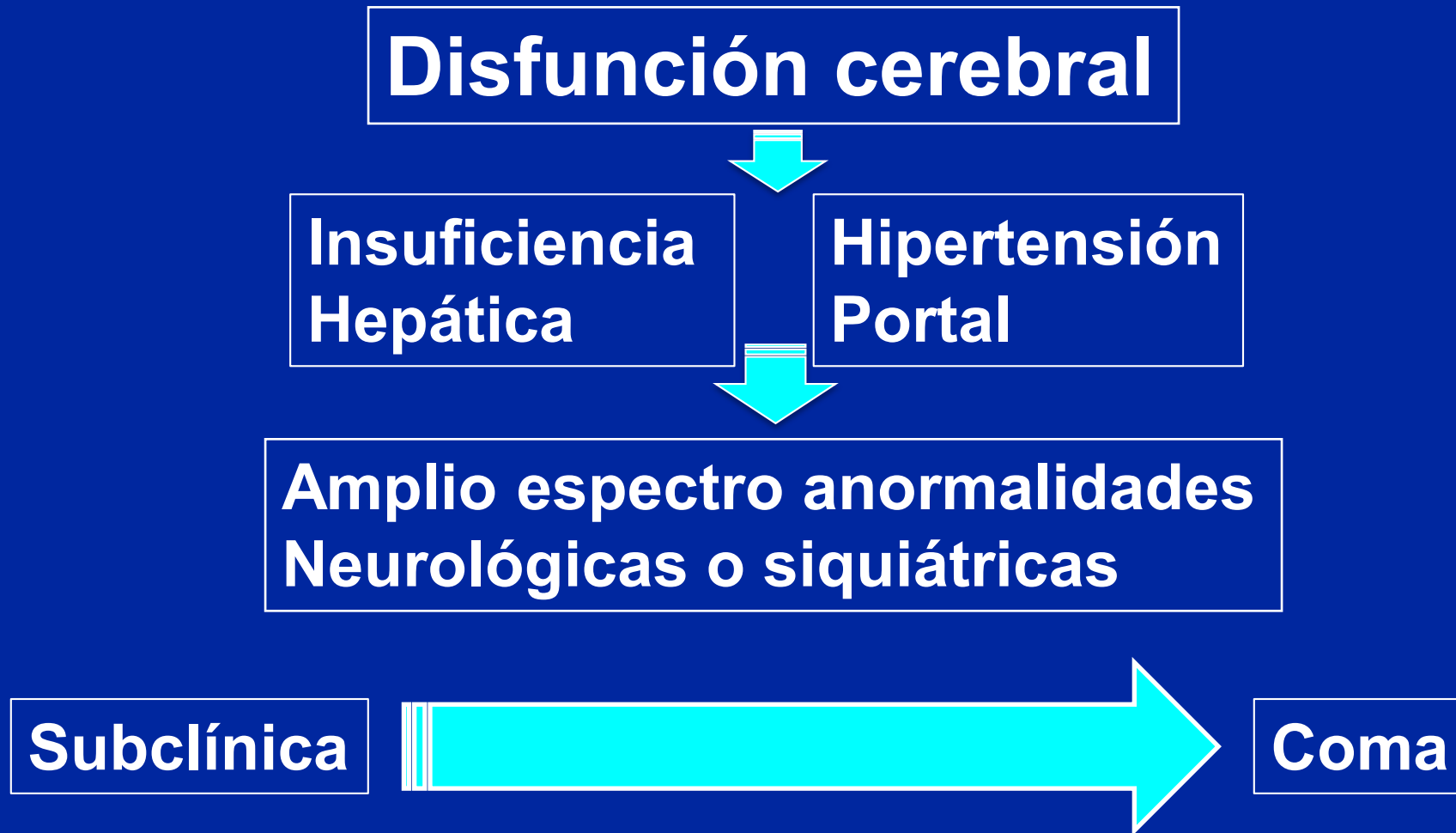
2

Cite

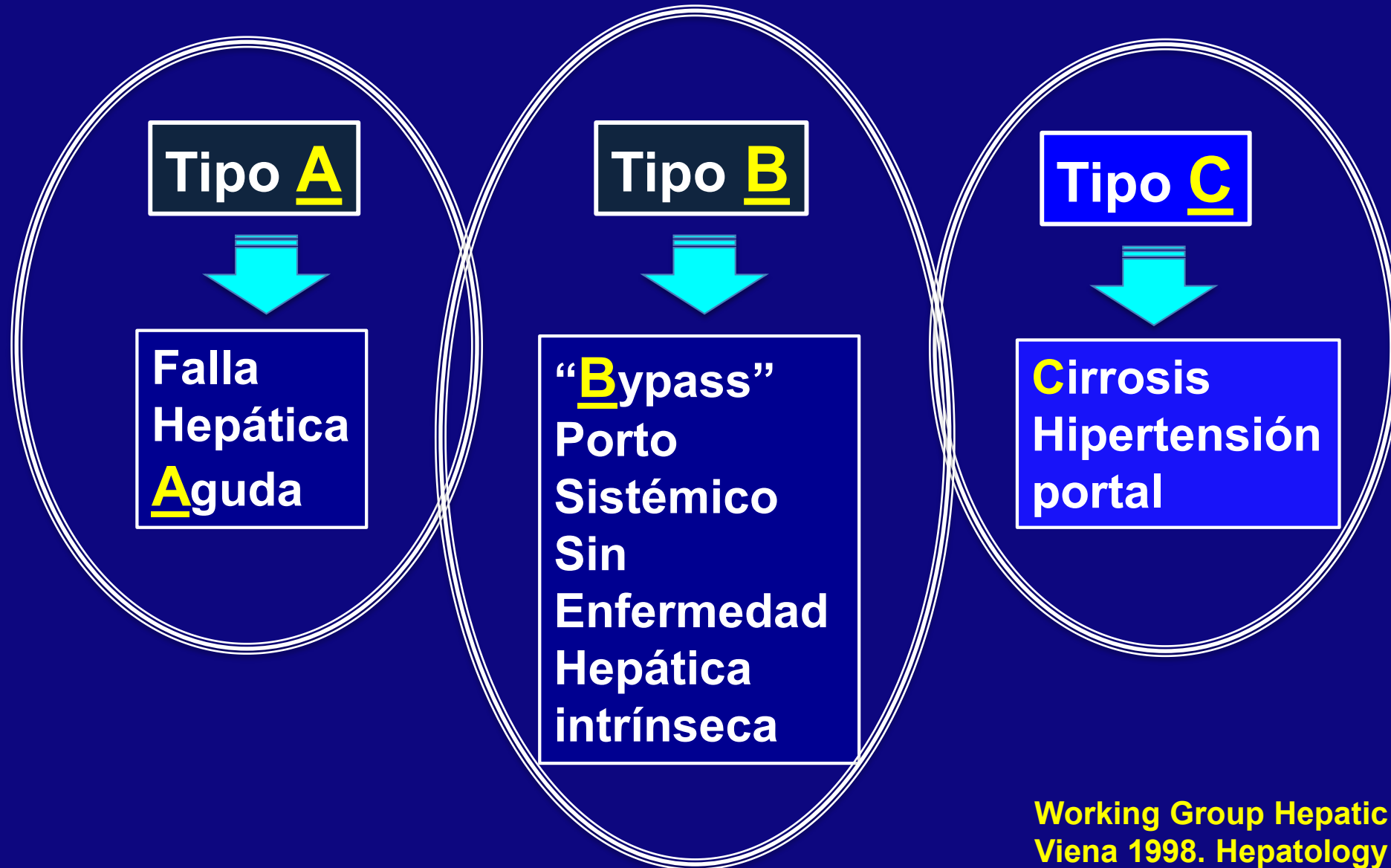
Smith ML, Wade JB, Wolstenholme J, Bajaj JS.

Hepatology. 2023 Mar 6. doi: 10.1097/HEP.0000000000000344. Online ahead of print.

Encefalopatía, Hepática



Encefalopatía Hepática



Encefalopatía Hepática



Working Group Hepatic Encephalopathy
Viena 1998. Hepatology 2002;35:716-21

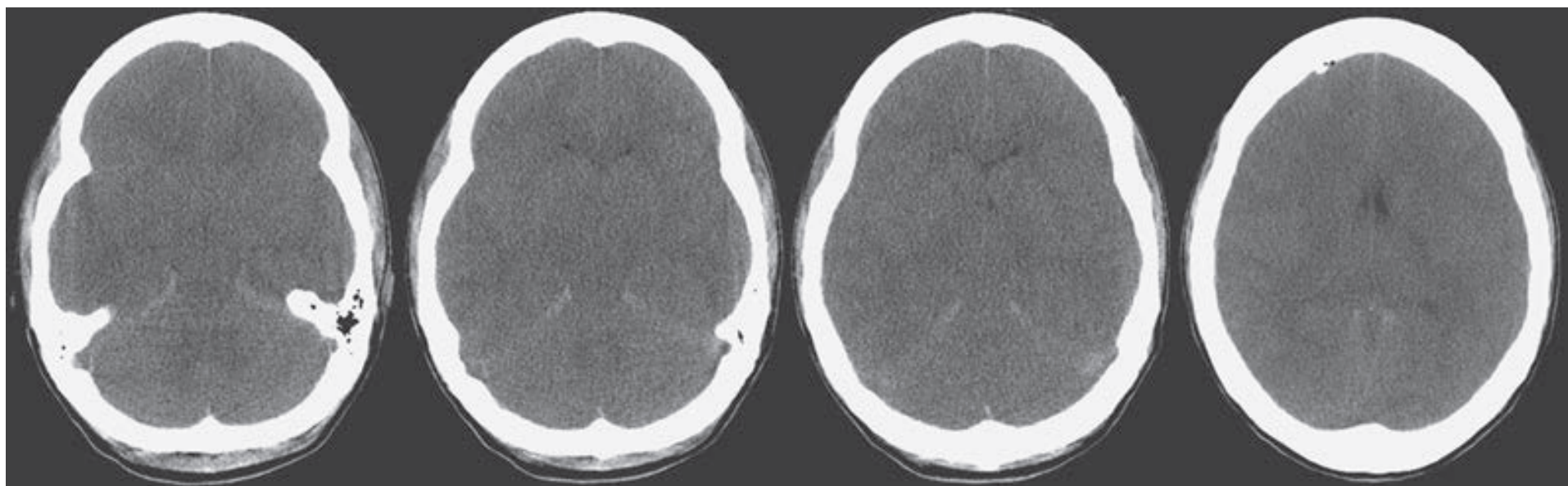
Falla hepática aguda (fulminante)

Falla hepática aguda (fulminante)

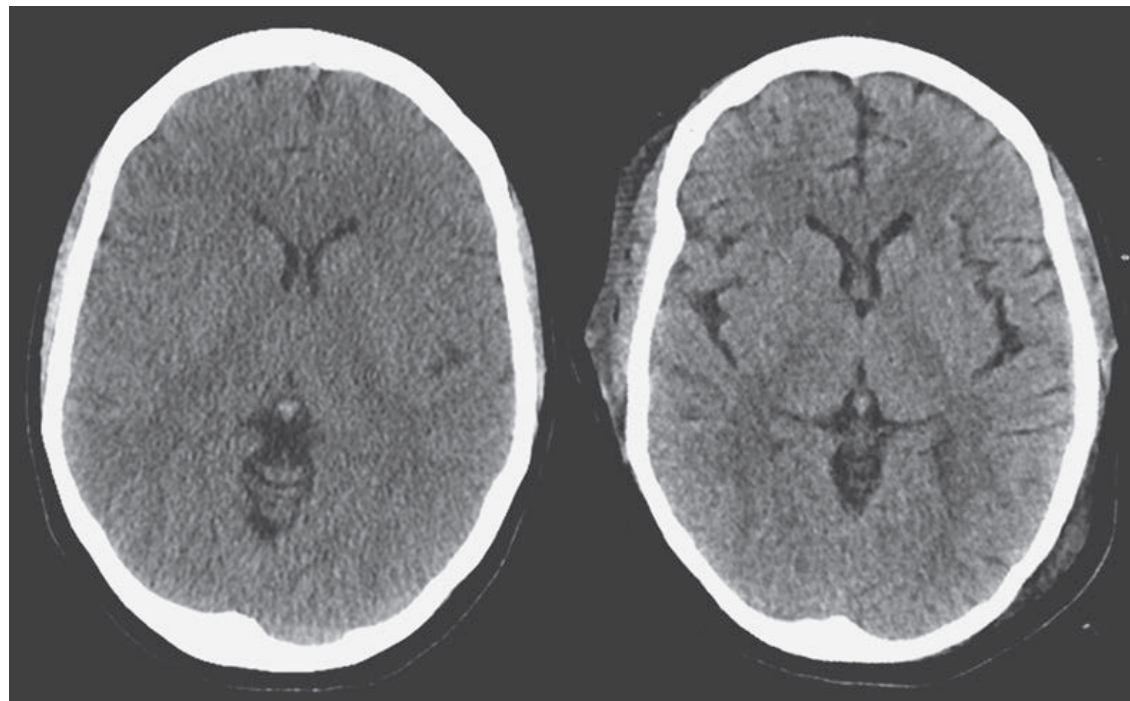
Encefalopatía Manifiesta 10-30 días, después de ictericia + Hepatitis + TP > 3" o INR > 1.5 (?) +
Por daño hepático

Injuria Hepática Aguda

Ictericia + Hepatitis + TP > 3" o INR > 1.5
Por daño hepático:
Sin encefalopatía



Manitol



Edema cerebral



Encefalopatía Hepática

Tipo **C**



Cirrosis
Hipertensión
portal

Conceptos claves

30-50% de hospitalizaciones de los cirróticos

10-14% al diagnóstico

16-21% cirrosis descompensada

40% en el primer año

74% fallecen en 12-17 meses

Costo anual : >1 billón de dólares

EH mínima 20-80%

Cada día >>cirrosis: VHB, VHC, **MAFLD**, etc

Agency Healthcare Research Quality www.ahrq.gov/datahcup, acces Dic 20,2016

AASLD 2014

Rose CF, J Hepatol 2020;73:1526-47

Association of Nonalcoholic Fatty Liver Disease With Lower Brain Volume in Healthy Middle-aged Adults in the Framingham Study

JAMA Neurol. 2018;75:97-104

Galit Weinstein, PhD; Shira Zelber-Sagi, PhD; Sarah R. Preis, ScD, MPH; Alexa S. Beiser, PhD; Charles DeCarli, MD; Elizabeth K. Speliotes, MD, PhD, MPH; Claudia L. Satizabal, PhD; Ramachandran S. Vasan, MD; Sudha Seshadri, MD

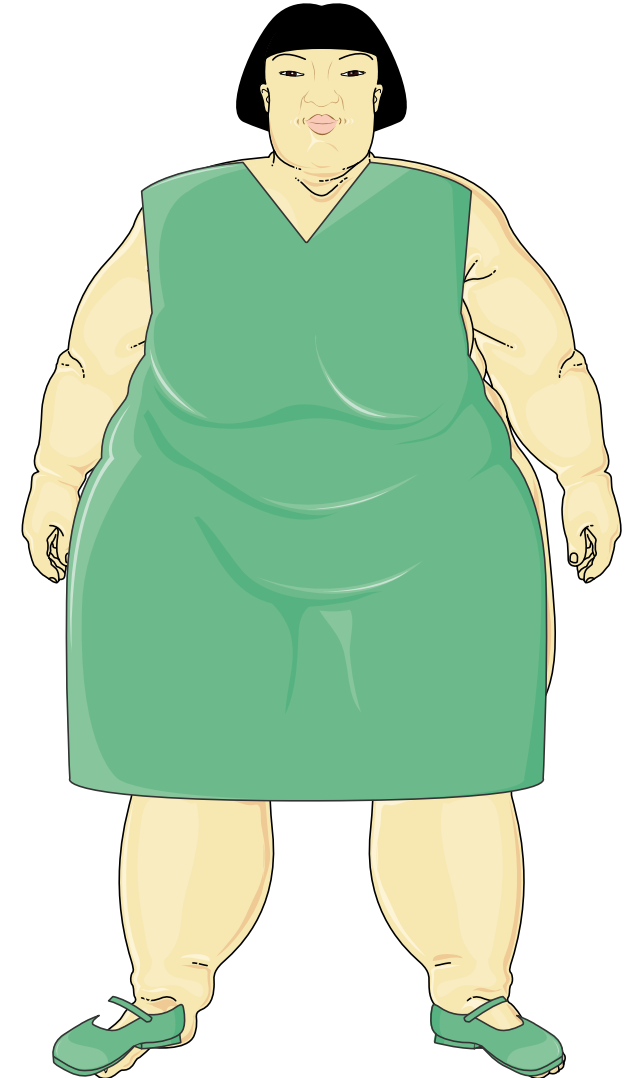
CONCLUSIONS AND RELEVANCE Nonalcoholic fatty liver disease is associated with a smaller total cerebral brain volume, independent of visceral adipose tissue and cardiometabolic risk factors, pointing to a possible link between hepatic steatosis and brain aging.

