Paciente con cirrosis y alteración de conciencia. Diagnóstico diferencial

IV Curso Hepatología General ACHHEP

Santiago, 16 de mayo 2019

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Diferencias en urgencias según estado mental

TABLE 1. Demographics and Clinical Characteristics

	NMS (n = 869), n (%)	AMS (n = 349), n (%)	*P*
Age, mean (SD), y	51.7 (10.6)	52.3 (9.6)	0.373
Sex, female	283 (32.6)	108 (30.9)	0.584
Ethnicity			0.037
African American	216 (24.9)	105 (30.1)	
White	330 (38.0)	134 (38.4)	
Hispanic	247 (28.4)	94 (26.9)	
Other*	76 (8.7)	16 (4.6)	
Cirrhosis etiology			<0.0001
Alcohol	198 (22.8)	114 (32.7)	
Hepatitis C	302 (34.8)	72 (20.6)	
Hepatitis B	32 (3.7)	10 (2.9)	
HCV + HBV	19 (2.2)	12 (3.4)	
HCV + alcohol	194 (22.3)	102 (29.2)	
Cryptogenic	66 (7.6)	27 (7.7)	
Other†	58 (6.7)	12 (3.4)	
CTP Class‡			<0.001
A	235 (27.0)	34 (9.7)	
B	422 (48.6)	139 (39.8)	
C	212 (24.4)	176 (50.4)	

