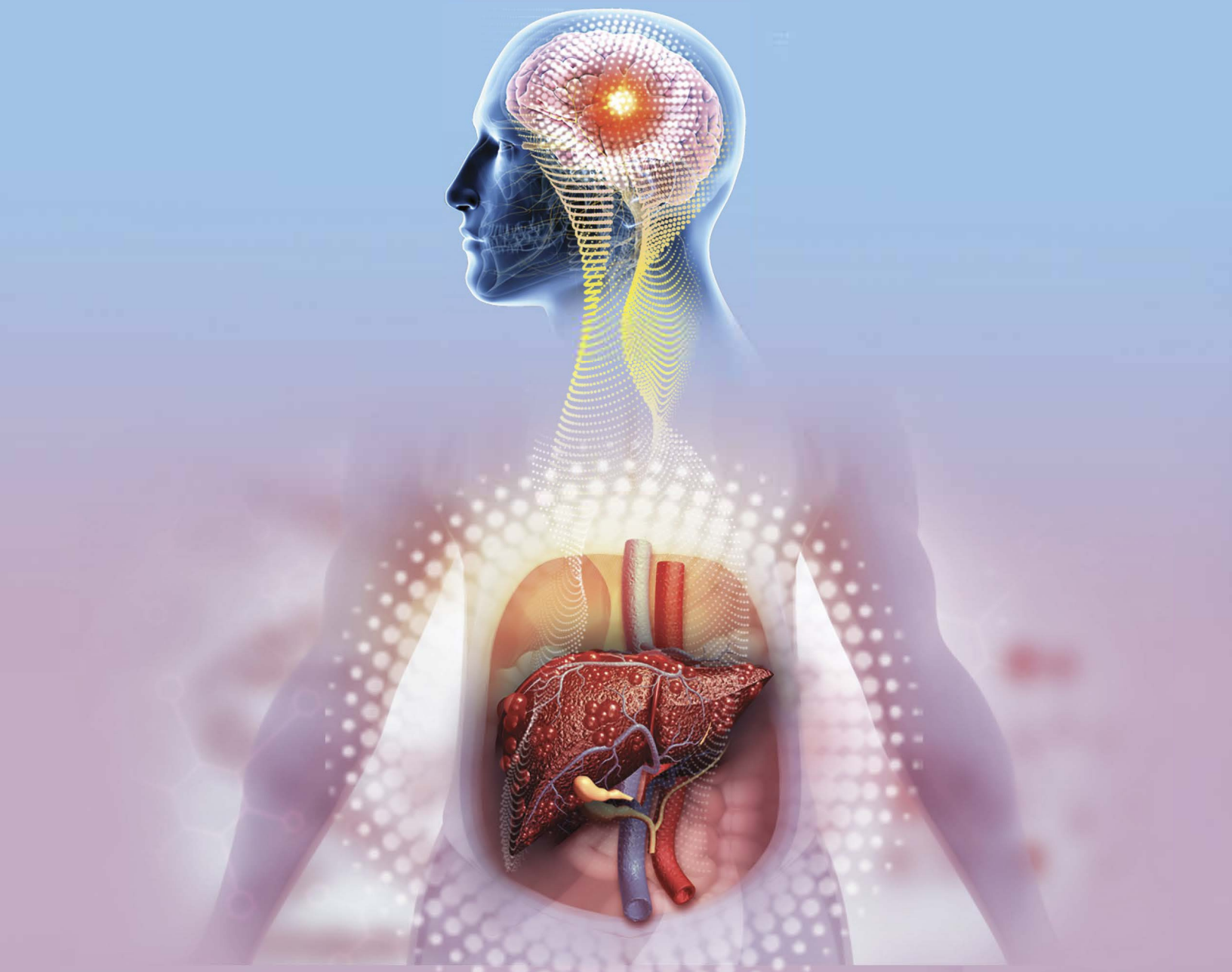

STRATEGIES FOR

Rapid Recognition *and* Effective Management *of* Hepatic Encephalopathy *in* U.S. VETERANS

MED LEARNING GROUP

This activity is provided by Med Learning Group.
This activity is supported by an educational grant from Salix Pharmaceuticals, a division of Bausch Health US, LLC.

Strategies for Rapid Recognition and Effective Management of Hepatic Encephalopathy in U.S. Veterans

PROGRAM CHAIR
Nancy Reau, MD
Professor of Medicine
Richard B. Capps Chair of Hepatology
Chief, Section of Hepatology
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Rush University Medical Center
Chicago, Illinois

PROGRAM OVERVIEW

This educational activity is designed to help clinicians enhance the care of patients with hepatic encephalopathy (HE), with a special emphasis on the U.S. veteran population. The program will explore the pathophysiology, risk factors, and clinical manifestations of HE, provide a comprehensive overview of evidence-based diagnostic strategies, and explore treatment options across the HE continuum, highlighting their application in patient care.

TARGET AUDIENCE

This activity is designed to meet the educational needs of hepatologists, gastroenterologists, hospitalists, and long-term care clinicians.

LEARNING OBJECTIVE

Upon the completion of this program, attendees should be able to:

- Explain the pathophysiology, risk factors, and clinical presentations of HE in U.S. Veterans
- Enhance the speed and accuracy of HE diagnosis in U.S. Veterans
- Summarize the clinical profiles of treatment options for HE in U.S. Veterans

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Faculty Member	Disclosures
Nancy Reau, MD	Discloses that she receives consulting fees from Gilead Sciences, Vir Biotechnology, Arbutus Biopharma, GlaxoSmithKline, and Salix Pharmaceuticals. Additionally, she has done contracted research with Salix Pharmaceuticals, Gilead Sciences, and AbbVie Inc.

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This activity is provided by Med Learning Group.

This activity is supported by an educational grant from Salix Pharmaceuticals, a division of Bausch Health US, LLC.