Research Article

Cognitive Changes and Brain Volume Reduction in Patients with Nonalcoholic Fatty Liver Disease

Branka Filipović^{1,2}, Olivera Marković^{1,3}, Vesna Đurić⁴, and Branislav Filipović^{1,5}

Alteración cognitiva RR 3.9, Depresión 1.65

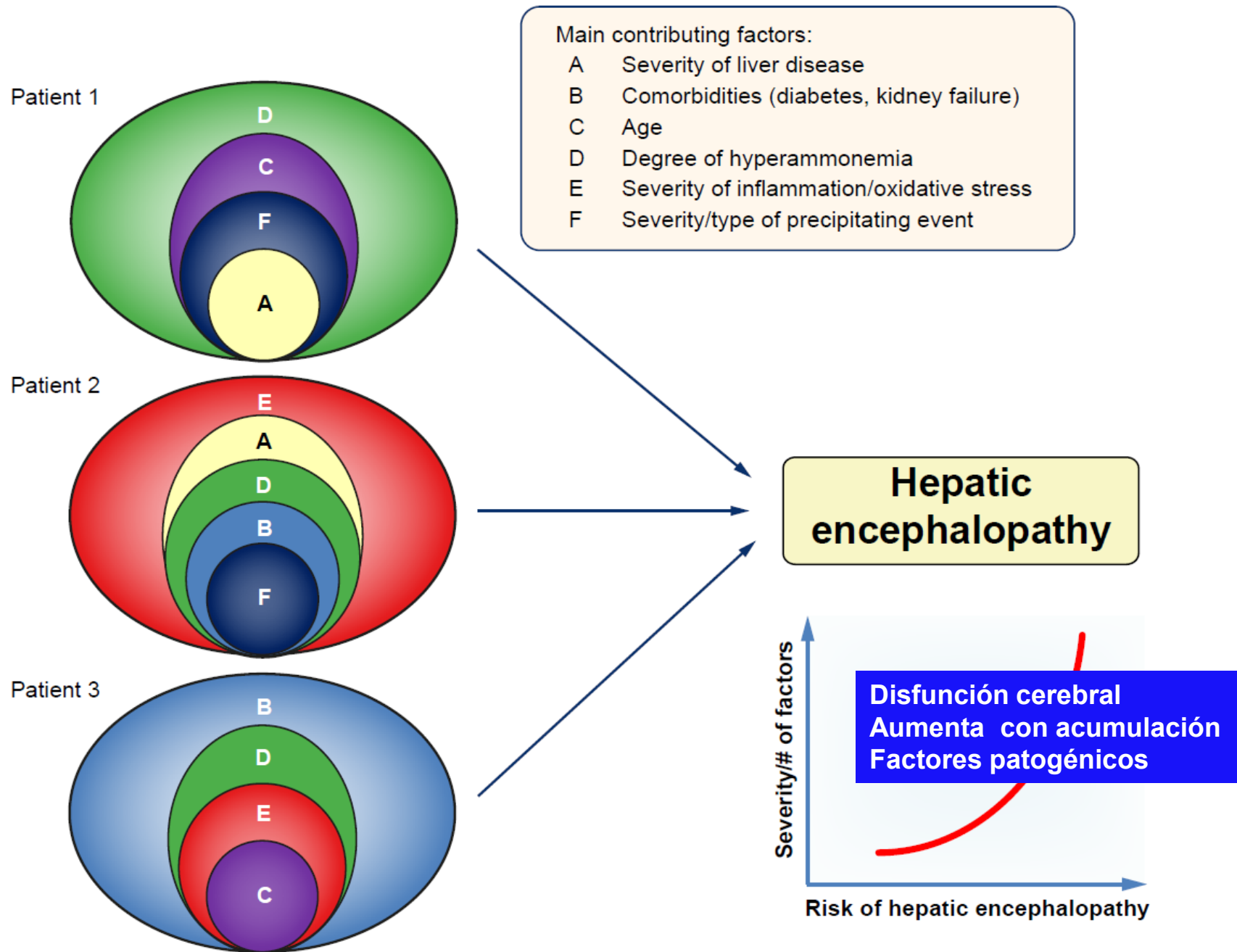


Important Unresolved Questions in the Management of Hepatic Encephalopathy: An **ISHEN** Consensus

Jasmohan S. Bajaj, MD¹, Mette Lauridsen, MD, PhD², Elliot B. Tapper, MD³, Andres Duarte-Rojo, MD⁴, Robert S. Rahimi, MD⁵, Puneeta Tandon, MD⁶, Debbie L. Shawcross, MD, PhD⁷, Dominique Thabut, MD, PhD⁸, Radha K. Dhiman, MD⁹, Manuel Romero-Gomez, MD¹⁰, Barjesh C. Sharma, MD¹¹ and Sara Montagnese, MD, PhD¹²

Sociedad Internacional de Encefalopatía Hepática y Metabolismo de Nitrógeno

Am J Gastroenterol 2020;115:989-1002



Desorden metabólico



Neuroinflamación muerte cerebral



Daños irreversibles



Persisten postrasplante 8-47%

Garcia-Martinez R, et al. Liver Transpl 2011;17:38–46
Sotil EU, et al. Liver Transpl 2009;15:184–192.

Falla hepática aguda



Sobre falla hepática crónica

Pacientes cirróticos hospitalizados

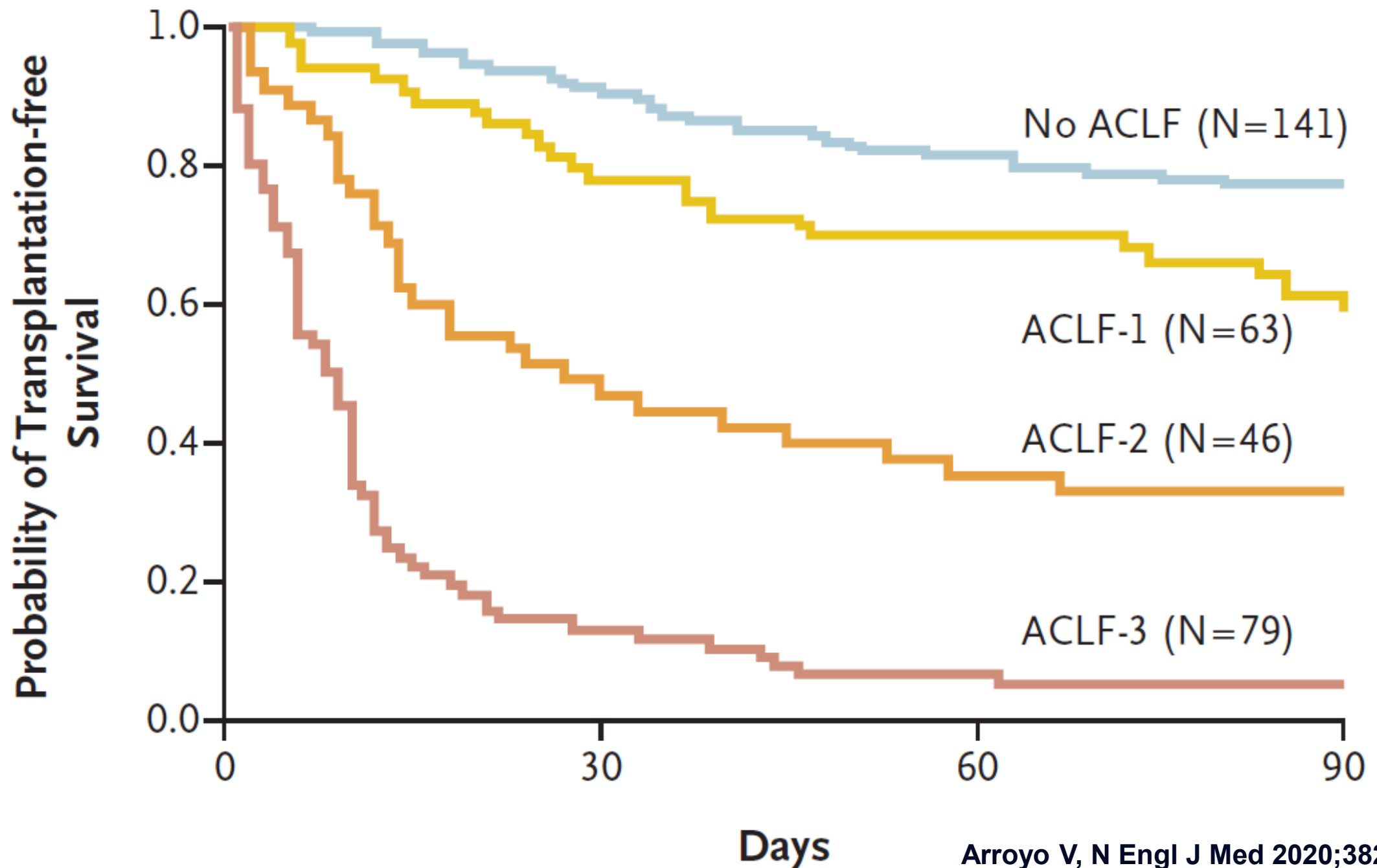
Descompensación aguda de cirrosis: Ascitis, ictericia, infecciones, encefalopatía hepática)

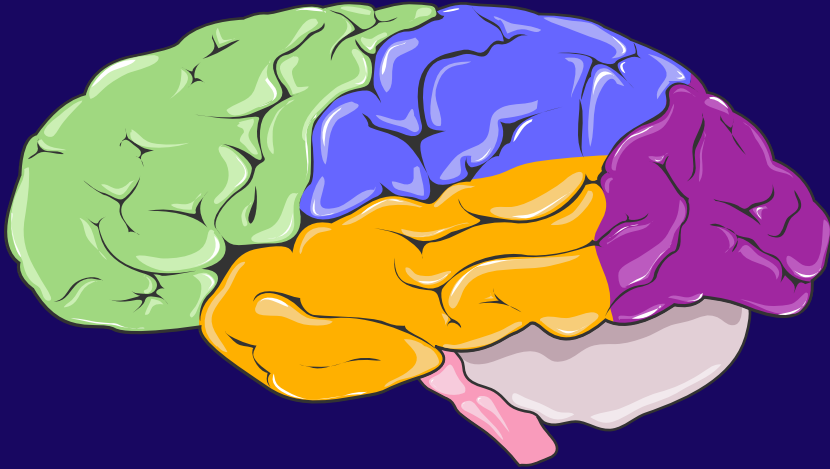
Asociada a falla en diferentes órganos

Arroyo V, NEJM 2020;382:2137-45

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

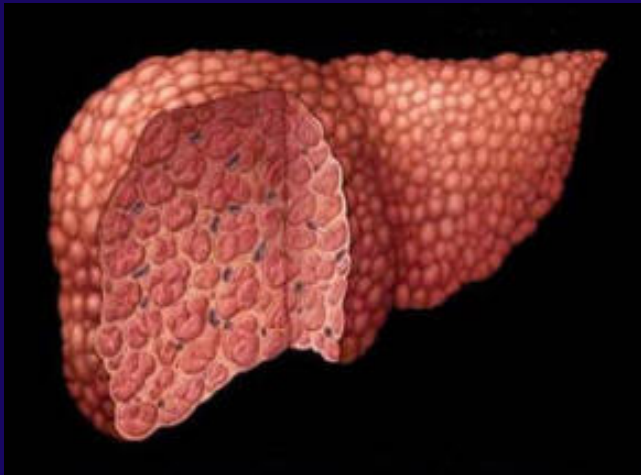
Arroyo V, N Engl J Med 2020;382:2137-45





Encefalopatía Hepática

“Espectro de anomalías neuro-siquiátricas en pacientes con disfunción hepática aguda o crónica”



***Falla hepática Aguda sobre
Falla hepática crónica***

Ferrenchi P, Hepatology 2002;35:716-21
Curr Opin Gastroenterol 2016;

Encefalopatía Hepática

Manifiesta
“Overt”

**Clínicamente
Evidente**
30-45%

Subclínica/mínima
“Covert”

No Evidente
Necesita pruebas
Sicométricas especiales
60-80%

Pruebas neurosicológicas

Test	Test type	Test description
Psychometric hepatic encephalopathy score (PHES)	Neuropsychological, paper & pencil	The PHES consists of 5 paper-pencil tests evaluating cognitive/psychomotor processing speed and visuomotor coordination. They are relatively easy to administer, have good external validity and have been translated/validated into several languages and countries. ²⁵¹
Animal naming test (ANT)	Neuropsychological, bed-side	The ANT (<i>i.e.</i> the number of animals listed in 60 seconds, no equipment required except a stopwatch) has recently been shown to compare favourably with more established mHE measures and to predict overt HE. ¹⁸⁶
Continuous reaction time (CRT)	Neuropsychological, computerised	The CRT test relies on repeated registration of the motor reaction time (pressing a button) to auditory stimuli (through headphones). The most important test result is the CRT index, which measures the stability of the reaction times. Age and sex seem to exert limited influence and there are no learning/tiring effects either. ²⁴⁵
The inhibitory control test (ICT)	Neuropsychological, computerised	ICT is a computerised test of response inhibition and working memory and is freely downloaded at www.hecme.tv . The ICT test has been judged to have good validity but requires highly functional patients. ²⁴⁶
Stroop test	Neuropsychological, computerised	The Stroop test evaluates psychomotor speed and cognitive flexibility by the interference between recognition reaction time to a coloured field and a written colour name; also available in app form. ²⁶
SCAN test	Neuropsychological, computerised	The SCAN test is a computerised test that measures speed and accuracy to perform a digit recognition memory task of increasing complexity. It has been shown to have prognostic value. ²⁴⁷
Electroencephalogram (EEG)	Neurophysiological	The EEG can detect changes in cortical cerebral activity across the spectrum of HE and its reliability increases with quantitative analysis. More recently, a cheap gaming device has been shown to produce similar results compared to a standard EEG machine across the HE spectrum. ²⁴⁸
Critical flicker frequency (CFF)	Psychophysical	CFF is defined as the frequency at which a flickering light (from 60 Hz downwards) appears to be flickering to the observer. Studies have shown its reduction with worsening cognition and improvement after therapy. It requires specialized equipment. ²⁴⁹

Encefalopatía hepática subclínica “encubierta”, “covert”, mínima

Cambios neuropsicológicos sutiles

Diagnóstico con pruebas sicomotoras

Altera calidad de vida y < sobrevida

Reversible con tratamiento

Incapacidad para conducir autos

Wijdicks EFM, N Engl J Med 2016;375:1660-70
Bajaj JS, APT 2010;31:537-47



**Alteración calidad de vida
Incapacidad funcional diaria
>mortalidad**

**Poodad F, Aliment Pharmacol Ther 2007;25 (supp.1):3-9
Bajaj JS, Am J Gastroenterol 2009;104:898-905
Groeneweg M, Hepatology 1998;28:45-9**