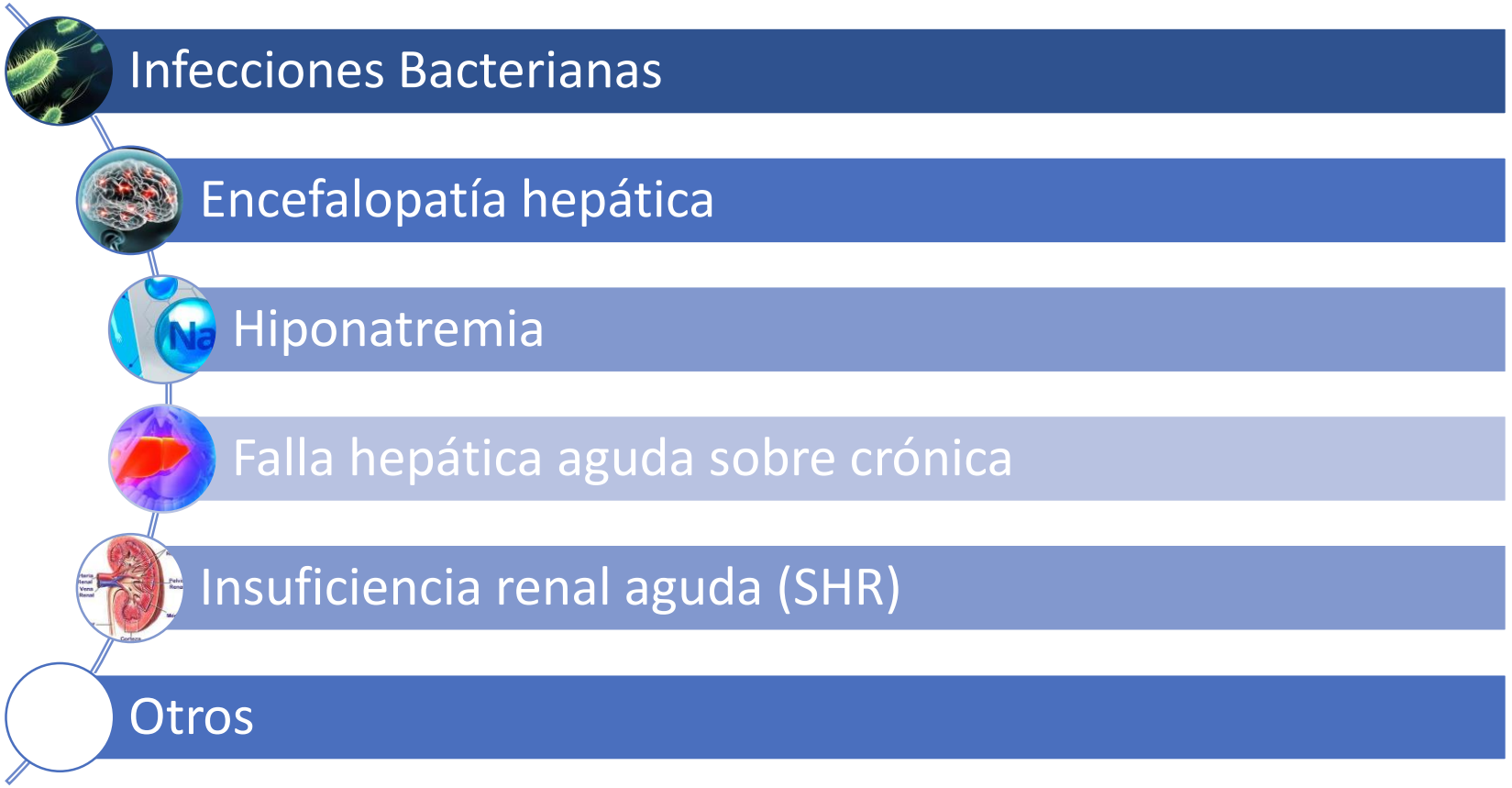
Encefalopatía Hepática

Table 3 Factors that may precipitate hepatic encephalopathy

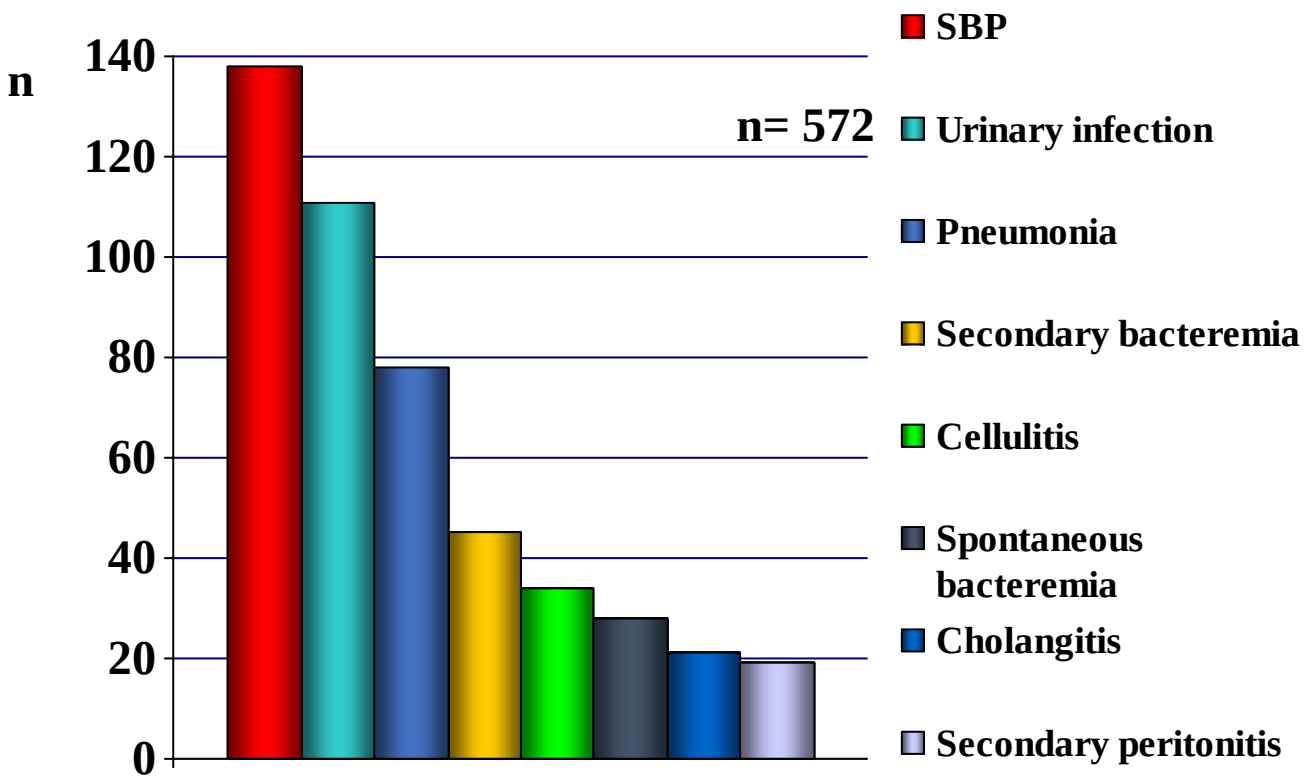
Oral protein load Upper gastrointestinal bleed Constipation	Act through gut factors
Diarrhoea and vomiting Diuretic therapy Abdominal paracentesis	Dehydration; electrolyte and acid/base imbalance (for example, hypokalaemic alkalosis)
Hypoxia Hypotension Anaemia Hypoglycaemia	Adverse effects on both liver and brain
Sedative/hypnotic drugs* Azotaemia† Infection‡ Induction of medical or surgical portal-systemic shunt General surgery	

*Includes drugs acting on the $GABA_A$/benzodiazepine receptor complex.
†Blood urea is a source of intestinal ammonia.
‡May cause dehydration and augmented release of nitrogenous substances.