5 min.	Opening Remarks
25 min.	• **An Overview of HE in U.S. Veterans** ○ Incidence/prevalence of cirrhosis ○ Risk factors and staging of cirrhosis ○ Burden of undiagnosed cirrhosis & its complications in U.S. Veterans ○ Pathophysiology of HE ○ Clinical presentation of HE • **Diagnosing HE in U.S. Veterans** ○ The importance of early and accurate diagnosis of HE ○ Diagnostic guidelines and best practices ○ Diagnostic challenges in U.S. Veterans ○ The spectrum of HE and diagnostic challenges • **Managing HE in U.S. Veterans** ○ Approaches for managing HE ○ MOAs and clinical profiles of current therapies ○ Practical considerations for current treatment options ○ Treatment guidelines and best practices in the VA system ○ Optimizing treatment for overt HE and minimizing risk of recurrence ○ *Whiteboard Animation*: Overview of treatment options for overt HE
20 min.	**Patient Case Studies** • Case 1: 70-year-old male Veteran with cirrhosis and dementia-like symptoms • Case 2: 73-year-old female Veteran with HE responding poorly to treatment
10 min.	**Conclusions and Q&A**

Strategies for Rapid Recognition and Effective Management of Hepatic Encephalopathy in U.S. Veterans

Nancy Reau, MD
Professor of Medicine
Richard B. Capps Chair of Hepatology
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Associate Director, Solid Organ Transplantation
Rush University Medical Center
Chicago, Illinois

Disclosures

- **Dr. Nancy S. Reau** discloses that she receives consulting fees from Gilead Sciences, Vir Biotechnology, Arbutus Biopharma, GlaxoSmithKline, and Salix Pharmaceuticals. Additionally, she has done contracted research with Salix Pharmaceuticals, Gilead Sciences, and AbbVie Inc.
- During the course of this lecture, the presenter may mention the use of medications for both US Food and Drug Administration (FDA)-approved and non-FDA-approved indications
- All relevant financial relationships have been mitigated

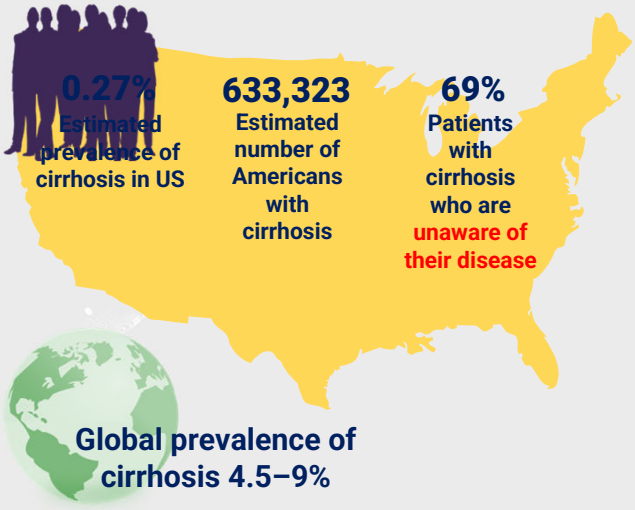
This activity is supported by an educational grant from Genentech, a member of the Roche Group.

Learning Objectives

- Explain the pathophysiology, risk factors, and clinical presentations of HE in US veterans
- Enhance the speed and accuracy of HE diagnosis in US veterans
- Summarize the clinical profiles of treatment options for HE in US veterans

HE = hepatic encephalopathy; US = United States.

Prevalence of Cirrhosis



Compensated cirrhosis often is undetected for long periods of time

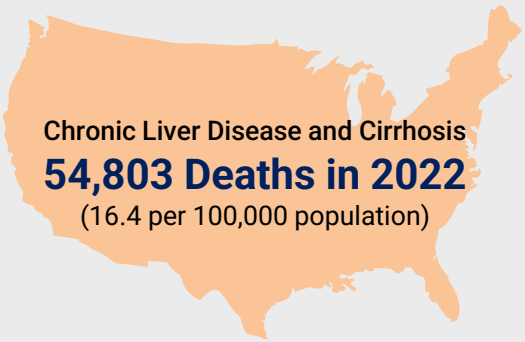
- Most patients remain asymptomatic until decompensation occurs
- Subtle clues may be overlooked
  - Thrombocytopenia
  - Muscle wasting
  - AST>ALT without alcohol consumption
  - Liver enzymes may not be abnormal
- Etiology may not be obvious
  - Prior alcohol use
  - Uncontrolled diabetes mellitus and obesity

ALT = alanine transaminase; AST = aspartate aminotransferase; US = United States.

Scaglione S, et al. *J Clin Gastroeneterol*. 2015;49:690-696. Marcellin P, Kutala BK. *Liver Int*. 2018;38(suppl 1):2-6. Tsochatzis EA, et al. *Lancet*. 2014; 383:1749-1761. Heidelbaugh JJ, Bruderly M. *Am Fam Physician*. 2006;74:756-762.

Background

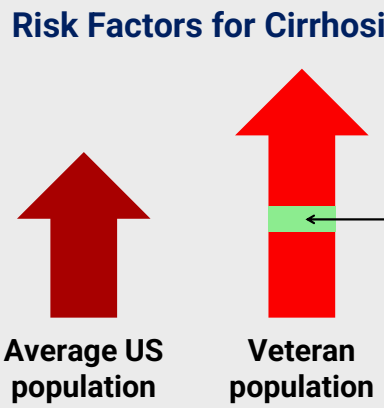
- Combination of chronic liver disease and cirrhosis is the 10th leading cause of death in the US
- In 2022, CDC/NCHS reported 54,803 deaths (16.4 per 100,000 population) attributed to chronic liver disease and cirrhosis
- Epidemiology is changing
  - Direct-acting antivirals have led to declines in HCV-related cirrhosis
  - MAFLD/MASH emerging as leading cause of chronic liver disease and cirrhosis
  - Increasing burden of alcohol-associated liver disease (ALD), which has been worsened during the COVID-19 pandemic



CDC = Centers for Disease Control and Prevention; COVID-19 = corona virus disease 2019; HCV = hepatitis C virus; MAFLD = metabolic dysfunction-associated fatty liver disease; MASH = metabolic-dysfunction-associated steatohepatitis; NCHS = National Center for Health Statistics.

CDC/NCHS. FastStats: Chronic liver disease and cirrhosis (www.cdc.gov/nchs/fastats/liver-disease.htm). Accessed 5/22/25. Dennis BB, et al. *World J Gastroenterol.* 2021;27:4818-4830. Guo Z, et al. *Sci Rep.* 2025;15:7083. Deutsch-Link S, et al. *Dig Liver Dis.* 2022;54:1459-1468. Gao X, et al. *J Hepatol.* 2023;78:16-27.