Encefalopatía hepàtica

Fisiopatologia



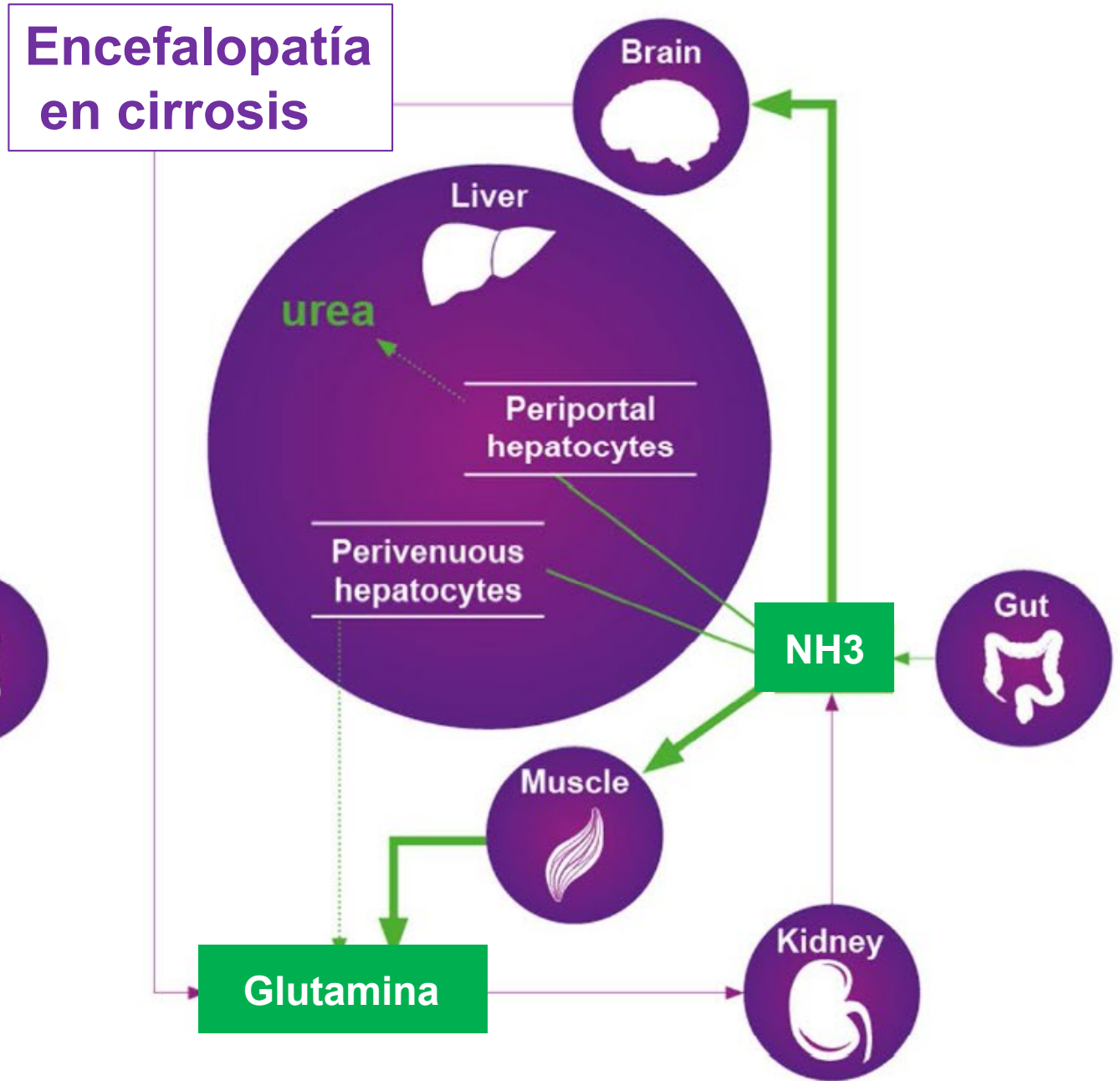
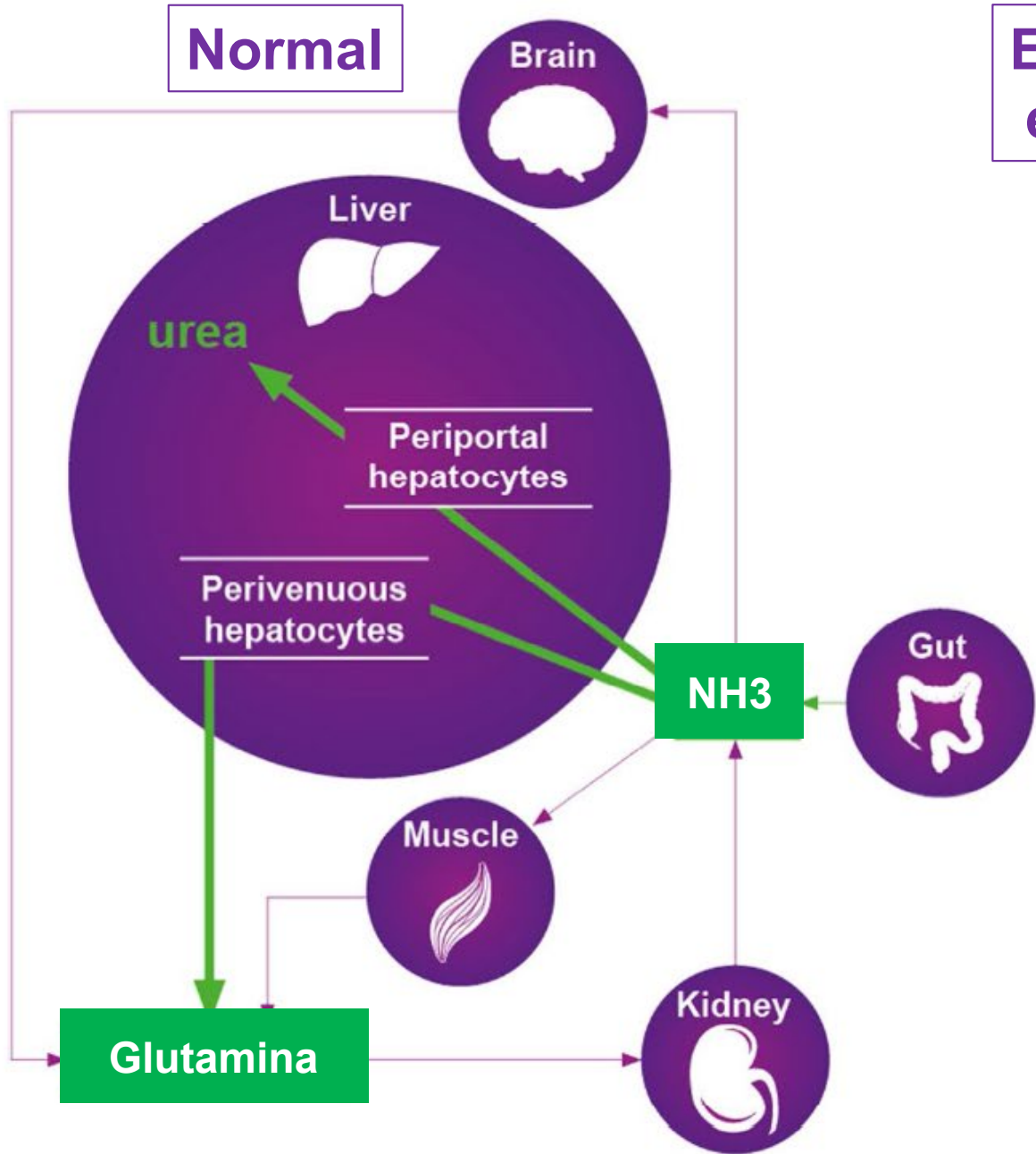
Desconocida