Compromiso de conciencia: diagnósticos diferenciales en el paciente cirrótico



Type of infection in cirrhosis



Fernández et al. Hepatology 2002

Dificultades Diagnósticas (inf. en el cirrótico):

- Pacientes oligosintomáticos
  - < % de fiebre
  - < % de síntomas y signos urinarios
  - < % de signología respiratoria
  - < % de signos meníngeos (+)
- Disminución síntesis hepática
  - ¿Nivel de corte VHS y PCR?

Examen físico completo (incluyendo la revisión piel)

+

- Hemograma-VHS
- PCR.
- Rx Tórax.
- Orina completa + urinocultivo.
- P. Hepáticas (c/TP e INR) / Creat. y ELP.
- Paracentesis Dg (PMN + GR + cultivo).
- Pancultivar.

Hiponatraemia

- Común en pacientes con cirrosis avanzada:
- Se define arbitrariamente como concentración sérica de sodio <130 mmol / L

  - Aumento de la morbilidad y mortalidad, particularmente complicaciones neurológicas.
  - Disminucion de la sobrevivencia despues del trasplante de Hígado

*Beyond fluid restriction, hypertonic saline should be limited to rare patients with life-threatening complications. It can be considered in patients with severe hyponatraemia who are expected to undergo LT within days. Correction of serum sodium concentration after attenuation of symptoms should be slow (≤8 mmol/L per day) to avoid irreversible neurological sequelae (II-3;1). Albumin can be administered but data are very limited (II-3;2). Use of vaptans should be limited to clinical trials (III;1)
EASL CPG decompensated cirrhosis. J Hepatol 2018;doi: 10.1016/j.jhep.2018.03.024

NEUROIMAGENES EN CH CON ALT MENTAL

TABLE 4. Structural lesion findings.

Neurologic deficits	Head CT scan findings: New infarct, hemorrhage or mass lesion(s) *N* (% total)	Head CT scan findings: Normal *N* (% total)
Aphasia	2 (8)	-
Babinski present	1 (4)	-
CN deficit or facial paresis	6 (24)	-
Decorticate posture	1 (4)	-
Hemiparesis	3 (12)	-
Hemiplegia	2 (8)	-
Seizure	4 (16)	*1 (4)
Unresponsive	5 (20)	-
Total, *N*	**24**	**1**

CN, cranial nerve; CT, computed tomography.
* Initial CT scan was described as normal, but repeat CT scan during the same hospitalization demonstrated a new structural lesion, specifically an intracranial hemorrhage.

AMS Etiology	Odds ratio
HE	0.75
Sepsis/ Infection	0.79
Metabolic	0.78
Drugs/Toxins	3.0
Structural	24.1
Psychiatric	0.56
Multiple causes	0.92

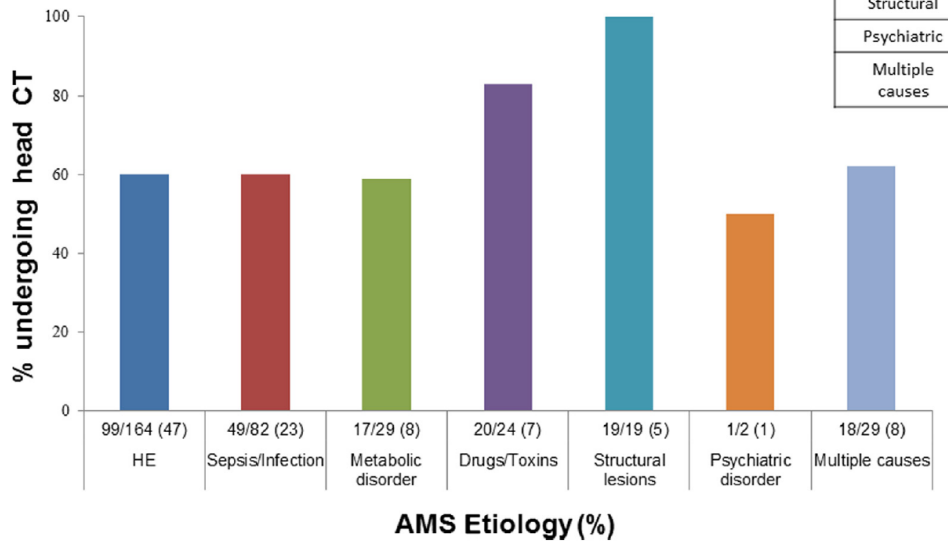


FIGURE 2. *Head computed tomography bar graph*. Shown on the y-axis are the percentage of patients with cirrhosis along with altered m status (AMS) undergoing head computed tomography scan once admitted. Associated etiologies of AMS are also shown on the x-axis. (ratio for an abnormal head CT scan are depicted in the figure legend.