Undiagnosed Cirrhosis in US Veterans

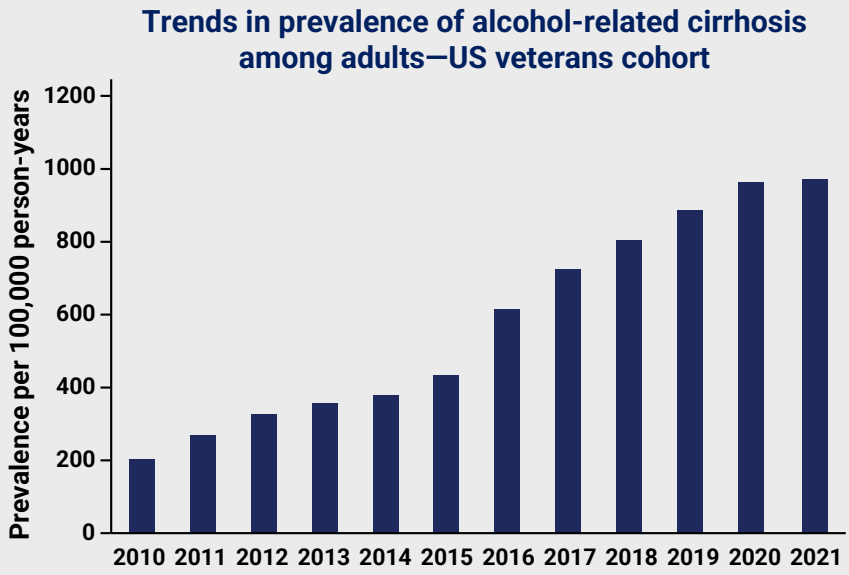


- Veterans in VHA care have increased risk factors for cirrhosis vs the average US population due to higher rates of AUD, metabolic syndrome, and HCV
- Estimates suggest that only **10% of veterans** with risk factors and high FIB-4 are diagnosed with cirrhosis
- VHA does not currently employ standard population-level, risk-based screening for cirrhosis, resulting in potentially missed opportunities and increased impact of cirrhosis complications

AUD = alcohol-use disorder; FIB-4 = Fibrosis 4 (scoring system); VHA = Veterans Health Administration.

Dounel J, et al. *BMC Health Serv Res.* 2025;25:168.

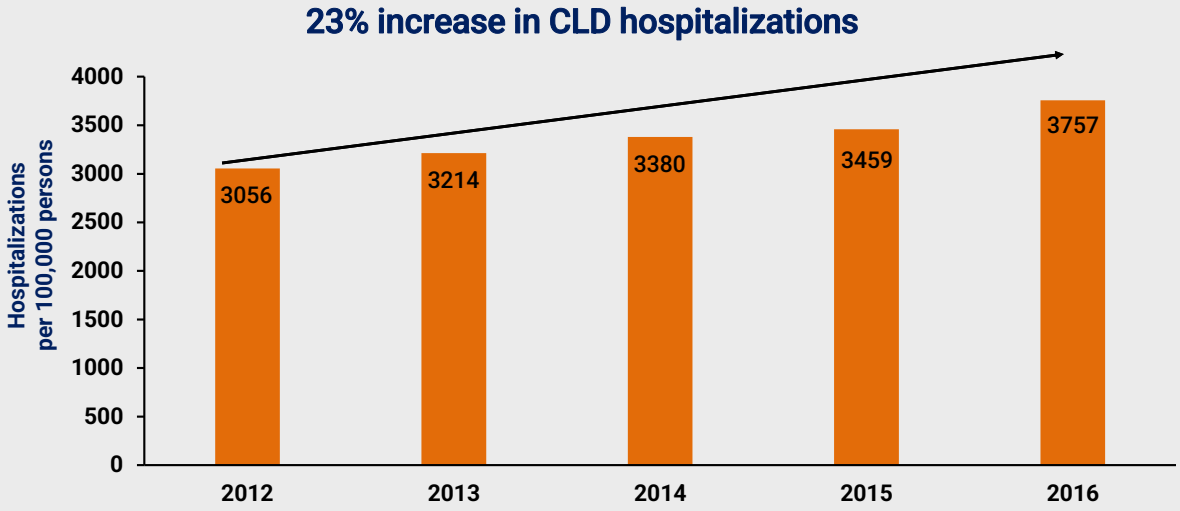
Risk factors for Cirrhosis in US Veterans—Increase in AUD and MAFLD



30–40%
Estimated prevalence of NAFLD/MAFLD in US veterans
Higher burden of cardiometabolic comorbidities (especially obesity, diabetes, and dyslipidemia)

Thrift AP, et al. *Clin Gastroenterol Hepatol*. 2023;21.5:1252-1260.e5. Wong R, et al. *J Hepatol*. 2024.

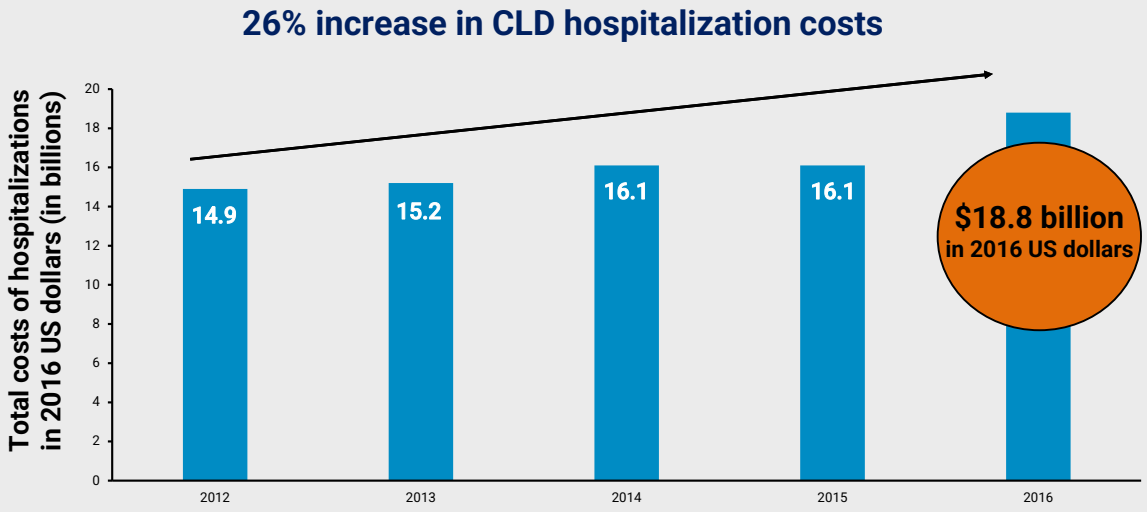
Chronic Liver Disease Hospitalizations in the U.S.