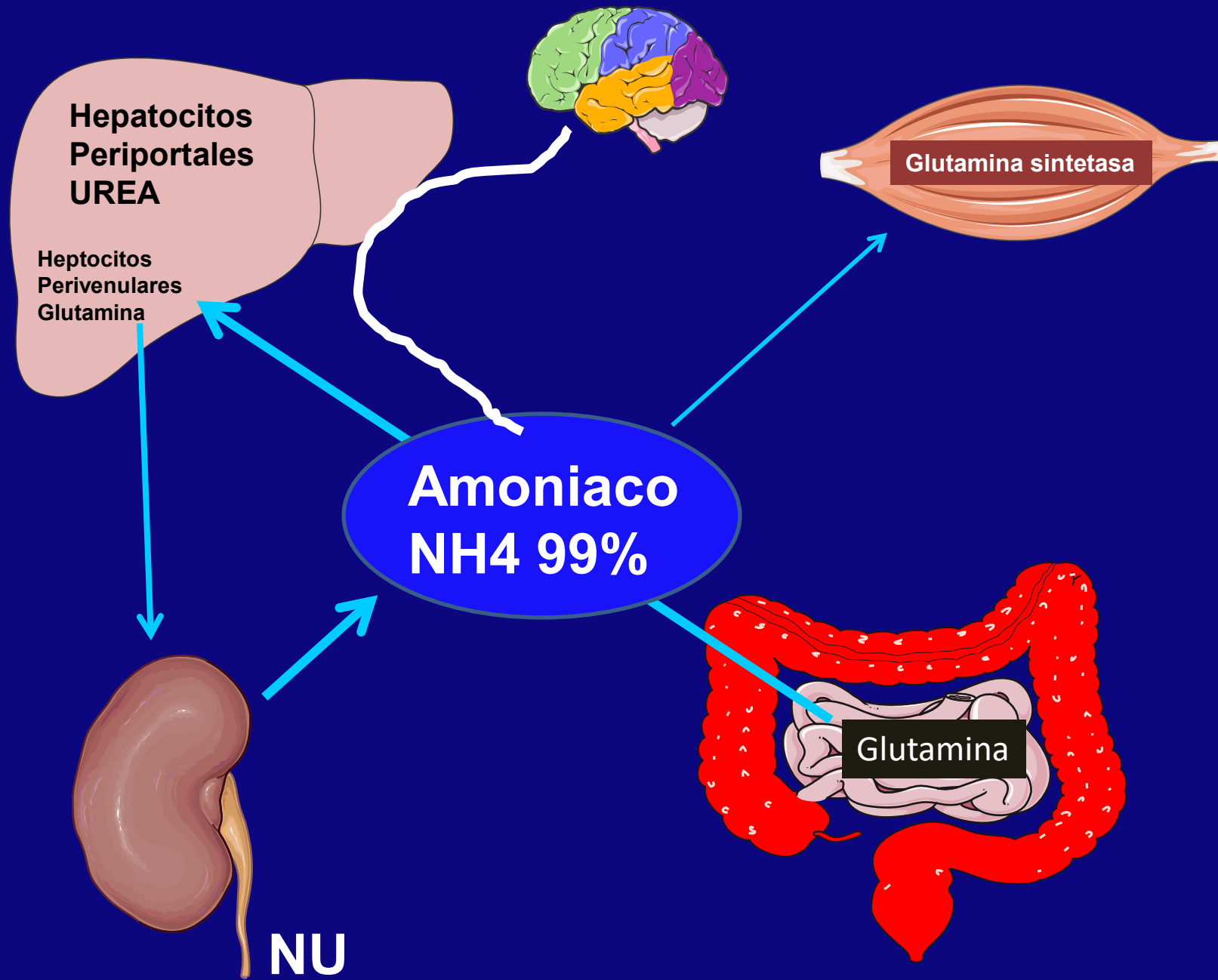


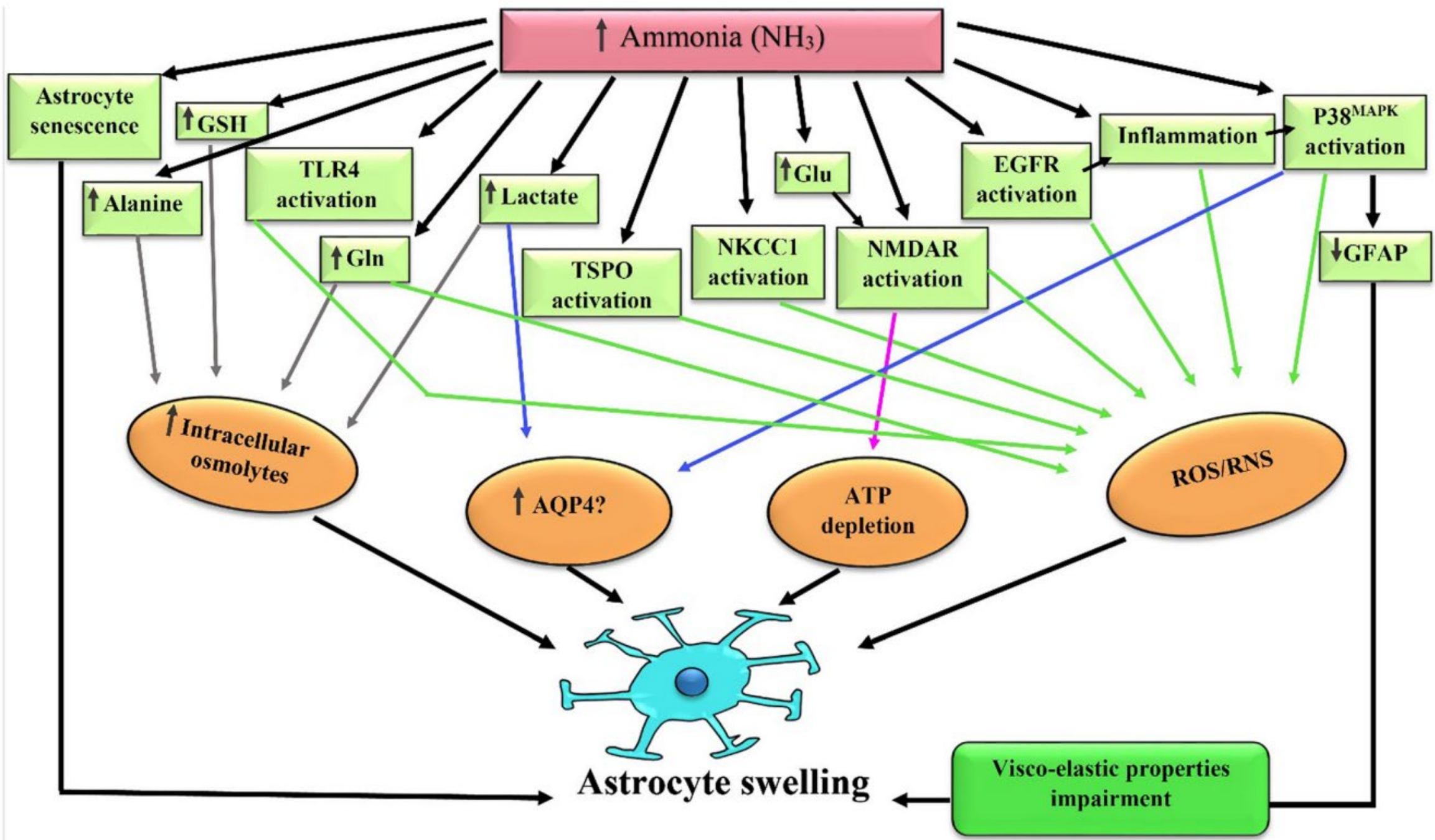
NH₃/+



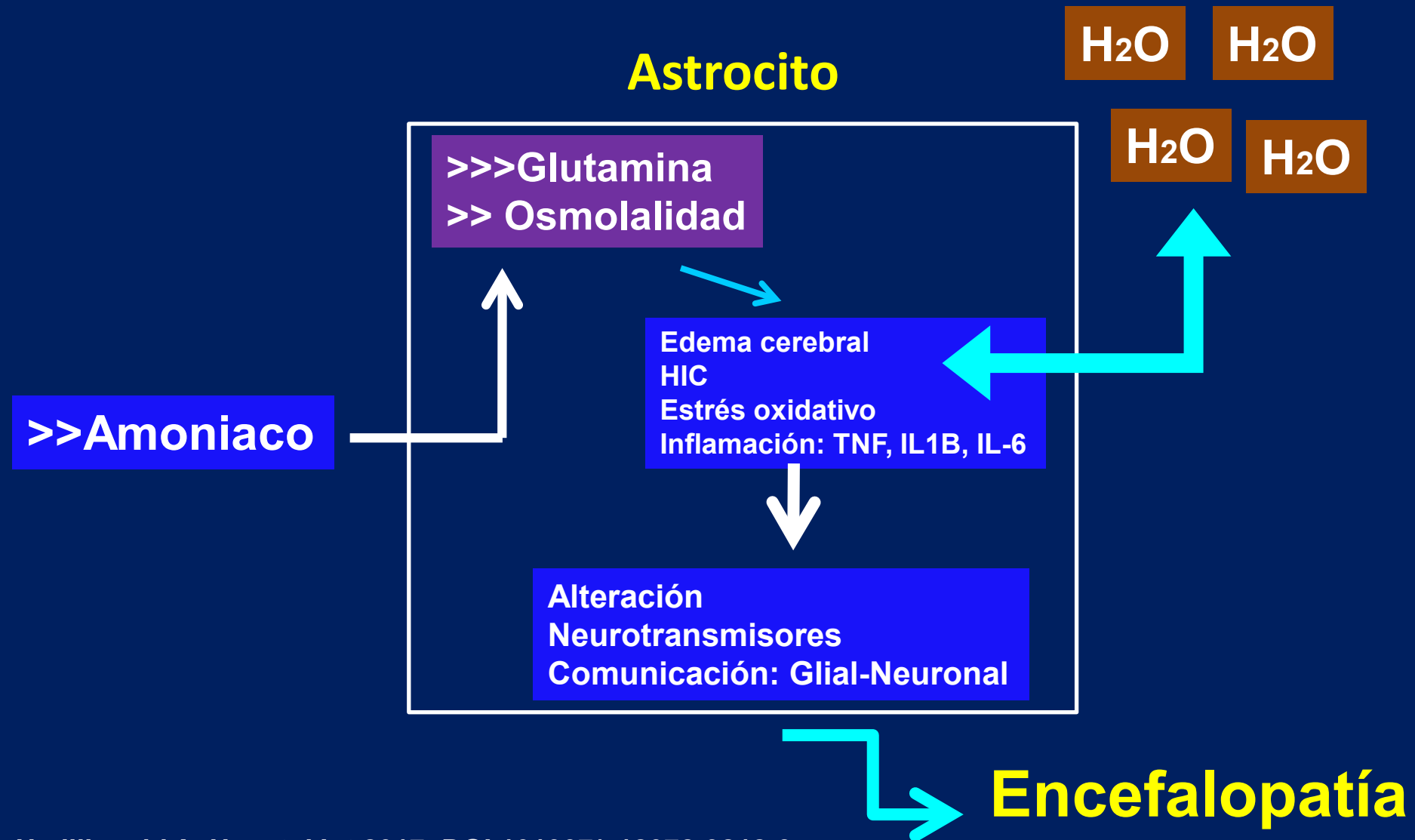
Neurotoxina fundamental, 1896

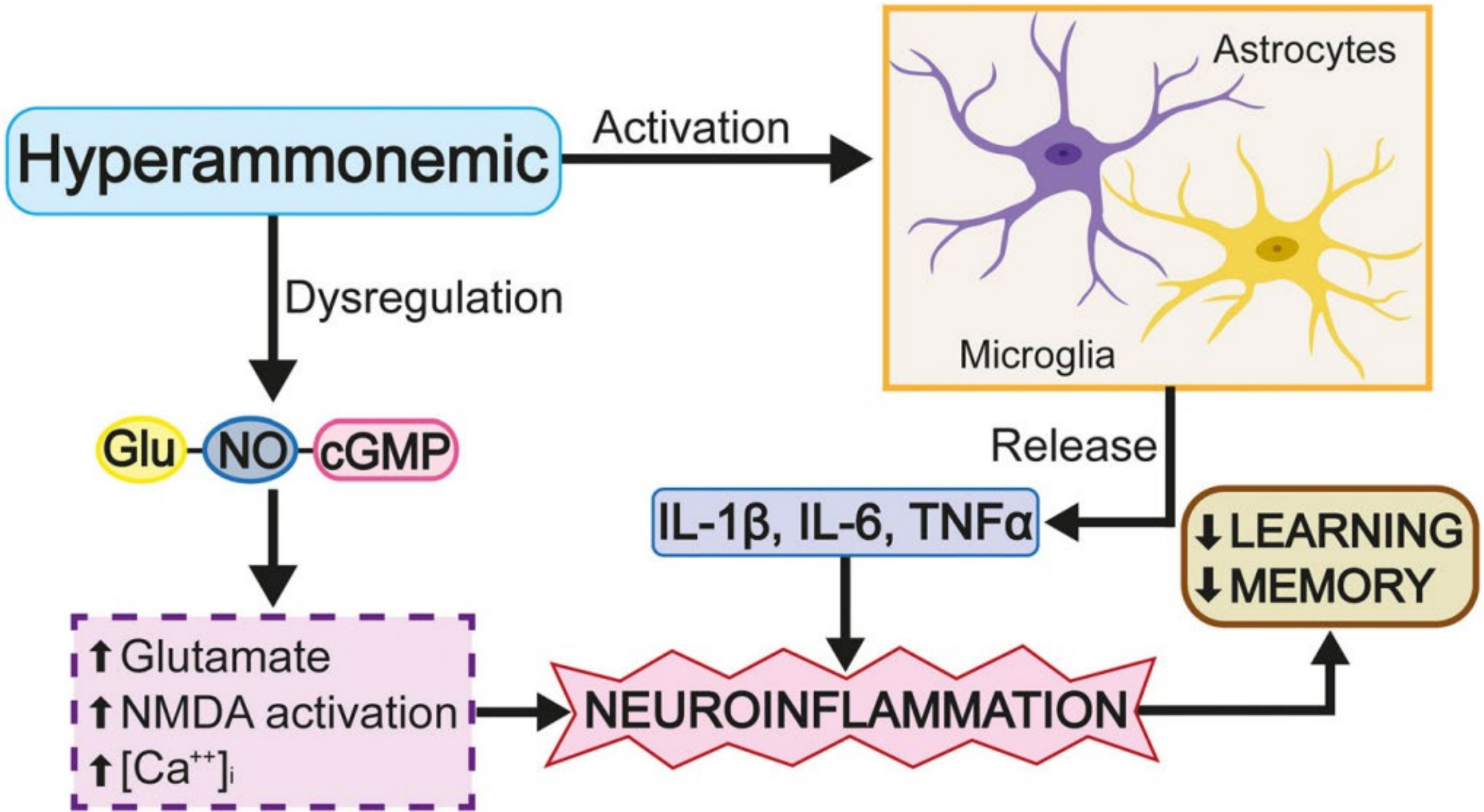


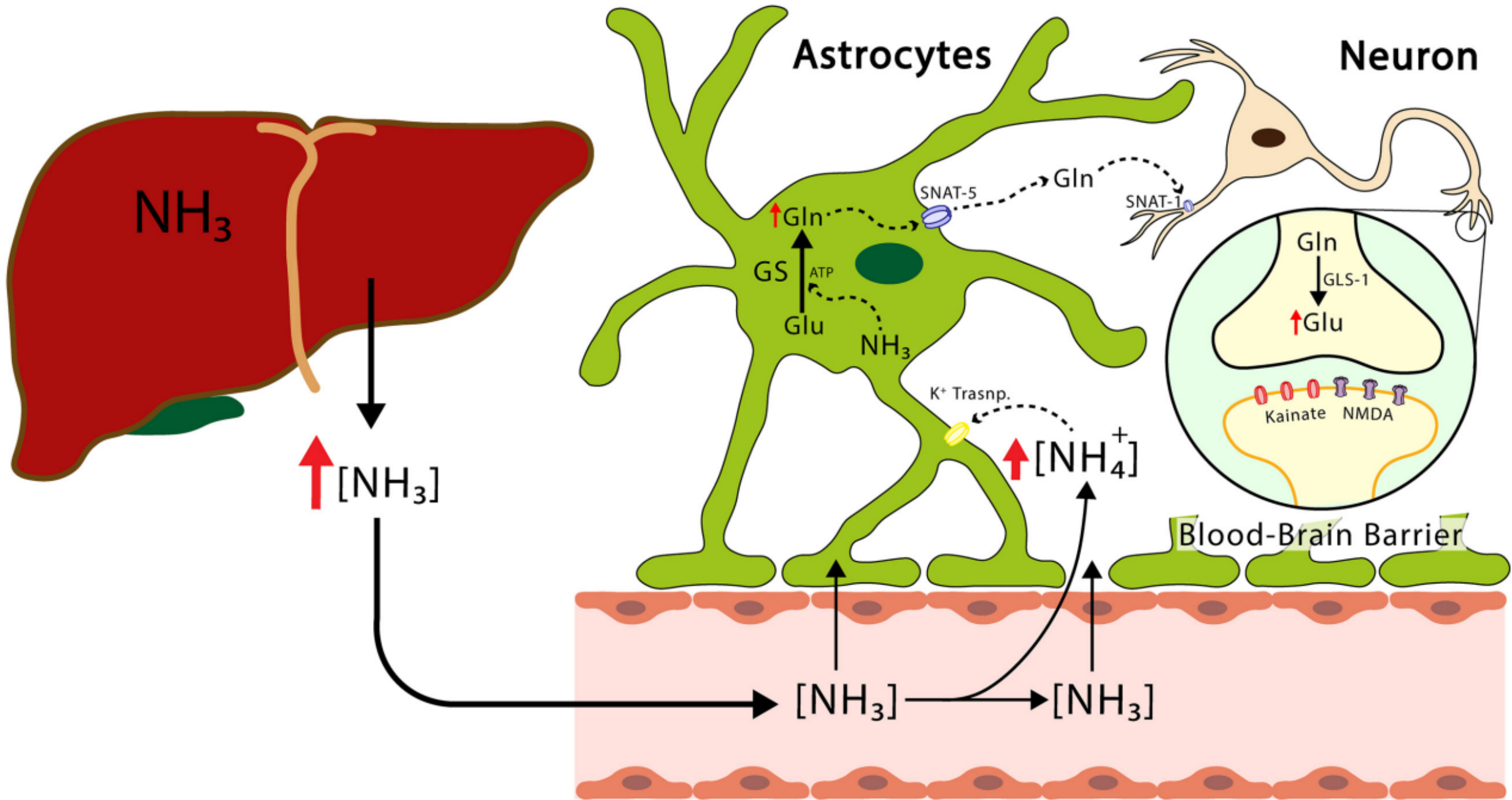




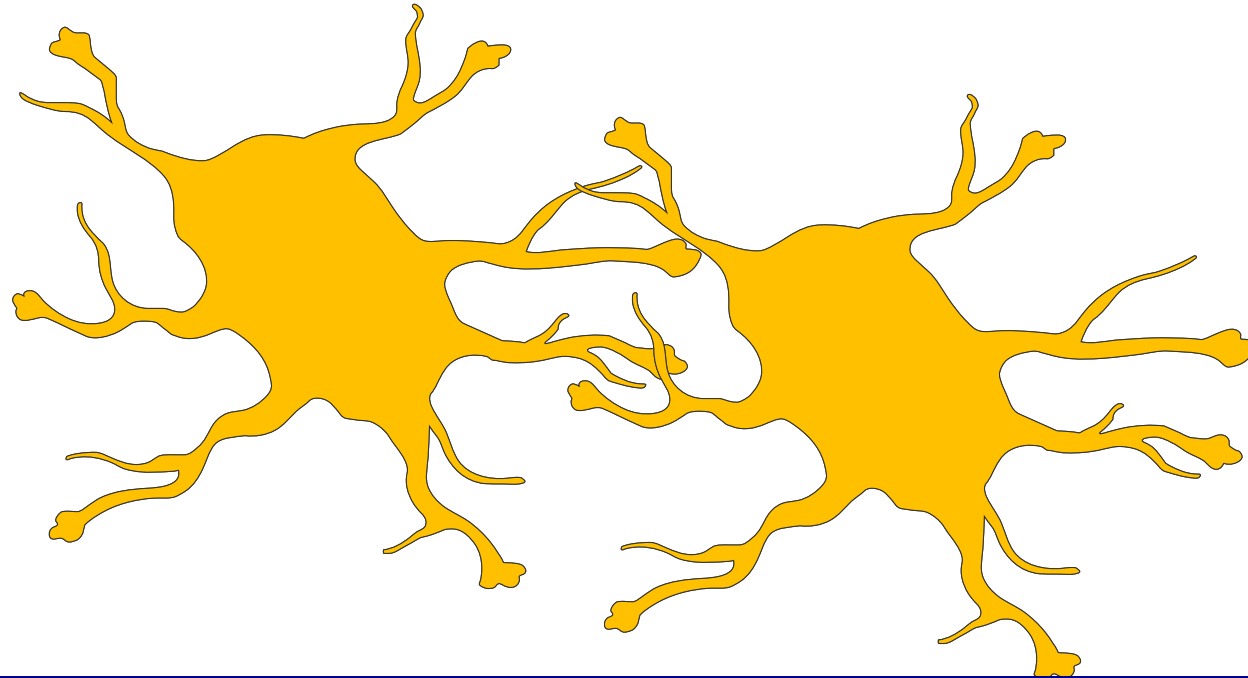
Imbalance osmótico en astrocitos





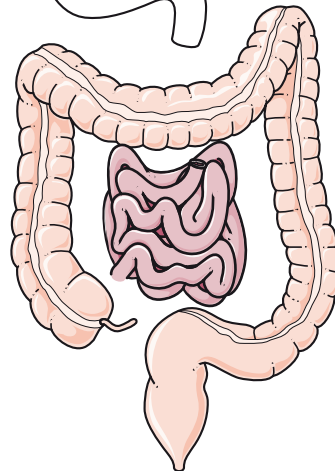
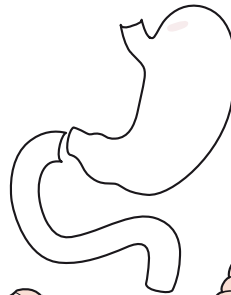
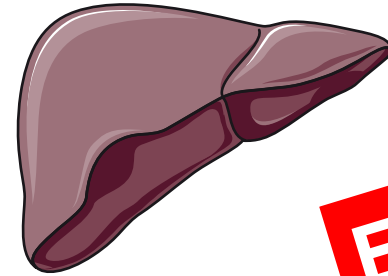
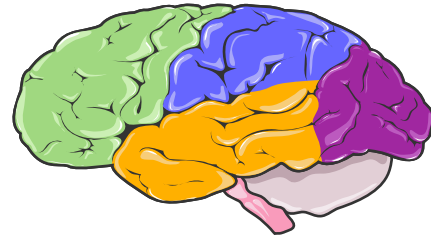


Astrocito



33% volumen cortical
Regulan la barrera hemato-encefálica
Mantienen la homeostasis de electrolitos cerebrales
Proporciona nutrientes y precursores de neurotransmisores
Únicas células del cerebro que metabolizan el NH₃

Norenberg MD, Metab Brain Dis 2007;22:219-34
Cooper AJ, Physiol Rev 1987;67:440-519



**Eje Intestino
Hígado Cerebro**

**Microbioma
Fundamental**

**Vilstrup H, Hepatology 2014;60:715-35
Rose CF, J Hepatol 2020;73:1526-47**

Encefalopatía hepática



Manifestaciones clínicas

Sicomotoras

Funciones Motoras Finas

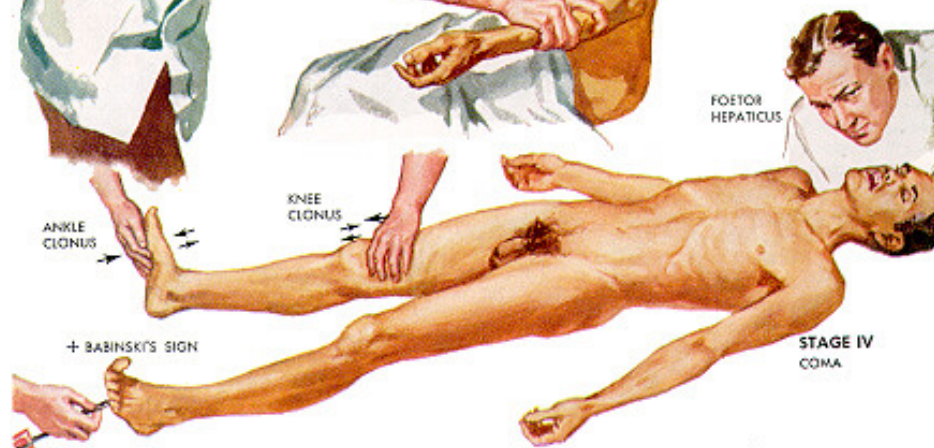
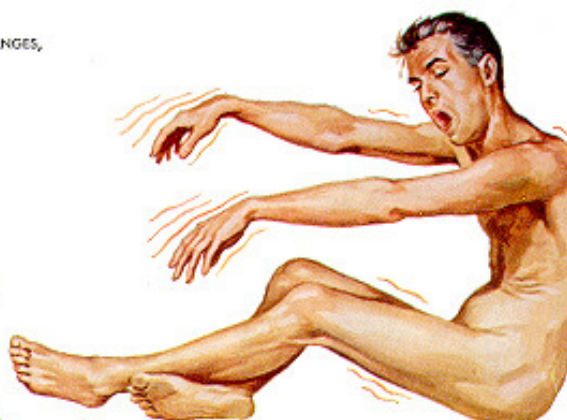
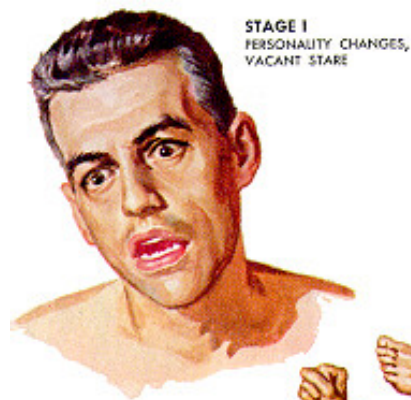
Intelectual