Overuse of Head Computed Tomography in Cirrhosis With Altered Mental Status

Robert S. Rahimi, MD, MS and Don C. Rockey, MD

Conclusions: Nearly two-thirds of patients with cirrhosis along with AMS had head CT scans performed on admission; all patients with a structural lesion on head CT scan had abnormal neurologic examinations. The data suggest that routine brain imaging in patients with cirrhosis that do not have focal neurologic findings is likely not indicated.

Our findings underscore the diminishingly low likelihood of acute intracranial findings on CT in patients with cirrhosis who present only with "AMS" and no evidence of focal neurologic deficits or trauma. Despite deranged hemostatic indices, confusion in cirrhotic patients does not necessarily require a head CT scan to exclude ICH. For the clinician faced with a patient with

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RESUMEN Dg DIFERENCIAL

- DECARTAR DIRIGIDAMENTE :
  - INFECCIONES (NO BASTA CLÍNICA: EXAMENES)
  - IATROGENIA (Fármacos: diuréticos, BZD)
  - ALTERACIÓN RENAL
- CONSIDERAR HIPONATREMIA
- NEUROIMAGENES NO DE PRIMERA LÍNEA EXCEPTO FOCALIDAD NEUROLÓGICA

¿Que tratamiento no farmacológico y farmacológico debo indicar en el paciente con encefalopatía hepática?