CLD = chronic liver disease.

Hirode G, et al *JAMA Netw Open*. 2020;3:e201997.

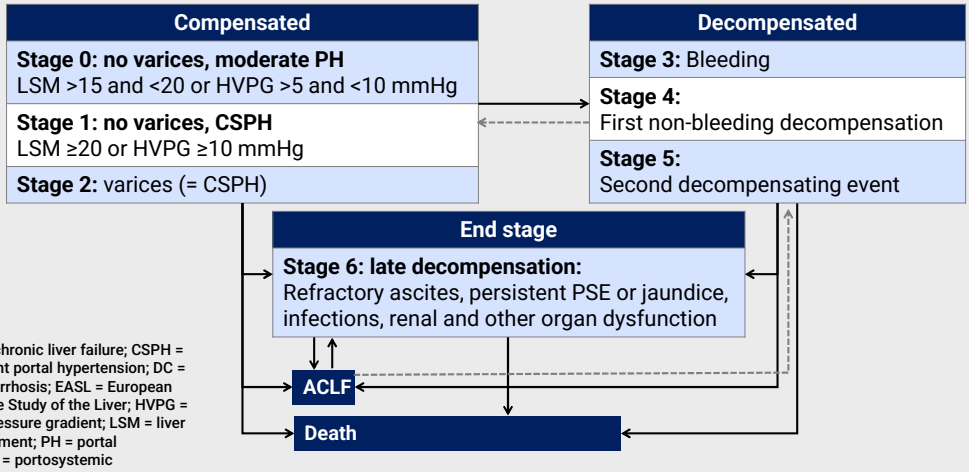
Total Hospitalization Costs for CLD in US



Hirode G, et al *JAMA Netw Open.* 2020;3:e201997.

Multi-stage Model for Clinical Course of Cirrhosis

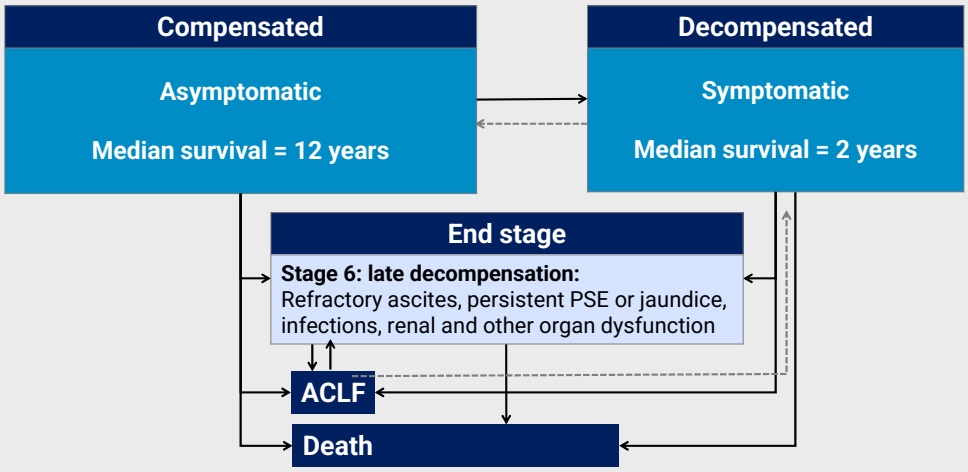
- Transition from compensated cirrhosis to DC occurs at a rate of ~5–7% per year
- DC is a systemic disease, with multi-organ/multi-system dysfunction



ACLF = acute-on-chronic liver failure; CSPH = clinically significant portal hypertension; DC = decompensated cirrhosis; EASL = European Association for the Study of the Liver; HVPG = hepatic venous pressure gradient; LSM = liver stiffness measurement; PH = portal hypertension; PSE = portosystemic encephalopathy.

D'Amico G, et al. *J Hepatol.* 2018;68:563-576. EASL. *J Hepatol.* 2018;69:406-460.

Multi-stage Model for the Clinical Course of Cirrhosis
(Continued)



D'Amico G, et al. *J Hepatol.* 2018;68:563-576. EASL *J Hepatol.* 2018;69:406-460.

The Stages of Cirrhosis and Advanced Chronic Liver Disease

Stages of chronic liver disease	No cirrhosis	Compensated cirrhosis		Decompensated cirrhosis	
		Lower risk of decompensation	Higher risk of decompensation	First decompensation	Further decompensation
Clinical features (ascites, VH, or HE)	None	None	None	One event	>1 event or complication of event
Histological diagnosis	F0–F2	F3/F4 (thin septa)	F4 (thick septa)	Clinical	Clinical
Hemodynamic features (HVPG mmHg)	3–5	5–10	>10 (CSPH)	>20 worse outcomes in VH	>20 worse outcomes in VH
Endoscopic features	None	No varices	± varices	± varices	± varices

Risk of death

Advanced chronic liver disease (ACLD)

Use a NIT!

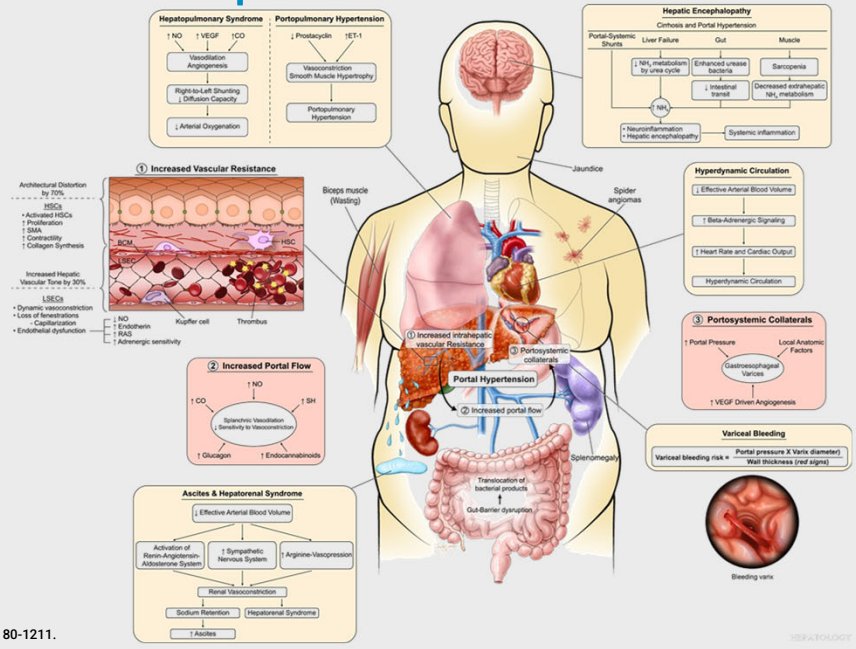
Noninvasive staging of chronic liver disease	No cACLD	Possible cACLD	Highly suggestive of cACLD	cACLD	
Liver stiffness (kPa)	<10	10–15	15–20	20–25	>25
Platelet count (K/mm^3)	NR	NR	If <110 = CSPH	If <150 = CSPH	CSPH