**Rango de
alteraciones**

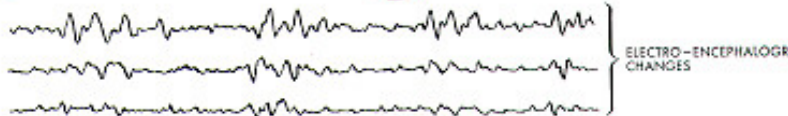
Emocional

Comportamiento

Cognitiva



F. Netter
M.D.
© CIBA



Grados de encefalopatía

Grado 0. EH mínima (subclínica). Ausencia de cambios detectables En personalidad, o comportamiento, cambios mínimos de memoria, Concentración, función intelectual

Grado 1. Hipersomnias, insomnio Inversión del patrón del sueño. Euforia, depresión, irritabilidad, confusión leve, lentitud para cálculos mentales

Grado 2. Apatía, letargo, desorientación, comportamiento inapropiado, **asterixis**, Incapacidad para cálculos mentales, cambios obvios de la personalidad

Grado 3. Somnolencia (despertable), incapacidad para cálculos mentales, desorientación en tiempo y lugar, confusión marcada, amnesia, lenguaje incomprensible

Grado 4. Coma con o sin respuesta a estímulos dolorosos

Encefalopatía hepática

“Sterixis”



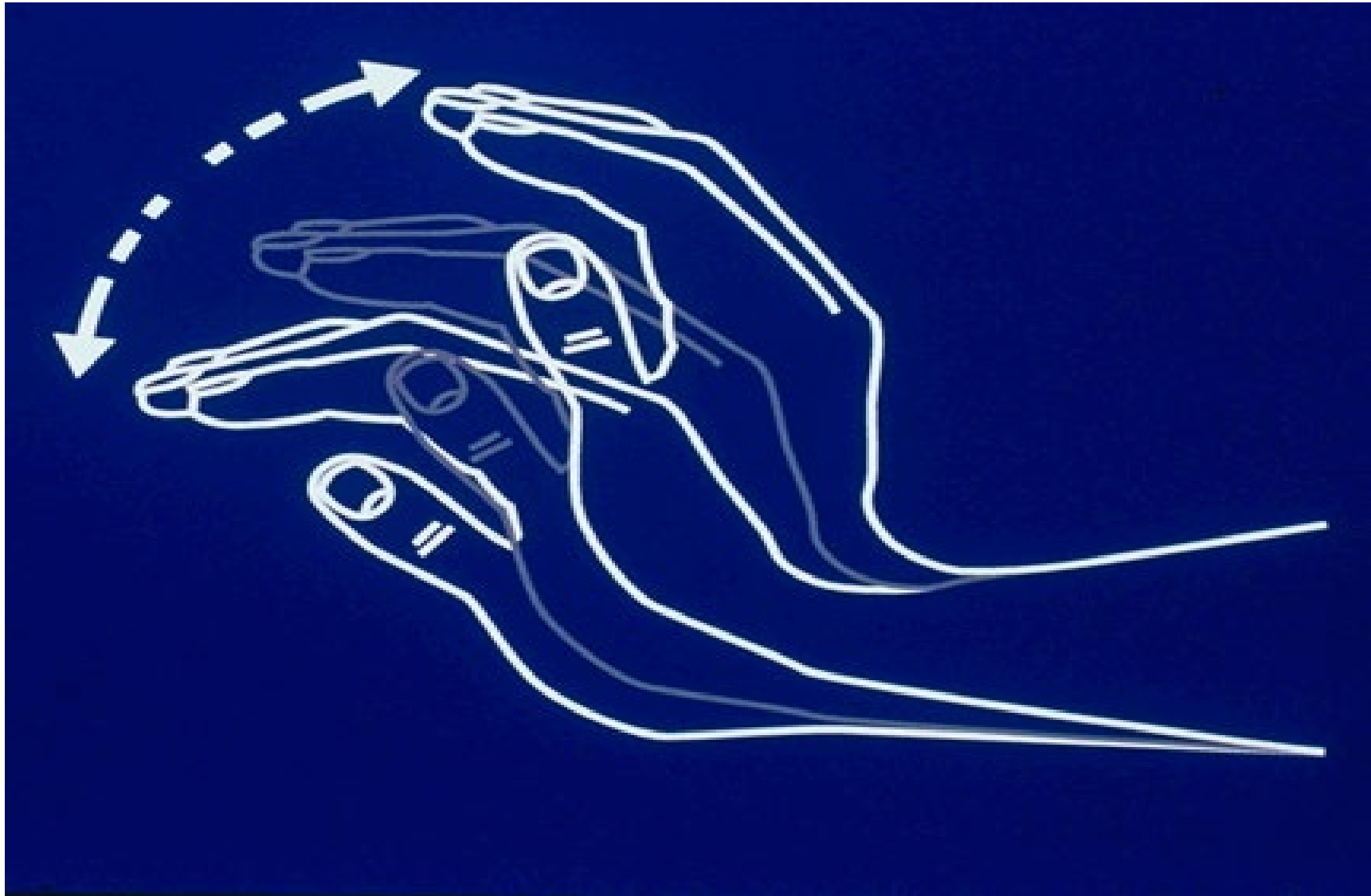
Posición fija

Asterixis



**Incapacidad
para mantener
la posición**





Encefalopatía hepática

Diagnóstico diferencial

Diagnóstico diferencial

Encefalopatías metabólicas: Hipoxia, Hipercapnia, hipoglicemia
Uremia, Acidosis, alteraciones electrolíticas

Encefalopatías tóxicas: Alcohol, abstinencia, Wernicke

Encefalopatía medicamentos: Sedantes, hipnóticos, A. Sicóticos

Encefalopatía pos convulsión: Estados pos-ictales

Infección cerebral: meningitis, encefalitis, abscesos

Lesiones intracraneales : ECV, Hemorragia, Tumores, H. subdurales

HAS

Encefalopatía pancreática

Encefalopatía hepática

Exámenes

Neuro-imágenes

Imaging technique	Information
Volumetric T ₁ -weighted MR imaging	Regional or global changes in brain size. A reduction in brain volume is observed in patients with HE. ¹⁵³
Magnetisation-transfer MR imaging	Measures shifts in bound and free water content, which have been associated with intracellular and extracellular oedema and with alterations in cell membrane fluidity. In patients with HE there is evidence of reduced magnetisation transfer, indicating increased brain water. ¹⁵⁴
Diffusion-weighted MR imaging	Measures ADCs of water molecules. Associated with structural damage to white matter tracts. Changes in ADCs have been observed in patients with HE. ²⁵²
Functional MR imaging (fMRI)	Measures changes in blood flow in metabolically active areas of the brain, related to oxygenation and de-oxygenation of haemoglobin (BOLD response). Resting state or responses to cognitive tasks can be assessed in imaging paradigms. In patients with HE, changes in fMRI have been shown to occur. ¹⁵⁵
³¹ P MR spectroscopy	Measures high energy metabolites, such as ATP and phosphocreatine, together with cell membrane precursors (phosphomonoesters) and cell membrane degradation products (phosphodiesteres). Widespread changes in ³¹ P metabolites have been shown to occur in patients with HE. ¹⁵⁸
¹ H MR spectroscopy	Measures lactate, choline, glutamine and glutamate levels and fluxes in osmolytes such as myo-inositol and taurine. Neuronal integrity reflected by N-acetyl aspartate measurements. Cannot measure ammonia levels directly, but increased glutamine represents amidation by glutamine synthetase. This is the best validated imaging test that may be useful for the diagnosis of HE as the severity of HE has been shown to correlate with changes in metabolites. ¹⁵⁷
Positron emission tomography (PET)	Depending on the radioligand used, information can be obtained on a wide variety of brain activity including neurotransmitter binding (such as dopamine or GABA receptors), TSPO activity (as a measure of neuroinflammation) and glucose utilisation. Several studies using PET have revealed alterations in cerebral blood flow, perfusion, glucose utilisation, oxygenation, ammonia metabolism, benzodiazepine receptor expression and neuroinflammation in patients with HE. ²⁵⁰

Medición sanguínea *controvertida*

Infecciones
Urinario, Ureasa +

Hipotensión
Choque

“Shunt”
Portosistémico

Medicamentos

Hemorragia
Digestiva

Alcohol

Cirrosis no Correlación
Severidad 80umol/L
>mortalidad, No específico

Amoniaco
NH₄

**Nunca se solicita
en asintomáticos**

Falla hepática Aguda
>120umol/L
Hipertensión IC
Edema cerebral

Sangre arterial
Venosa
Plasma

Karanfilian BV, Clin Liver Dis 2020;24:197-208
Bajaj J, Am J Gastroenterol 2020;115:989-1002
Rose C, J Hepatol 2020; 73:1526-47

EH

Tratamiento

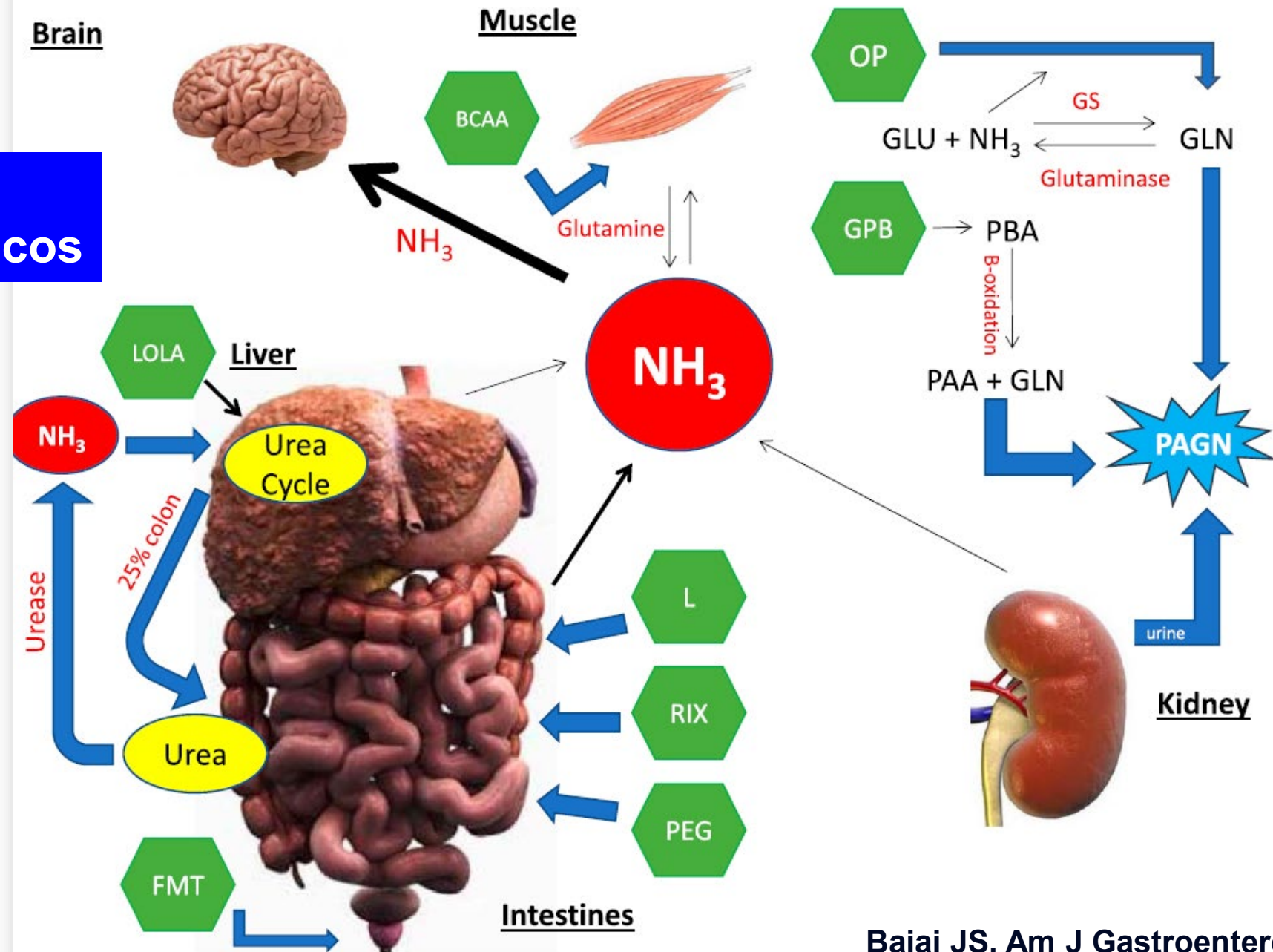
**No existe tratamiento específico!
Se ignora la historia natural**

Dirigido al intestino

Reducir, Inhibir la producción NH_3/H^+

Aumentar la eliminación de NH_3/H^+

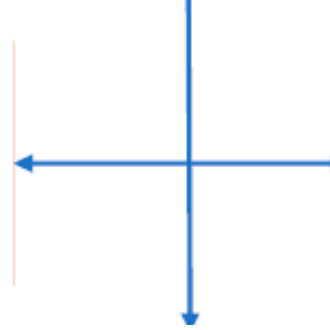
Blancos Terapéuticos



Pacientes con cirrosis y alteración del sensorio

Atender el ABC

Via aérea
Ventilación
Circulación



Excluir otras causas

Electrolitos, hipoglicemia
Falla renal, hipoxia,
Hipercapnia, Hemorragia
cerebral, benzodiazepinas

Encefalopatía aguda manifiesta → UCI si es avanzada

Identificar y tratar factor
Desencadenante 90%

Tratamiento

Encefalopatía

Infección: antibióticos
Sangrado GI: control
Deshidratación: expansión volumen
Estreñimiento: laxantes
Alcohol abstinencia: tiamina
Desnutrición: apoyo nutricional

Lactulosa/lactitol (oral/enemas)

Alternativa o adicionar si
No mejoría en 24 horas

Rifaximina

PEG

LOLA (L-ornitina L-aspartato)