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FISIOPATOLOGIA EH

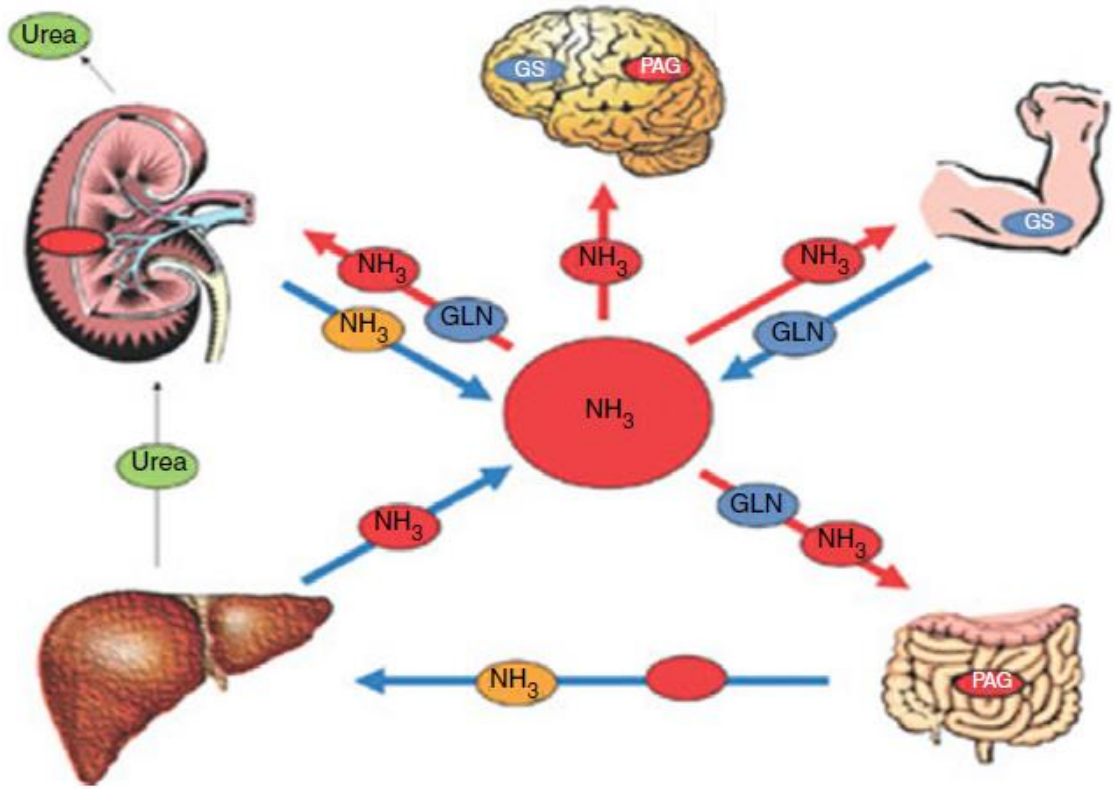
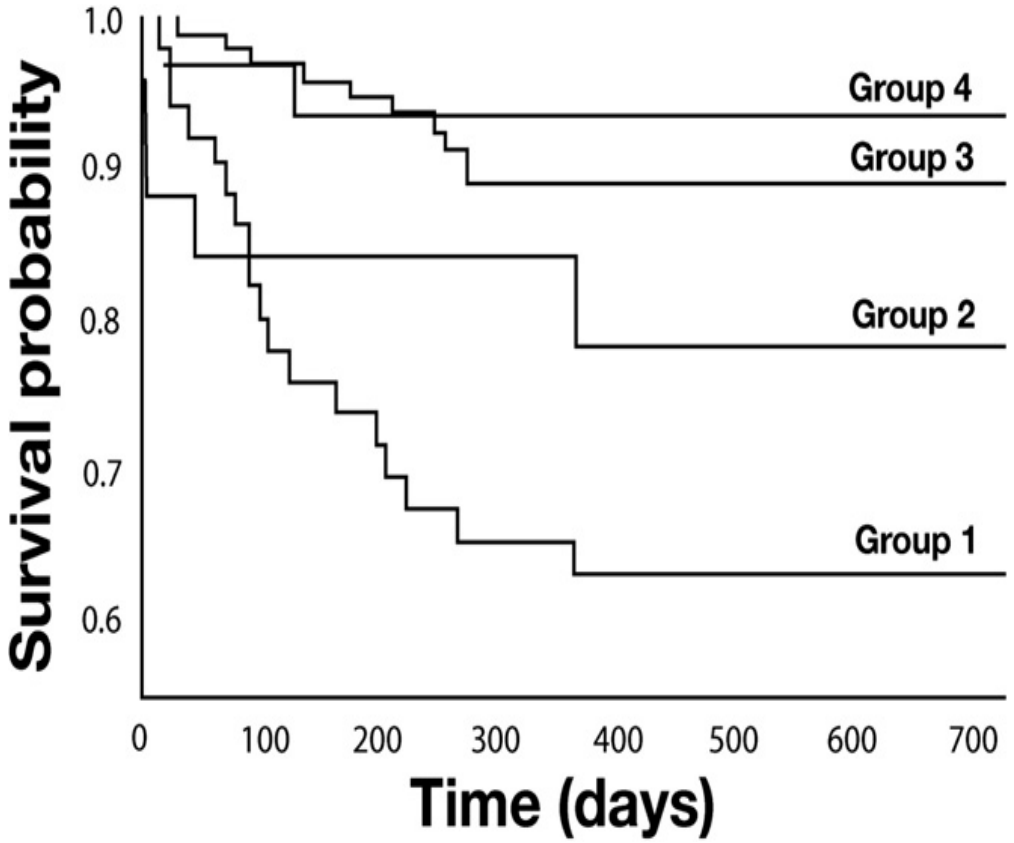


Figura 1 Fisiopatología de la EH. En los pacientes con cirrosis,

Sobrevida en CH según evaluación nutricional



- 65-90% Desnutrición.
- Osteoporosis.
- Déficit de proteínas, vitaminas, minerales.

Nutrition and survival in patients with cirrhosis. Nutrition 2001.

TRATAMIENTO:

- Disacaridos no Absorbibles
  - Lactulosa (Galactosa + Fructosa)
  - Lactitol (Galactosa + Sorbitol)
- Polietilenglicol (PEG)
- Antibióticos
  - Neomicina
  - Metronidazol
  - Vancomicina
  - Rifaximina

Comparación Lactulosa

Table I. Comparison of non-absorbable disaccharides and placebo or no treatment (NT) for hepatic encephalopathy treatment

Trial	Comparison (study design)	No. of patients	Treatment duration	Assessment	Overall efficacy
Uribe et al.[16]	Lactulose and lactitol enema (double-blind, randomized, parallel)	15	≈3 days	Psychometric tests, clinical grading, stool pH, mortality	Lactulose, lactitol > placebo
Horsmans et al.[19]	Lactulose (double-blind, randomized, parallel)	14	2 weeks	Psychometric tests, ammonia levels	Lactulose > placebo
Watanabe et al.[20]	Lactulose (open-label, randomized, parallel)	36	2 months	Psychometric tests, ammonia levels	Lactulose > NT
Dhiman et al.[21]	Lactulose (open-label, randomized, parallel)	26	3 months	Psychometric tests	Lactulose > NT
Prasad et al.[22]	Lactulose (open-label, randomized, parallel)	61	14 months	Psychometric tests, HR-QOL	Lactulose > NT

HR-QOL = health-related quality of life.