Risk of decompensation

"Because of the strong association with clinical outcomes, patients with compensated cirrhosis should be subclassified into those without and with CSPH during clinical encounters preferentially using noninvasive tests"

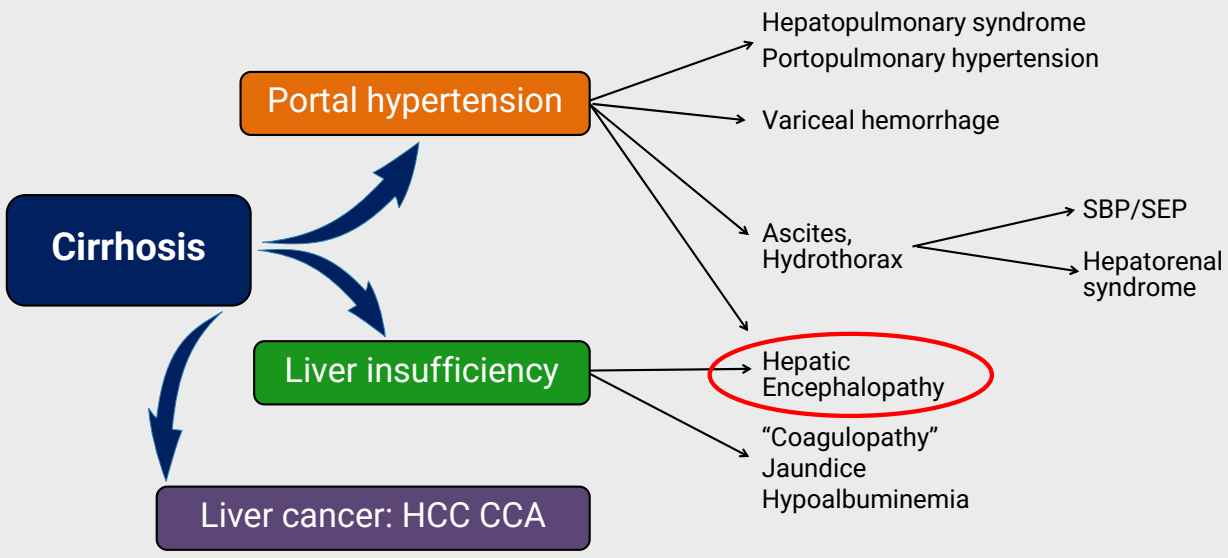
cACLD = compensated ACLD; HE = hepatic encephalopathy; NIT = noninvasive test; VH = variceal hemorrhage;
Kaplan DE, et al. *Hepatology.* 2024;79:1180-1211.

Pathophysiology of Portal Hypertension From Cirrhosis and Related Complications



Kaplan DE, et al. *Hepatology.* 2024;79:1180-1211.

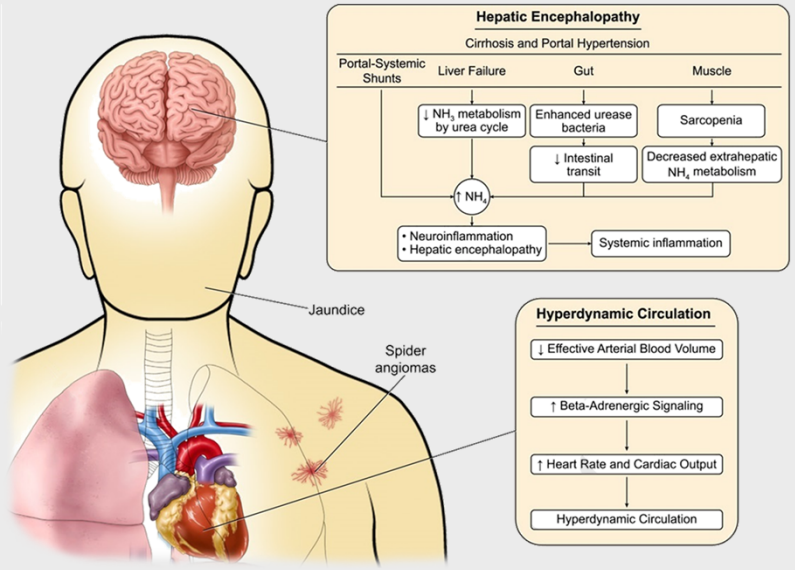
Complications of Cirrhosis



CCA = cholangiocarcinoma; HCC = hepatocellular cancer; SBP = spontaneous bacterial peritonitis; SEP = sclerosing encapsulating peritonitis.

Kaplan DE, et al. *Hepatology.* 2024;79:1180-1211.

Pathophysiology of Portal Hypertension from Cirrhosis and Related Complications: Focus on HE



NH_3 = ammonia; NH_4 = ammonium.

Kaplan DE, et al. *Hepatology*. 2024;79:1180-1211.

Practice Guidelines

FREE!

AASLD PRACTICE GUIDELINE

Hepatic Encephalopathy in Chronic Liver Disease: 2014 Practice Guideline by AASLD and EASL

CONTENTS | RECOMMENDATIONS | FULL TEXT | REFERENCES | WEB SITE

FREE!