Enfoque terapéutico

I. Episodio agudo

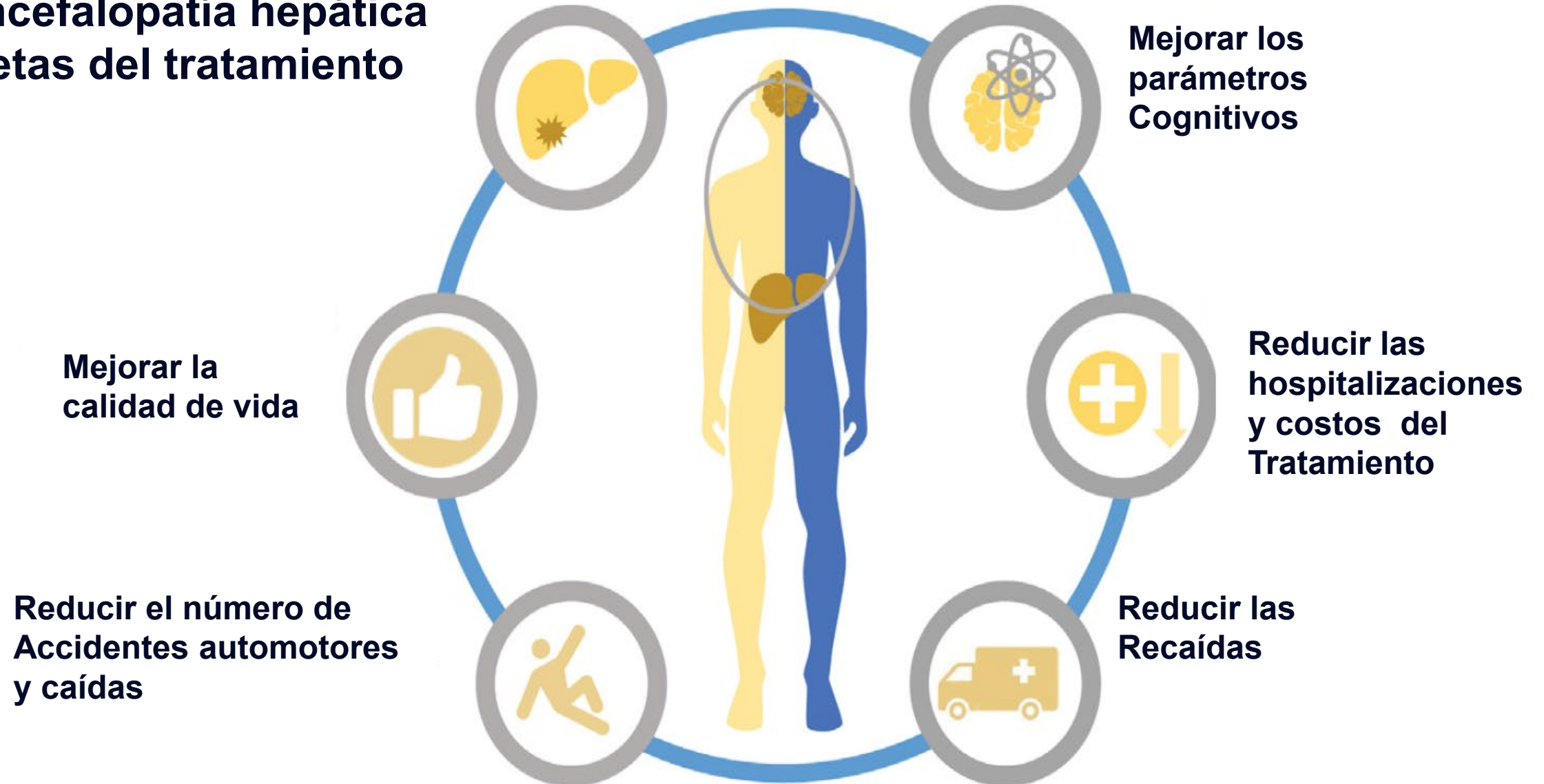
Tratamiento factores precipitantes
Disminuir producción de amoníaco
Evaluación para trasplante hepático

II. Profilaxis secundaria (Seguimiento)

Prevención de recurrencias
Mejorar desempeño diario
Evaluación para trasplante hepático

Encefalopatía hepática

Metas del tratamiento



Encefalopatía hepática

Piedra angular del tratamiento

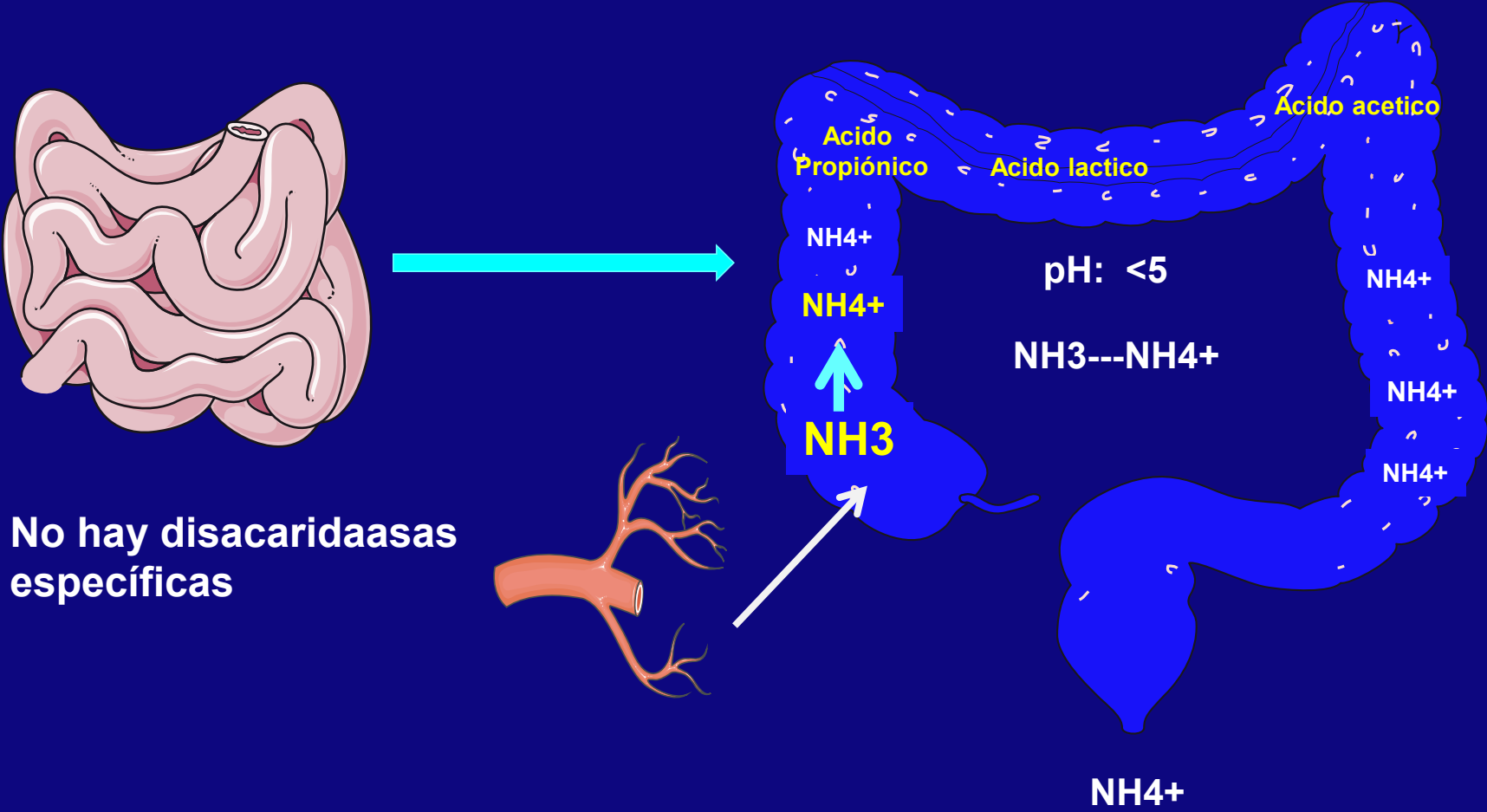
 **NH₃**

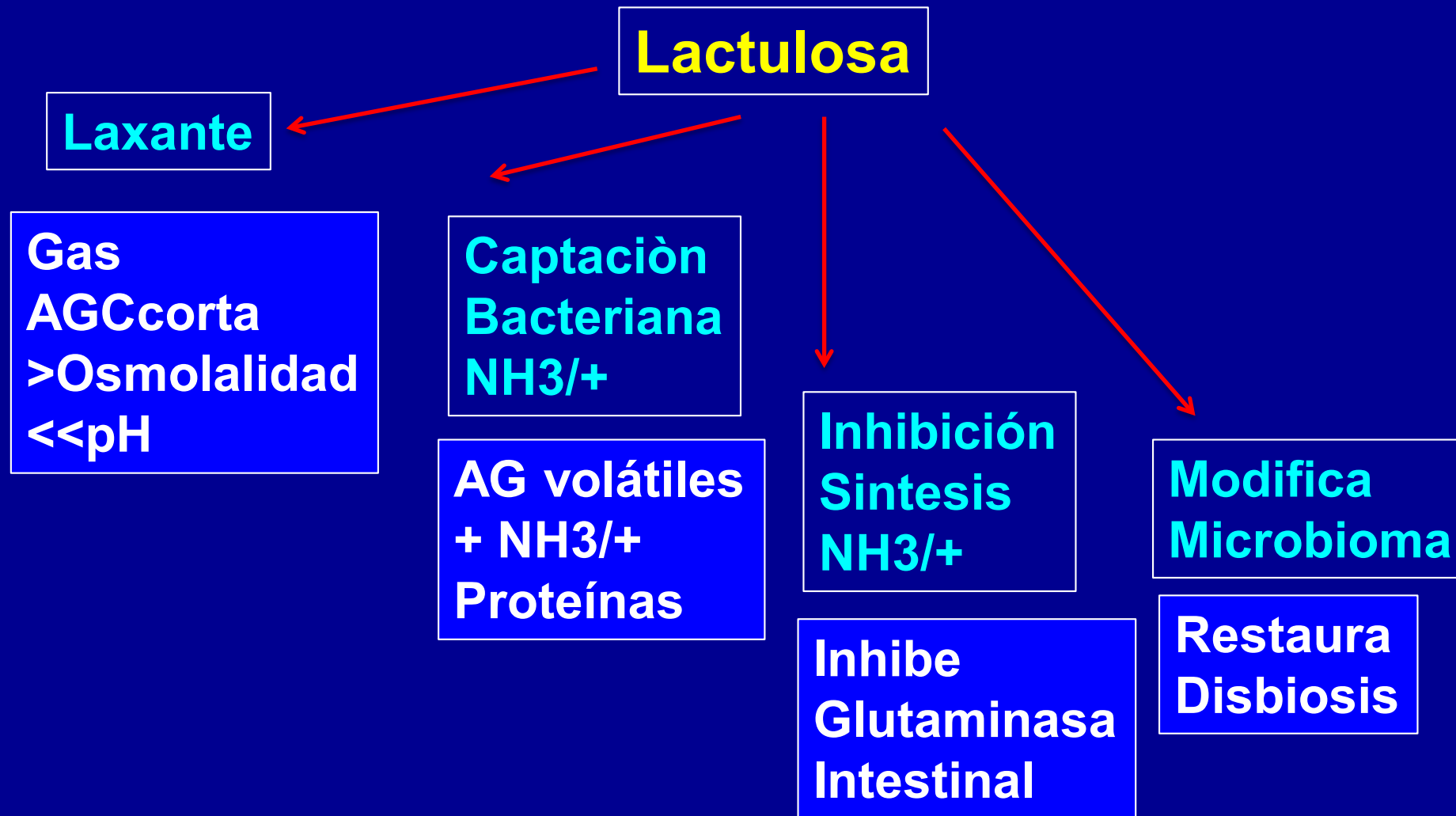
Lactulosa
Rifaximina

Alimirah M, Clin Liv Dis 2020;24:303-15
Mahpour NY, Clin Liv Dis 2020;24:231-42
Rose C, J Hepatol 2020;73:1526-47
Bajaj JS, Am J Gastroenterol 2020;15:889-1002

Lactulosa: Disacárido sintético

Fructosa-galactosa

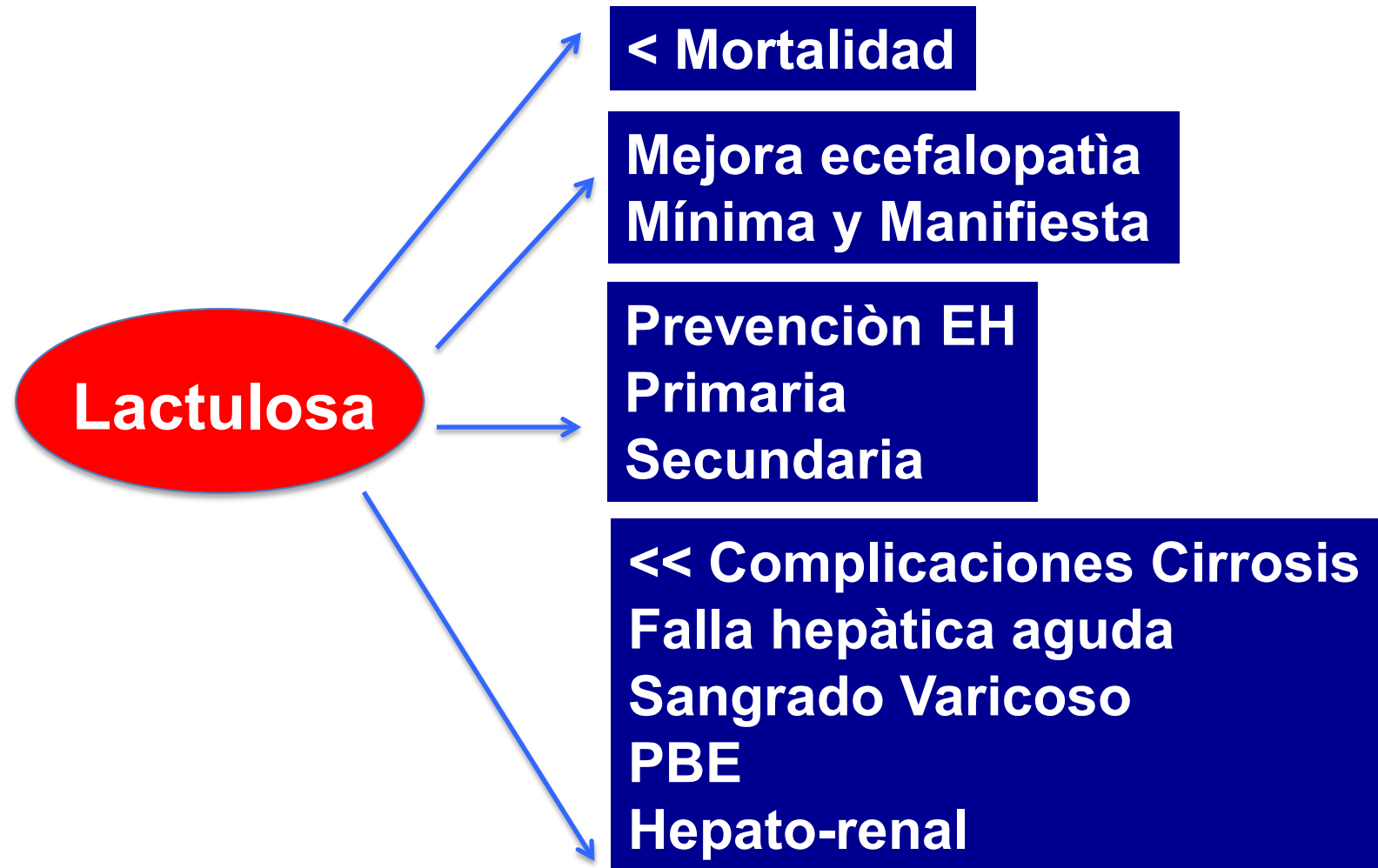




Nonabsorbable Disaccharides for Hepatic Encephalopathy: A Systematic Review and Meta-Analysis

Lise L. Glud,¹ Hendrik Vilstrup,² and Marsha Y. Morgan³

Hepatology 2016, On line





REVISTA DE GASTROENTEROLOGÍA DE MÉXICO

www.elsevier.es/rgmx



REVIEW ARTICLE

Efficacy of rifaximin in the different clinical scenarios of hepatic encephalopathy[☆]