Proporción de pacientes con episodios nuevos intratratamiento ~ 20% (vs 45%)

Drugs 2010; 70 (9)

Lactulosa

- Dosis:
  - VO: titulable (20g/30 ml 3-4 v/día).
  - Enemas de retención 300 ml en 700 ml agua cada 4 hrs

- **Efectos Adversos:**
  - **Distensión, flatulencia, nauseas, diarrea (deshidratación y alteración hidroelectrolítica)**

PEG

Tabla 2. Objetivos secundarios del estudio

	Grupo PEG	Grupo lactulosa	Valor p
Cambio promedio de *score HESA* a las 24 h	1,5	0,7	0,002
Tiempo de estadía (días)	4	8	0,07
Tiempo promedio de resolución de EH (días)	1	2	0,01
Amonemia basal (promedio)	146	175	0,19
Amonemia 24 h (promedio)	120	82	0,049
Diferencia amonemia	26	93	0,03

PEG: Polietilenglicol, EH: Encefalopatía hepática.

Conclusiones

En pacientes cirróticos con EH, el uso de PEG en comparación al uso de lactulosa mejoró significativamente el grado de EH en las primeras 24 h, redujo el tiempo necesario para la resolución y eventualmente podría acortar la estadía hospitalaria.

El uso de PEG podría ser una alternativa planteable como tratamiento para EH, dado su amplio uso, disponibilidad, seguridad y baja tasa de efectos adversos.

Gastroenterol. latinoam 2015; Vol 26, Nº 3: 169-172

ANTIBIOTICOS:

Table III. Comparison of neomycin and placebo or lactulose for hepatic encephalopathy (HE) treatment

Trial	Comparison (study design)	No. of patients	Treatment duration	Assessment	Overall efficacy
Strauss et al.[26]	Neomycin vs placebo (double-blind, randomized)	39	≈7 days	Time to HE grade level change	Neomycin ≈ placebo
Orlandi et al.[27]	Neomycin vs lactulose (single-blind, randomized)	173	14 days	Mental status, asterixis score, EEG, ammonia levels, HE change	Neomycin ≈ lactulose
Atterbury et al.[28]	Neomycin vs lactulose (double-blind, randomized)	35[a]	≈7 days	Mental status, asterixis score, EEG, ammonia levels, PSE index	Neomycin ≈ lactulose
Conn et al.[29]	Neomycin vs lactulose (double-blind, randomized, crossover)	29	10 days each arm before crossover	Mental status, asterixis score, EEG, ammonia levels, PSE index	Neomycin ≈ lactulose

a 35 patients, 45 episodes of HE.

PSE = portal systemic encephalopathy.

Drugs 2010; 70 (9)

Antibióticos

- Metronidazol
- Vancomicina

Efectividad Similar a Neomicina

Antibióticos

- Metronidazol

  Neurotoxicidad largo plazo

- Vancomicina

  Alto costo

  Posible sobrecrecimiento bacteriano

  Posibles resistencias bacterianas

Rifaximina

Efectividad similar o superior a lactulosa

Amplio espectro (aerobios y anaerobios Gram (+) y (-))

Mínima presión a resistencia (mutantes poco viables)

Sin sobrecrecimiento de cándida

Absorción sistémica mínima (< 0,4%)

Dosis 400 mg c/ 8 hrs
550 mg c/12 hrs } MAYOR 1 g/día

Table IV. Comparison of rifaximin and disaccharides for hepatic encephalopathy (HE) treatment