Clinical Practice Guidelines

JOURNAL OF HEPATOLOGY

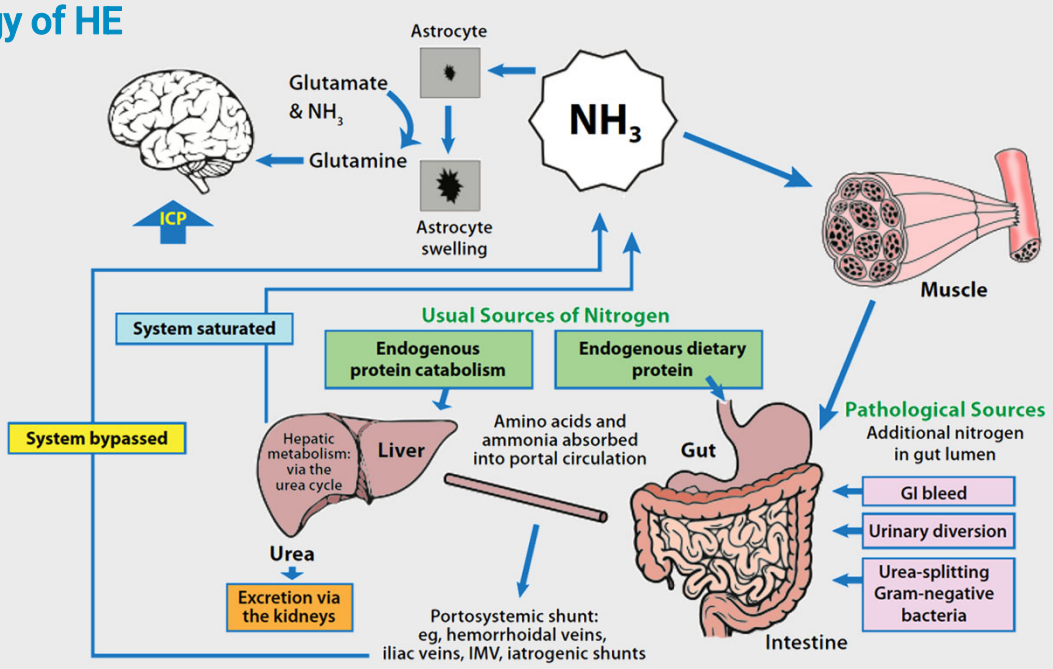
EASL Clinical Practice Guidelines on the management of hepatic encephalopathy☆

European Association for the Study of the Liver*

AASLD = American Association for the Study of Liver Disease.

Vilstrup H, et al. *Hepatology*. 2014;60:715-735. EASL. *J Hepatol*. 2022;77:807-824.

Etiology of HE



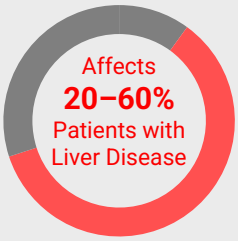
Modified from Reau NS, et al. *Gastroenterol Hepatol*. 2016;12(suppl 5):4-16.

GI = gastrointestinal; ICP = intracranial pressure; IMV = inferior mesenteric vein.

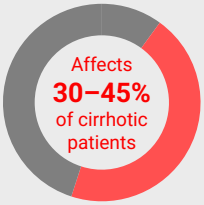
HE Background

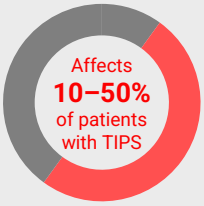
- HE is a chronically debilitating complication of cirrhosis
- A wide spectrum of neuropsychiatric abnormalities in patients with liver disease or portosystemic shunting
- Covert hepatic encephalopathy (CHE) affects approximately 20–60% of patients with liver disease
  - Has been called subclinical encephalopathy or minimal encephalopathy (MHE) in the past
- Overt HE (OHE) occurs in:
  - 30–45% of cirrhotic patients
  - 10–50% of patients with TIPS

Covert hepatic encephalopathy (CHE)



Overt hepatic encephalopathy (OHE)





TIPS = transjugular intrahepatic portosystemic shunt.

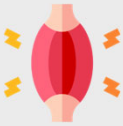
Bass NM, et al. *N Engl J Med*. 2010;362:1071-1081. Guevara M, et al. *Am J Gastroenterol*. 2009;104:1382-1389. Mas A. *Digestion*. 2006;73(suppl 1):86-93. Bajaj JS, et al. *Gastroenterology*. 2010;138:2332-2340.

HE Background
(Continued)

- HE can lead to a variety of disturbances, including impairment of quality of life (QoL), impairment of social and work functions, and coma or death

Patients may present with:

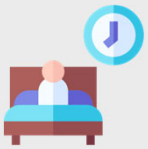
Reports of mental or personality changes from family or friends



Asterixis

Decreased energy level

Impaired cognition, consciousness, or motor function



Impaired sleep-wake cycle

Mullen KD, et al. *Semin Liver Dis*. 2007;27:32-48. Conn HO, Bircher J, eds. *Hepatic Encephalopathy: Syndromes and Therapies.* Medi-Ed Press;1994:1099-1100.

Overlap of Dementia and HE in US Veterans

Many US veterans in VHA care, but even outside the VA, have comorbid conditions that affect cognitive function, in addition to risk factors for cirrhosis

Among veterans with cirrhosis, concomitant dementia is common and challenging to distinguish clinically from HE

Undiagnosed cirrhosis among veterans with dementia can increase possibility that cognitive impairment may be due to reversible HE

VA = Veterans Administration.

Bajaj JS, et al. *JAMA Netw Open*. 2024;7:e2353965. Adejumo A, et al. 2023. *Am J Gastroenterol*. 2023;118:475-480. O'Malley KA, et al. *Public Policy Aging Rep*. 2020;30:19-23.