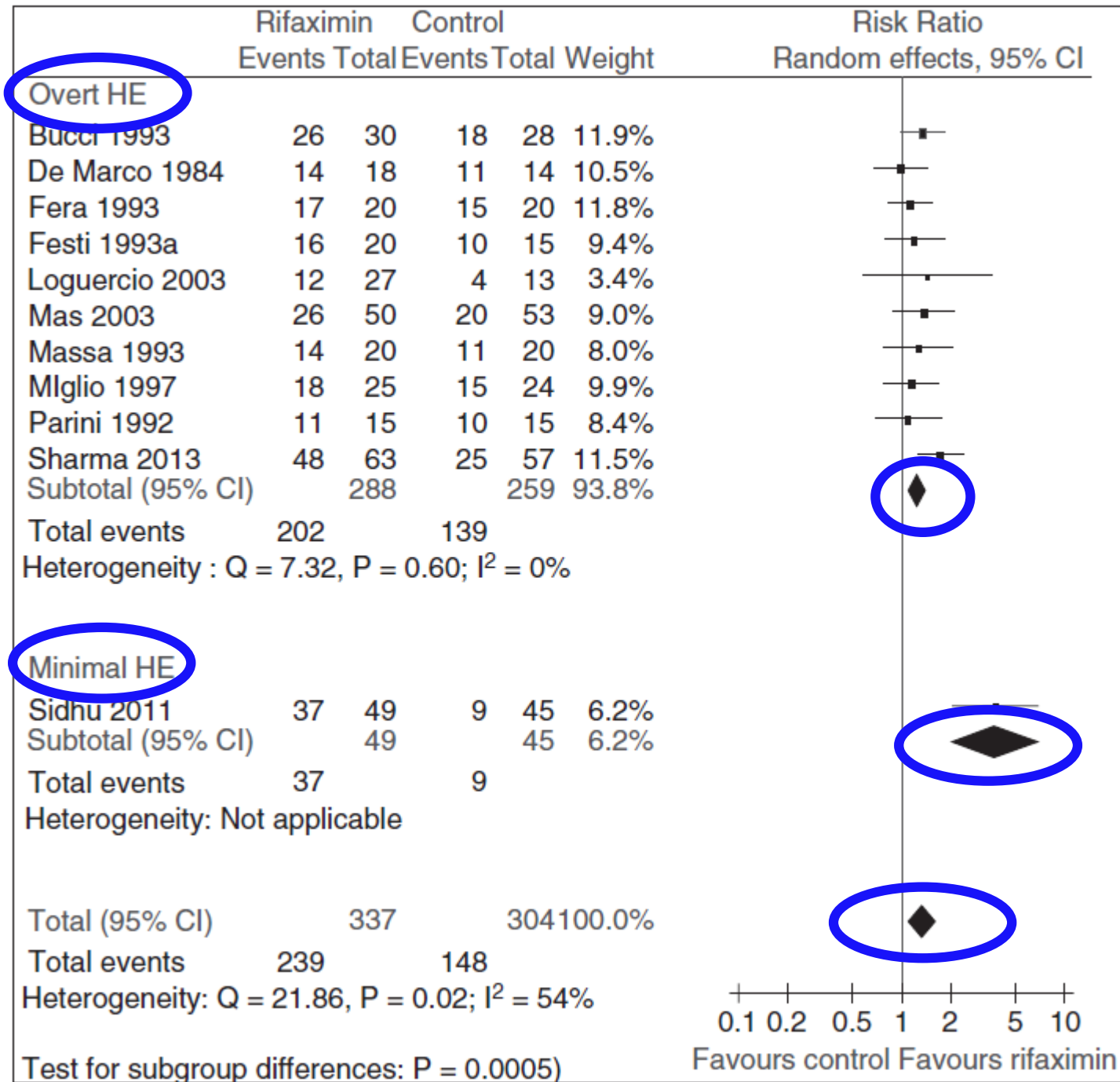


C.E. Coronel-Castillo^a, J. Contreras-Carmona^a, A.C. Frati-Munari^c,
M. Uribe^a, N. Méndez-Sánchez^{a,b,*}

Systematic review with meta-analysis: the effects of rifaximin in hepatic encephalopathy

N. Kimer^{*,†}, A. Krag[‡], S. Møller[†], F. Bendtsen^{*} & L. L. Gluud^{*}

Aliment Pharmacol Ther 2014; 40: 123-32

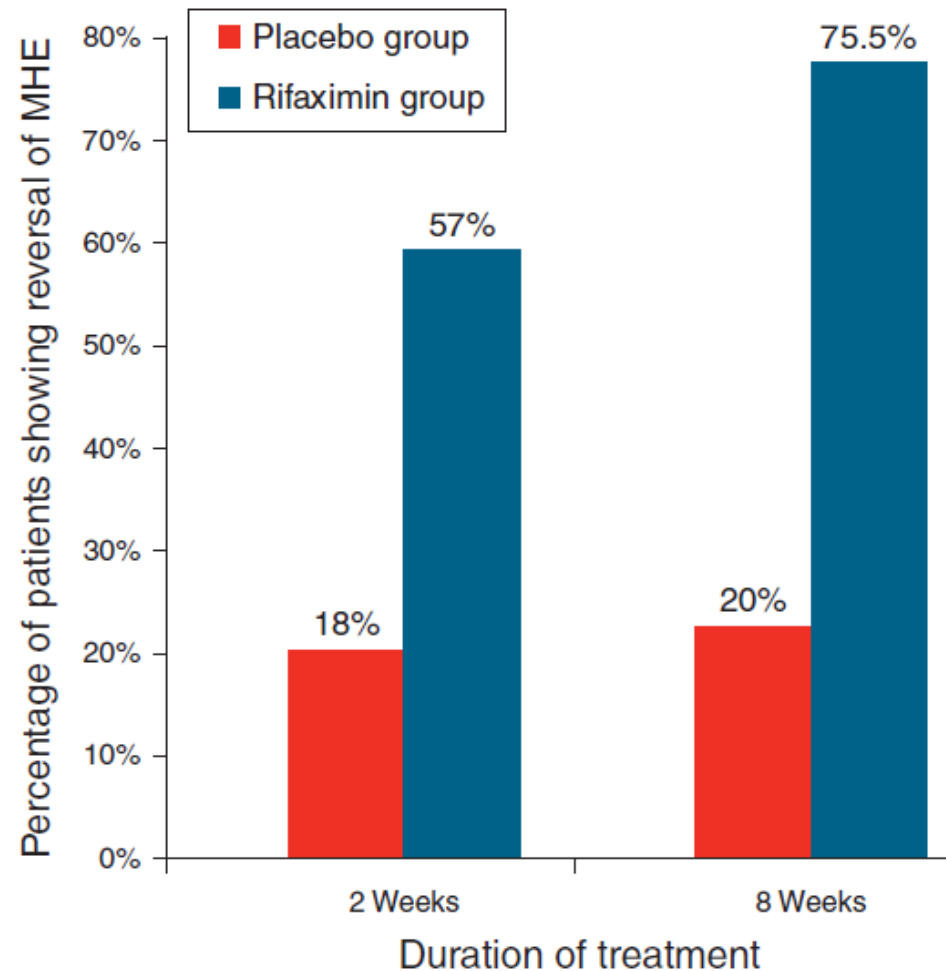


Encefalopatía Hepática Rifaximina

Kimer N, APT 2014; 40:123-32

Rifaximin Improves Psychometric Performance and Health-Related Quality of Life in Patients With Minimal Hepatic Encephalopathy (The RIME Trial)

Sandeep Singh Sidhu, MBBS, MD, DM¹, Omesh Goyal, MBBS, MD, DM¹, Bholeshwar Prashad Mishra, MBBS, PhD², Ajit Sood, MBBS, MD, DM¹, Rajoo Singh Chhina, MBBS, MD, DM¹ and Ravinder Kumar Soni, MBBS, MD³



Otros tratamientos

AA de cadena ramificada

L-Ornitina /L- Aspartato (LOLA)

Polietilen glicol

Albumina

Acarbosa (< Alfaglicosidasa)

<< Bacterias Proteolíticas: < mercaptanos,
<“BZD-like”, NH₃/NH₄



Cochrane Database of Systematic Reviews

Branched-chain amino acids for people with hepatic encephalopathy (Review)

Gluud LL, Dam G, Les I, Marchesini G, Borre M, Aagaard NK, Vilstrup H

**Faltan estudios con adecuado poder
Y comparador**



Cochrane Database of Systematic Reviews

L-ornithine L-aspartate for prevention and treatment of hepatic encephalopathy in people with cirrhosis (Review)

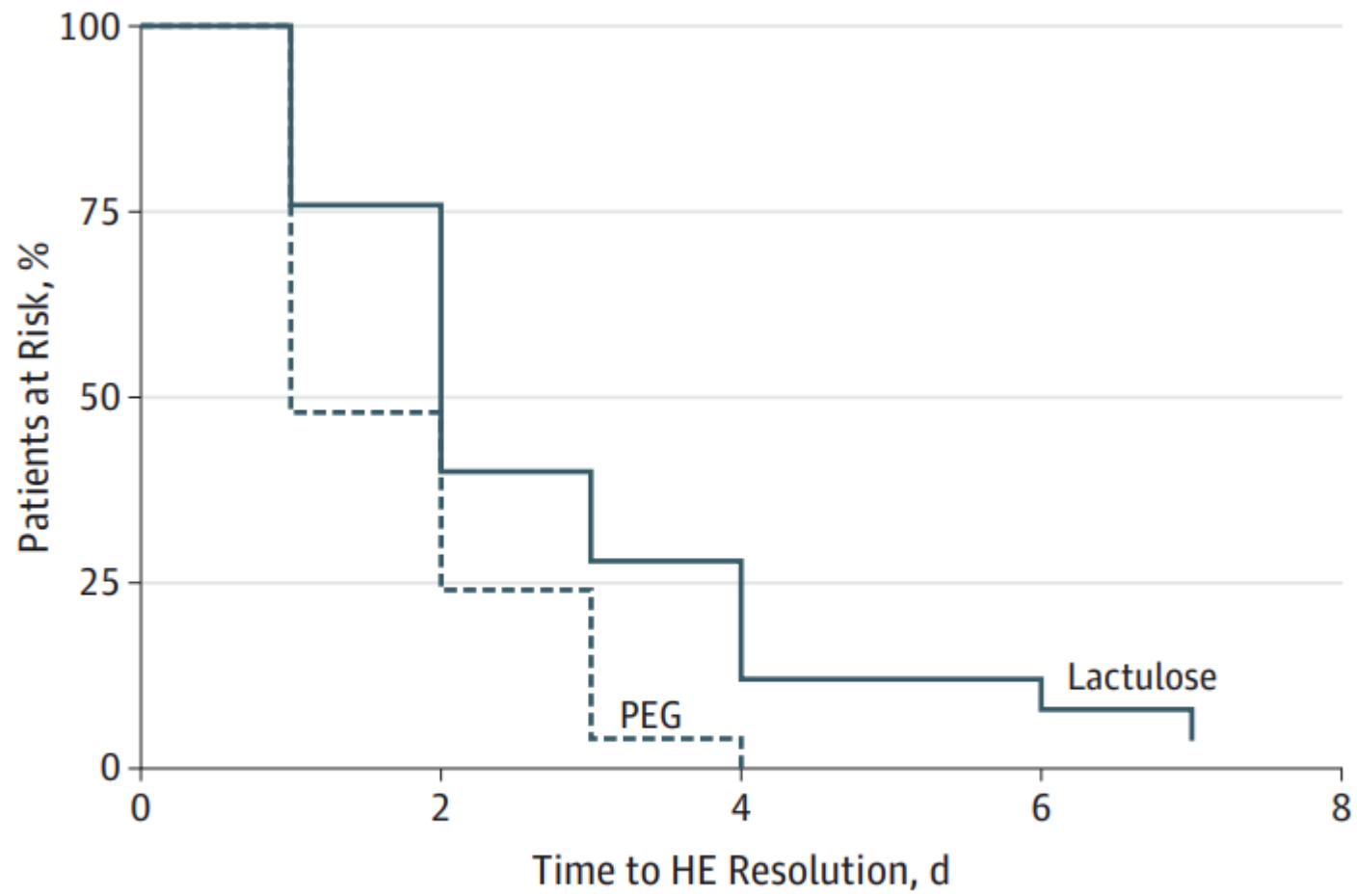
Goh ET, Stokes CS, Sidhu SS, Vilstrup H, Gluud LL, Morgan MY

**Faltan estudios
Baja calidad de la evidencia**

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

Robert S. Rahimi, MD, MS; Amit G. Singal, MD, MS; Jennifer A. Cuthbert, MD; Don C. Rockey, MD

PEG 4L en 4 horas
Lactulosa 3 o más dosis /24h



No. at risk						
Lactulose	25	19	7	3	1	
PEG	25	12	1	0	0	

Randomized controlled trial comparing lactulose plus albumin *versus* lactulose alone for treatment of hepatic encephalopathy

Barjesh Chander Sharma,* Jatinderpal Singh,* Siddharth Srivastava,* Alok Sangam,* Alok Kumar Mantri,* Nirupma Trehanpati[†] and Shiv Kumar Sarin[‡]

	Albumina 1.5 gr/kg + Lactulosa N=60	Lactulosa N=60	P
Reversión encefalopatía	75%	53.3%	0.03
Mortalidad	18.3%	31.6%	<0.005

Sharma BC, Gastroenterol Hepatol. 2017;32:1234-1239.

Terapias emergentes preclínicas

Diálisis peritoneal apoyada con liposomas
Antagonistas esteroides moduladores R- GABA A
Glutamina Sintetasa
Trasplante Fecal

Encefalopatía hepática

Seguimiento ambulatorio

Prevención secundaria

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Rifaximin Treatment in Hepatic Encephalopathy

Nathan M. Bass, M.B., Ch.B., Ph.D., Kevin D. Mullen, M.D., Arun Sanyal, M.D., Fred Poordad, M.D., Guy Neff, M.D., Carroll B. Leevy, M.D.,* Samuel Sigal, M.D., Muhammad Y. Sheikh, M.D., Kimberly Beavers, M.D., Todd Frederick, M.D., Lewis Teperman, M.D., Donald Hillebrand, M.D., Shirley Huang, M.S., Kunal Merchant, Ph.D., Audrey Shaw, Ph.D., Enoch Bortey, Ph.D., and William P. Forbes, Pharm.D.

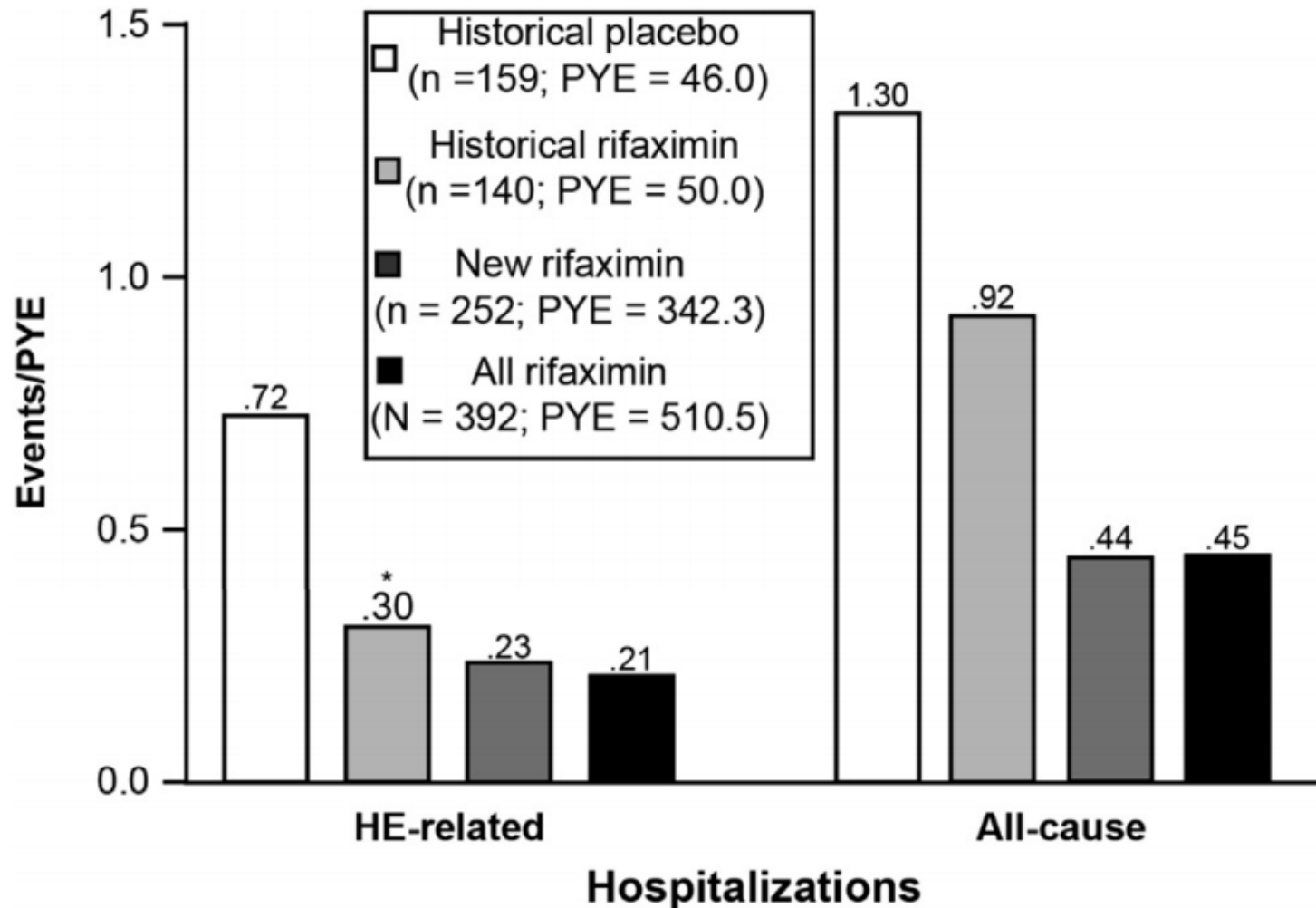
	Placebo	RFX	OR	p
Recurrencia 6 M%	45	22.1	0.42 (0.28-0.64)	<0.001
Pacientes/Hospital.	22.6	13.6	0.5 (0.29-0.87)	<0.01