Trial	Comparison (study design)	No. of patients	Treatment duration	Assessment	Overall efficacy
Festi et al.[30]	Lactulose (open-label)	21	21 days	Neurological signs of HE, asterixis score, HRNB, EEG, ammonia levels	Rifaximin ≈ lactulose
Bucci and Palmieri[31]	Lactulose (double-blind, double-dummy)	58	15 days	Neurological status, asterixis score, HRNB, cancellation tasks, EEG, ammonia levels	Rifaximin > lactulose
Massa et al.[32]	Lactulose (double-blind, double-dummy)	40	15 days	HE index severity, mental status, cancellation tasks, HRNB, EEG	Rifaximin ≥ lactulose
Fera et al.[33]	Lactulose (double-blind, double-dummy)	40	First 2 weeks of each month × 3 months	Mental status, asterixis score, cancellation tasks, HRNB, EEG, ammonia levels, PSE index	Rifaximin > lactulose
Mas et al.[34]	Lactitol (double-blind, double-dummy)	103	5–10 days	Mental status, asterixis score, EEG, ammonia levels, PSE index, psychometric tests	Rifaximin ≈ lactitol
Leevy and Phillips[35]	Lactulose (crossover)	145	≥6 months lactulose ≥6 months rifaximin	HE grade, asterixis score	Rifaximin > lactulose
Paik et al.[36]	Lactulose (open-label)	54	7 days	Ammonia levels, flapping tremor, mental status, HE index, psychometric tests	Rifaximin ≈ lactulose

HRNB = Halstead-Reitan Neuropsychological Test Battery; **PSE** = portal systemic encephalopathy.

Rifaximina

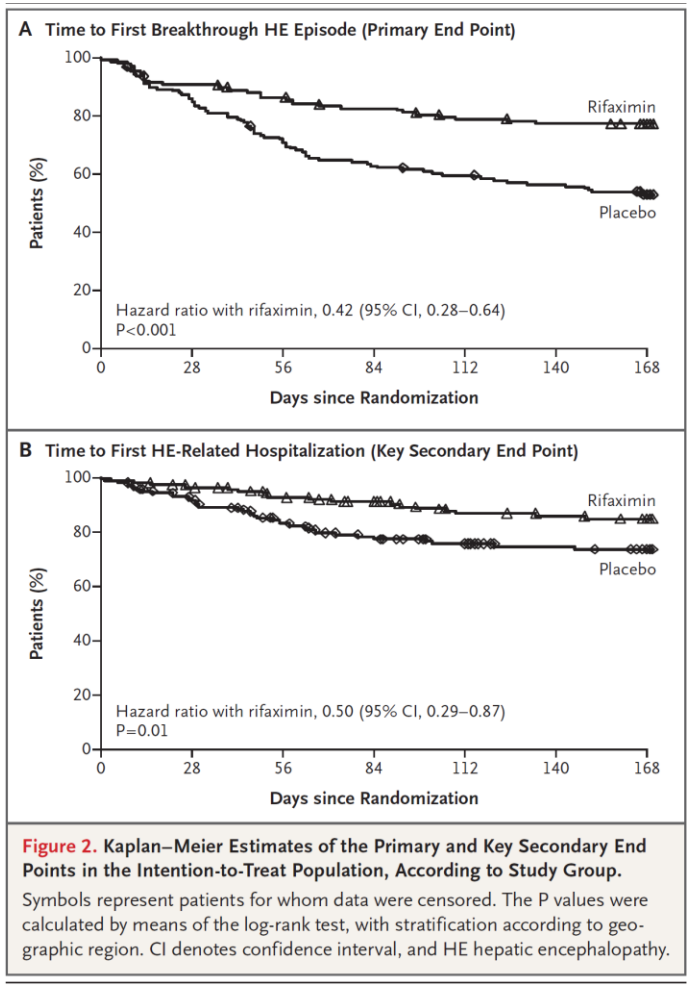


Figure 2. Kaplan–Meier Estimates of the Primary and Key Secondary End Points in the Intention-to-Treat Population, According to Study Group.
Symbols represent patients for whom data were censored. The P values were calculated by means of the log-rank test, with stratification according to geographic region. CI denotes confidence interval, and HE hepatic encephalopathy.

Porcentaje de Pacientes libre de 1° Episodio durante el seguimiento

Porcentaje de Pacientes sin hospitalizarse por EH durante seguimiento

Table 3: Change in simulator outcomes by group

	Rifaximin group (n=21)	Placebo Group (n=21)	P value
Reduced total driving errors	16 (76%)	7 (33%)	0.013
Reduced speeding tickets	17 (81%)	7 (33%)	0.005
Reduced illegal turns	13 (62%)	4 (19%)	0.012
Reduced collisions	9 (43%)	7 (33%)	0.751

Results are presented as numbers with percentage in parentheses. All driving outcon

improved significantly in the rifaximin group compared to placebo apart from collisi