FIB-4 Score Testing Can Help Detect Missed or Undiagnosed Cirrhosis With HE in US Veterans

- Prevalence of undiagnosed cirrhosis is higher in non-white and Hispanic patients, urban vs rural veterans, patients with more comorbidities, and patients with AUD and viral hepatitis
- Combination of high FIB-4 scores and other risk factors for liver disease in patients with dementia raises possibility that **HE could be a modifiable factor associated with cognitive impairment**

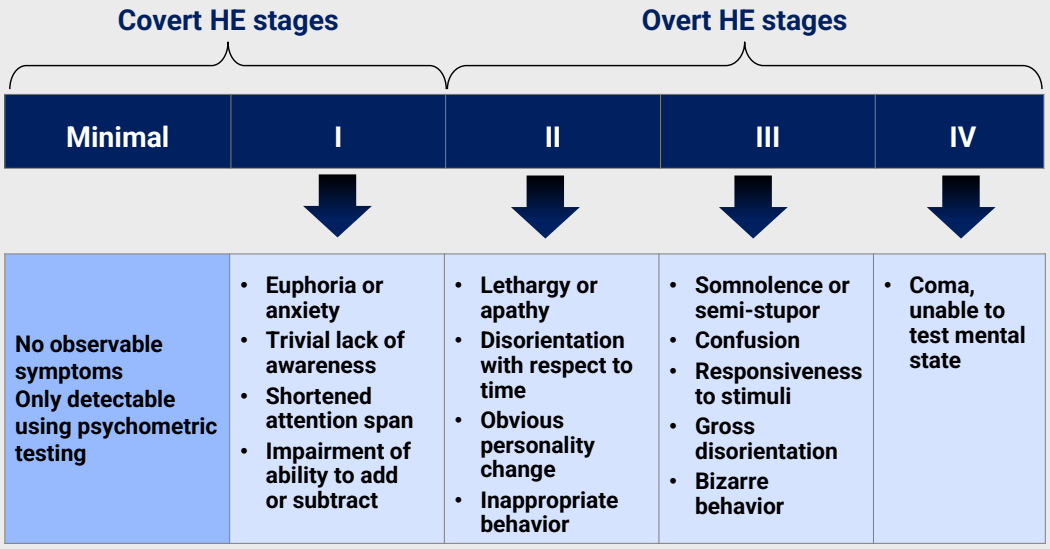
AUDIT-C = Alcohol Use Disorders Identification Test; CI = confidence interval; HIV = human immunodeficiency virus; OR = odds ratio.

Bajaj JS, et al. *JAMA Netw Open*. 2024;7:e2353965.

Logistic regression for overall cohort with dementia

Variable	FIB-4 score >3.25		FIB-4 score >2.67	
	OR (95% CI)	*P* -value	OR (95% CI)	*P* -value
Age (capped at 65 years)	1.07 (1.06–1.09)	<.001	1.09 (1.08–1.10)	<.001
Race, White (vs all others)	0.79 (0.73–0.85)	<.001	0.80 (0.76–0.85)	<.001
Ethnicity—Hispanic (vs all others)	1.08 (0.99–1.17)	.12	1.04 (0.97–1.11)	.28
Rural residence (vs urban)	0.92 (0.87–0.97)	.002	0.93 (0.90–0.97)	.001
Gender, male	1.43 (1.26–1.61)	<.001	1.51 (1.38–1.64)	<.001
Body mass index	0.97 (0.97–0.98)	<.001	0.98 (0.97–0.98)	<.001
Comorbidities				
Charlson Comorbidity Index	1.07 (1.06–1.09)	<.001	1.04 (1.03–1.05)	<.001
Chronic kidney disease	1.11 (1.04–1.17)	.002	1.12 (1.07–1.17)	<.001
Hypertension	1.10 (1.04–1.17)	.003	1.03 (0.98–1.08)	.22
Diabetes	0.78 (0.73–0.84)	<.001	0.77 (0.73–0.81)	<.001
Hyperlipidemia	0.84 (0.79–0.89)	<.001	0.89 (0.85–0.93)	<.001
Stroke	0.85 (0.79–0.91)	<.001	0.88 (0.83–0.92)	<.001
Peripheral vascular disease	1.04 (0.98–1.10)	.19	1.07 (1.07–1.12)	.004
Sleep apnea	0.99 (0.92–1.06)	.83	0.98 (0.92–1.03)	.42
Head injury	0.95 (0.80–1.09)	.44	0.92 (0.81–1.03)	.13
Congestive heart failure	1.48 (1.43–1.54)	<.001	1.52 (1.48–1.56)	<.001
Hepatitis B or C	1.79 (1.66–1.91)	<.001	1.79 (1.69–1.89)	<.001
Problem drinking, AUDIT-C	1.56 (1.44–1.68)	<.001	1.41 (1.32–1.50)	<.001
Tobacco use disorder	0.78 (0.70–0.87)	<.001	0.77 (0.71–0.84)	<.001
HIV	0.87 (0.56–1.18)	.39	1.11 (0.87–1.35)	.39
Major depressive disorder	0.96 (0.91–1.02)	.20	0.96 (0.92–1.00)	.06
Posttraumatic stress disorder	0.93 (0.86–1.00)	.05	0.92 (0.86–0.97)	.001
Regions (vs Northeast)				
Continental	0.99 (0.92–1.07)	.81	1.00 (0.95–1.06)	.92
Midwest	0.84 (0.77–0.91)	<.001	0.79 (0.74–0.84)	<.001
Pacific	1.07 (0.99–1.15)	.09	1.04 (0.99–1.10)	.14
Southeast	1.07 (1.00–1.14)	.05	1.09 (1.04–1.14)	.001

HE Symptoms Can Be Subtle and Should Be Considered in Any Patient With Cirrhosis



Modified from Reau NS, et al. *Gastroenterol Hepatol*. 2016;12:4-16.

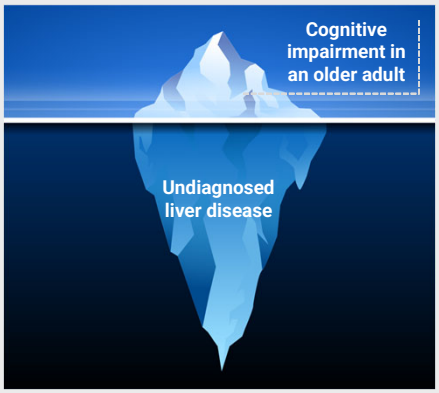
Diagnosis of HE

- Recognize patients at risk—diagnosis is clinical
- Exclude alternative etiologies
  - Biochemical studies and imaging to **exclude**
  - Consider cerebral imaging
- Identify precipitating factors
- Gauge response to therapy
  - Grade encephalopathy

Reau NS, et al. *Gastroenterol Hepatol.* 2016;12(suppl 5):4-16.