Rifaximin Is Safe and Well Tolerated for Long-term Maintenance of Remission From Overt Hepatic Encephalopathy

Kevin D. Mullen,* Arun J. Sanyal,† Nathan M. Bass,§ Fred F. Poordad,||
Muhammad Y. Sheikh,¶ R. Todd Frederick,# Enoch Bortey,** and William P. Forbes**

550 mg 2v/DÍA
Dos AÑOS

Clin Gastroenterol Hepatol 2014;12:1390-7



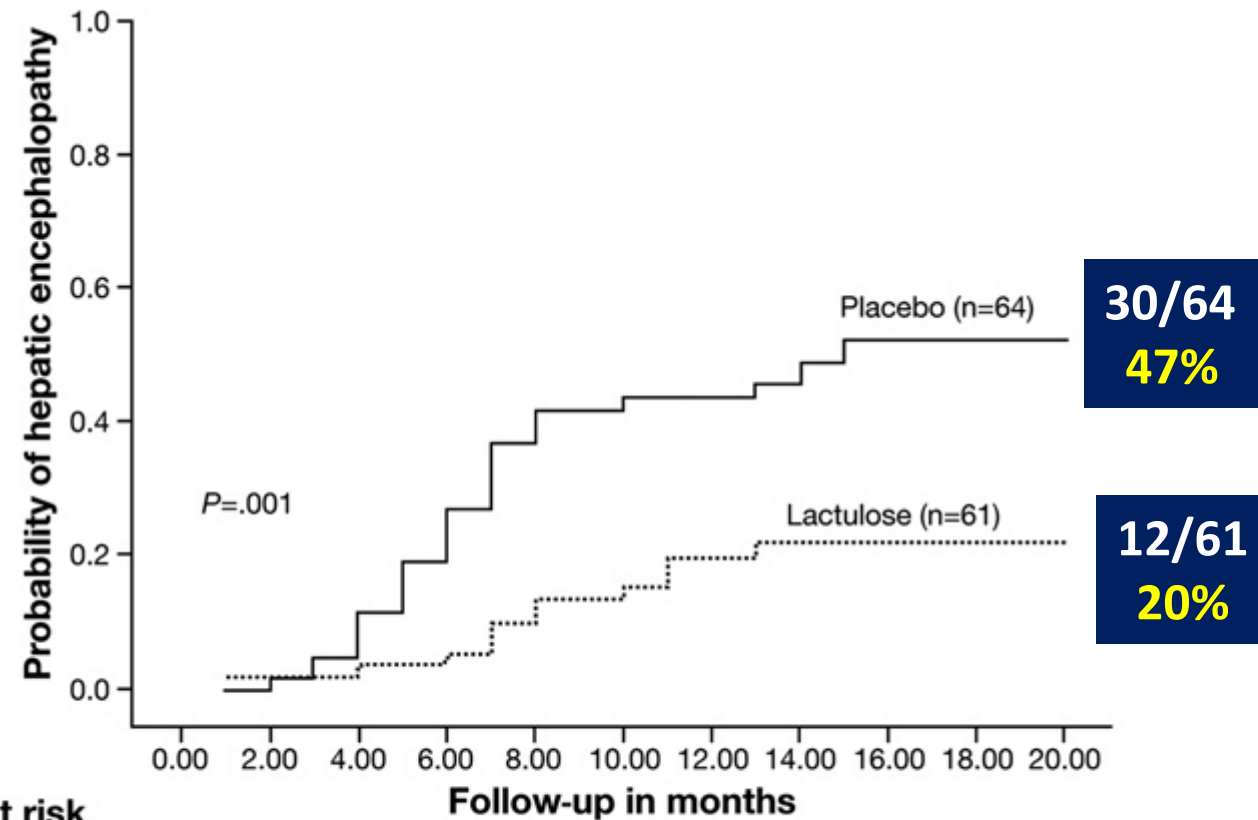
Lactulosa

Prevención secundaria

Secondary Prophylaxis of Hepatic Encephalopathy: An Open-Label Randomized Controlled Trial of Lactulose Versus Placebo

BARJESH CHANDER SHARMA, PRAVEEN SHARMA, AMIT AGRAWAL, and SHIV KUMAR SARIN

Department of Gastroenterology, G. B. Pant Hospital, New Delhi, India



Patients at risk

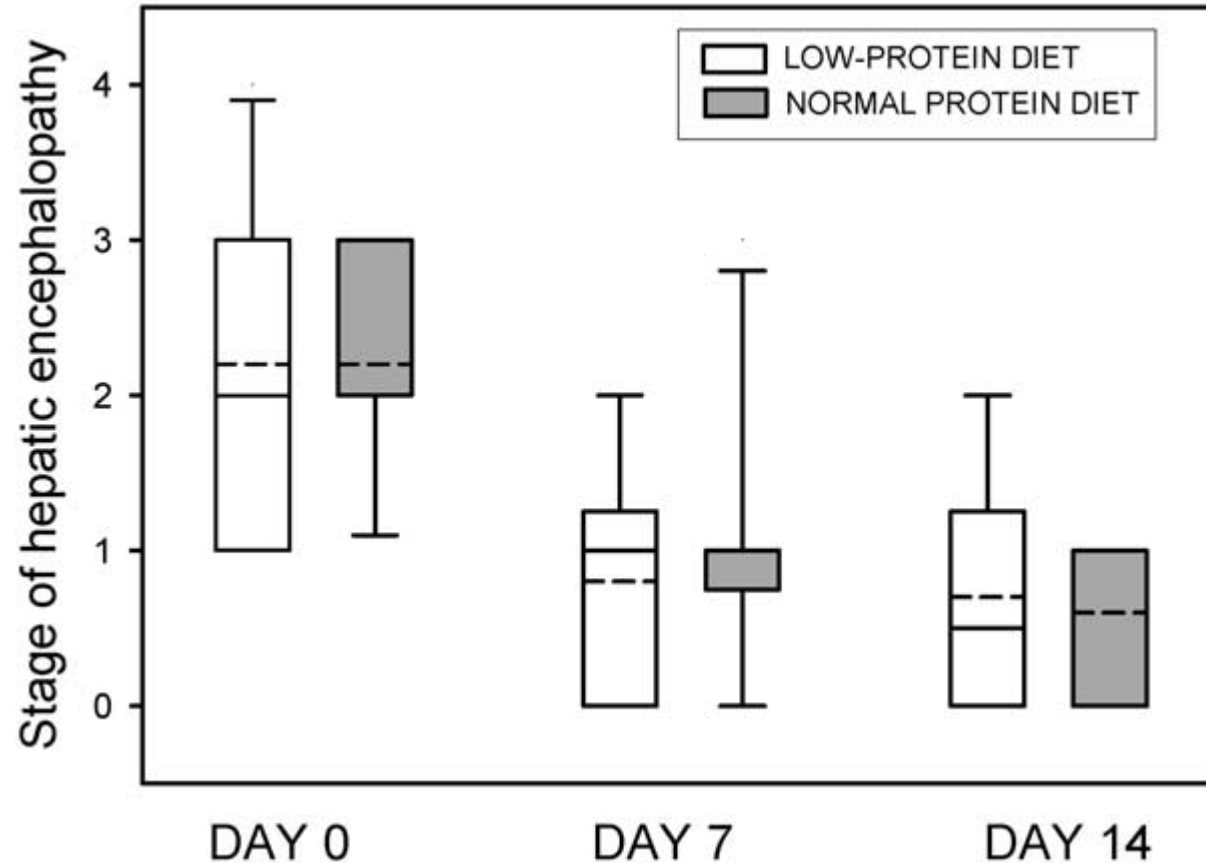
Lactulose	61	60(1)	59(2)	58(3)	51(8)	45(9)	38(11)	28(12)	10(12)	7(12)	1(12)
Placebo	64	62(1)	59(4)	50(13)	37(24)	33(27)	28(27)	19(29)	13(30)	8(30)	4(30)

Encefalopatía hepática

Proteínas: Si , No ?
Dogma antiguo

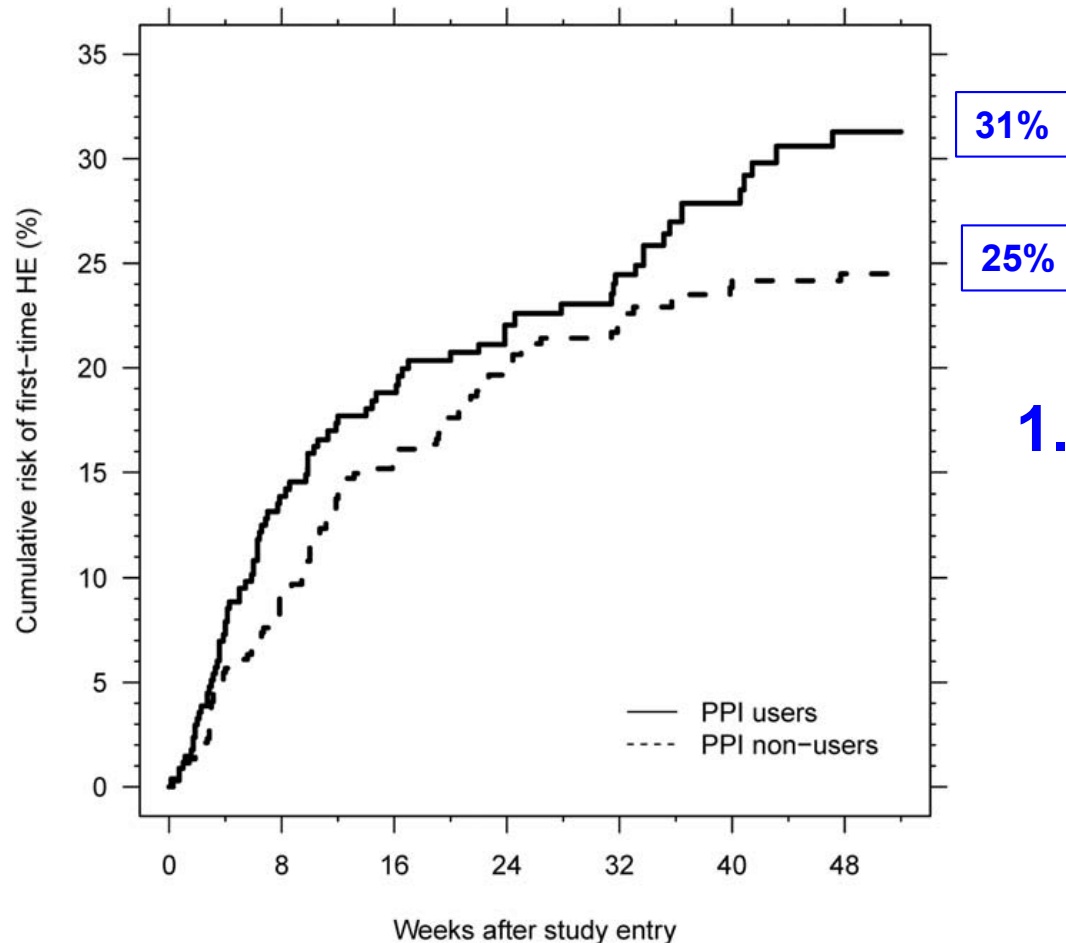
Normal protein diet for episodic hepatic encephalopathy: results of a randomized study

Juan Córdoba^{1,*}, Juan López-Hellín², Mercé Planas³, Pilar Sabín⁴, Francesc Sanpedro¹,
Francisco Castro¹, Rafael Esteban¹, Jaume Guardia¹



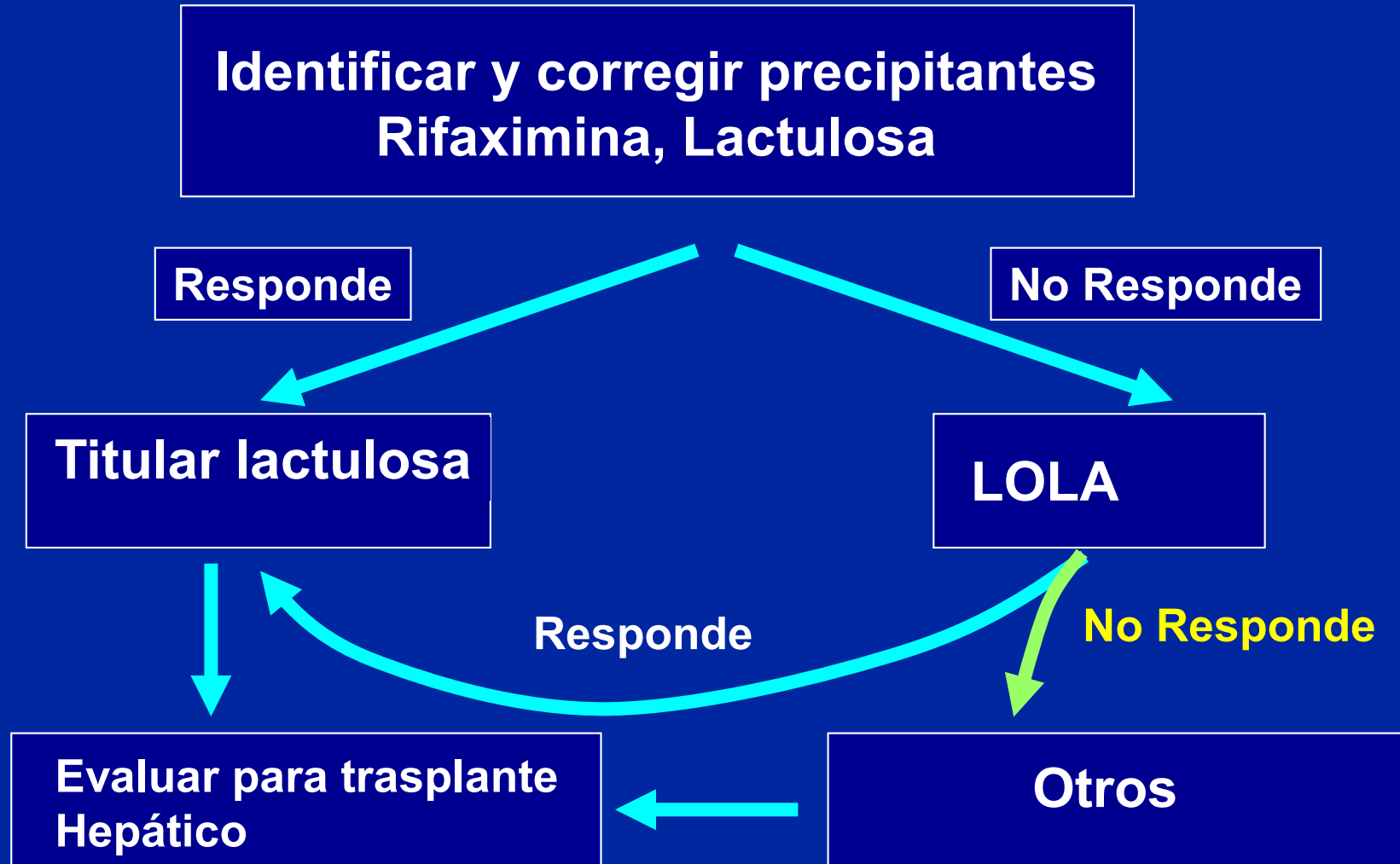
Proton Pump Inhibitors as a Risk Factor for Hepatic Encephalopathy and Spontaneous Bacterial Peritonitis in Patients With Cirrhosis With Ascites

Gitte Dam,¹ Hendrik Vilstrup,¹ Hugh Watson,² and Peter Jepsen^{1,3}



1.72 (IC 95% 1.10-2.69).

Encefalopatía hepática, Manejo



Mensajes para la casa

Identificar factores precipitantes: 90%

Disminuir efectos del amoniaco

Rifaximina y lactulosa en todos los escenarios

A todo cirròtico lactulosa de por vida

Remitir para trasplante

Muchas gracias!