SARCOPENIA y EH

	MHE - (n=32)	MHE + (n=32)	P value
Sex (M/F)	24/8	24/8	1
Age (y)	56.2 ± 9.7	57.2 ± 10.5	0.69
Aetiology (virus/alchol/other)	21/6/5	24/7/1	0.22
MELD	13.3 ± 5.2	14.2 ± 5.7	0.48
Child Pugh class (A/B/C)	15/12/5	6/21/5	0.06
Child Pugh score	7.4 ± 1.9	8 ± 1.7	0.14
Previous HE (no/yes)	28/4	16/16	0.001
Ascites (no/yes)	18/14	9/23	0.02
GI bleeding (no/yes)	24/7	25/6	0.75
Bilirubin (mg/dl)	2.5 ± 2.6	4.1 ± 8.2	0.30
Albumin (g/dl)	3.5 ± 0.5	3 ± 0.6	0.004
INR	1.5 ± 0.4	1.5 ± 0.4	0.83
Sodium (mEq/L)	136.6 ± 3.9	134.8 ± 4.3	0.09
NH3 (µg/dl)	43.5 ± 16.3	63.8 ± 18.1	<0.001
Animal Naming Test (n° of animals)	15.3 ± 5.2	11.4 ± 2.5	<0.001
SMI (cm^2/m^2)	50.7 ± 10.9	41.8 ± 7.7	<0.001
Sarcopenia (no/yes) (%)	22/10 (31)	5/27 (84)	<0.001
Muscle attenuation (HU)	37.2 ± 8.1	29.1 ± 7.4	<0.001
Myosteatosis (no/yes) (%)	28/4 (12.5)	12/20 (62.5)	<0.001

Table 2. The impact of sarcopenia and frailty on the risk of HE

Study	Patient population	Diagnostic test	Prevalence of sarcopenia	Relation to HE
Kalaitzakis et al.[59]	128 patients with cirrhosis	Anthropometry	40%	HE in 46% with malnutrition vs. 27% without malnutrition (*P*=0.03)
Huisman et al.[60]	84 patients with cirrhosis	Jamar hand grip strength	67%	HE in 29% with malnutrition vs. 0% without malnutrition (*P*<0.01)
Meza-Junco et al.[61]	116 patients with HCC being evaluated for LT	Skeletal muscle mass at the third lumbar spine	35%	HE in 23% with sarcopenia vs 12% without sarcopenia (*P*=0.2)
Merli et al.[14]	300 patients with cirrhosis	Anthropometry	48%	Overt HE in 30% with sarcopenia vs. 15% without sarcopenia (*P*=0.003) Minimal HE in 49% with sarcopenia vs. 30% without sarcopenia (*P*=0.001)
Montano-Loza et al.[62]	248 patients with cirrhosis undergoing LT	3rd lumbar spine area	45%	HE in 60% with sarcopenia vs. 49% without sarcopenia (*P*=0.10)
Verna et al.[63]	82 patients on the LT wait list	Fried Frailty Instrument	38%	HE in 65% of frail patients vs. 46% who were not frail (*P*=0.10)
Lai et al.[64]	294 patients on the LT wait list	Fried Frailty Instrument	17%	HE in 26% of frail patients vs. 17% who were not frail (*P*=0.17)

HE, hepatic encephalopathy; HCC, hepatocellular carcinoma; LT, liver transplantation.

https://doi.org/10.3350/cmh.2019.0015

Encefalopatía Persistente

Estudio Angiográfico buscando grandes shunts.

(71% v/s 14%)

Embolizaciones y Coils

Aliment Pharmacol Ther **31,** 537–547

- RESUMEN TRATAMIENTOS:

  - LACTULOSA /PEG
  - Antibióticos (RIFAXIMINA)
  - MANEJO MUSCULAR (al menos intentar)
  - COILS (MANEJO SHUNTS)
  - Varios (Zinc, Probióticos y otras alternativas en evaluación)

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Tabla 1 Opciones terapéuticas en EH

Órgano	Mecanismo	Tratamiento planteado
Hígado	UT-B gen *SLC14A2*	Inhibición por antagonismo de receptores o manipulación génica en su expresión
Músculo	Aumento de GDF-8	Folistatina
	Aumento de la GS	Ejercicio
SNC	Generación de ureagénesis	Acetil-L-carnitina
	Antioxidante potente	Taurina
	Quelantes de manganeso	EDTA y PAS
	Glucólisis infectiva	Inhibición de la folistatina 1
Riñón	UT-A	Aumentar la expresión génica o crear una proteína humanizada *in vitro*
Intestino	Aumentar el tránsito orofecal	Procinéticos
	Disminuir el amonio arterial	Probióticos

EH: encefalopatía hepática; GDF-8: factor de crecimiento y diferenciación 8; GS: glutamina sintetasa; SNC: sistema nervioso central; UT: transportador de urea.