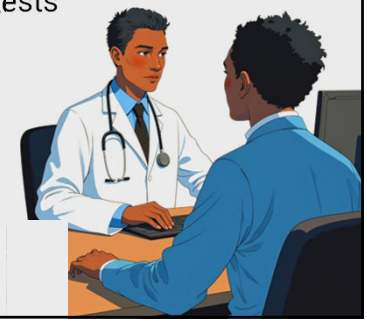
Misdiagnosis and Underdiagnosis of HE

- Misdiagnosis and underdiagnosis of HE due to overlap with MCI, dementia, or delirium in patients with undiagnosed liver disease
- Another potential contributor to undiagnosed HE is minimal HE that is missed due to lack of testing, even in cases of known liver disease



Patient with minimal hepatic encephalopathy

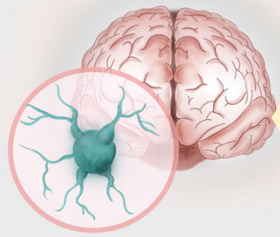
- No evidence of mental impairment
- Signal from psychometric or neuropsychological tests



MCI = mild cognitive impairment.

Bloom PP. *Clin Transl Gastroenterol.* 2025;16:e00784.

Precipitating Factors for HE



Increased ammonia production

GI hemorrhage

Excessive dietary protein

Blood transfusion

Electrolyte imbalance (eg, hyponatremia, hypokalemia)

Constipation

Portosystemic shunts

Spontaneous

Iatrogenic (eg, TIPS)

Other

Drugs (eg, opioids, benzodiazepines)

Infections (eg, UTI, SBP)

Malignancy (eg, hepatoma)

UTI = urinary tract infection.

Vilstrup H, et al. *Hepatology*. 2014;60:715-735.

Role of Ammonia Testing in HE

"Increased blood ammonia alone does not add any diagnostic, staging, or prognostic value for HE in patients with CLD. A normal value calls for diagnostic reevaluation (Grade II-3, A, 1)."

Ammonia level >200 µmol/L is predictive of poor outcome in acute liver failure

Vilstrup H, et al. *Hepatology*. 2014;60:715-735. Bernal W, et al. *Hepatology*. 2007;46:1844-1852.

Differential Diagnosis of HE Compared With Other Common Neurological Conditions in Patients with Cirrhosis

Recommendation

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

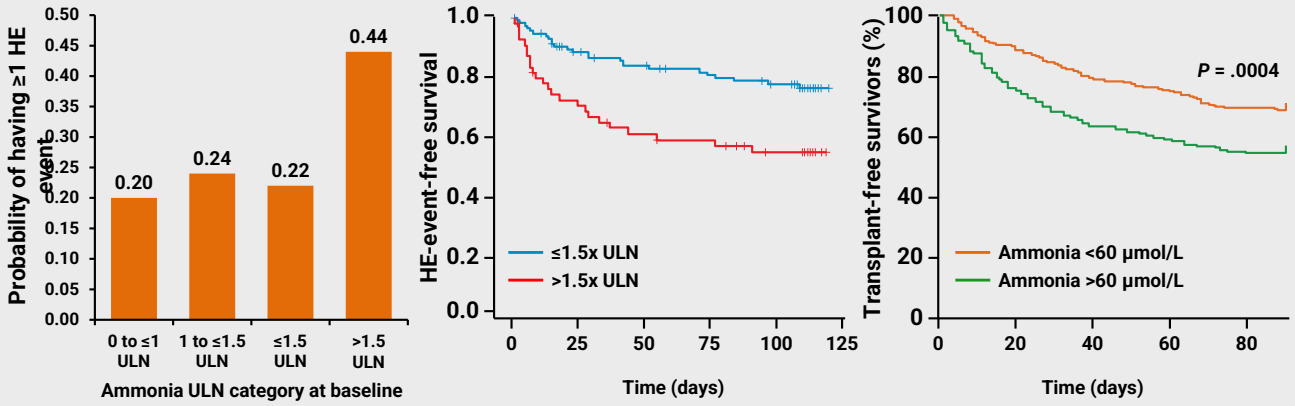
Condition	Brain regions involved	Clinical symptoms/ classic manifestations	Validated neurological tests for diagnosis
HE	Basal ganglia	Vary by severity, but include: ▪ Altered sleep patterns ▪ Lethargy or apathy ▪ Confusion ▪ Personality changes ▪ Inappropriate behavior ▪ Asterixis ▪ Coma	West Haven Criteria (minimal and grades 1–4) ▪ Minimal HE – No gold standard – Tests include psychometric HE score, Animal Naming Test, EncephalApp Stroop Test Sickness Impact Profile, and Inhibitory Control Test ▪ Overt HE: ≥grade 2
Mild cognitive impairment	Hippocampus is smaller in size compared with healthy individuals	Changes in cognitive function	DSM-5 criteria: ▪ Modest decline in ≥1 cognitive domain ▪ Decline in cognitive test performance ▪ Insufficient to interfere with IADLs ▪ Not from delirium or other disorders Brief cognitive assessment: ▪ Calibrated to maximize sensitivity ▪ Patients with positive results should undergo further evaluation ▪ Tests include ACE-R, CERAD, CDT, Memory Alteration Test, MiniCog, MMSE, MoCA, and Qmci screen
Dementia (Alzheimer disease)	Cerebral cortex (amyloid plaque) Hippocampus (neurofibrillary tangle within pyramidal neuron, smaller in size vs healthy individuals) Basal forebrain (cholinergic neurons)	Declining cognitive function, comprehension, judgment, memory, and self-control	DSM-5 criteria: ▪ Substantial decline in ≥1 cognitive domain ▪ Decline in cognitive test performance ▪ Interferes with IADLs ▪ Not exclusively from delirium or other disorder ▪ Cognitive assessments same as mild cognitive impairment
Delirium	Frontal lobe Limbic system	Acute change in menial status, with altered consciousness and decrease in ability to focus coupled with cognitive changes or development of perceptual disturbance	DSM-5 criteria: ▪ Disturbed attention, awareness, and cognition ▪ Developed acutely from baseline ▪ Not explained by neurocognitive disorder ▪ Direct physiological consequence of another medical condition

ACE-R = Addenbrooke Cognitive Examination-revised; CDT = Clock Drawing Test; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition; IADL = instrumental activities of daily living; LoE = level of evidence; MMSE = Mini-Mental State Examination; MoCA = Montreal cognitive Assessment; Qmci = Quick Mild Cognitive Impairment.

Bloom PP. *Clin Transl Gastroenterol.* 2025;16:e00784.
EASL. *J Hepatol.* 2022;77:807-824.

Hyperammonemia is Associated with Clinical Events

Fasting blood ammonia predicts risk and frequency of hepatic encephalopathy episodes in patients with cirrhosis



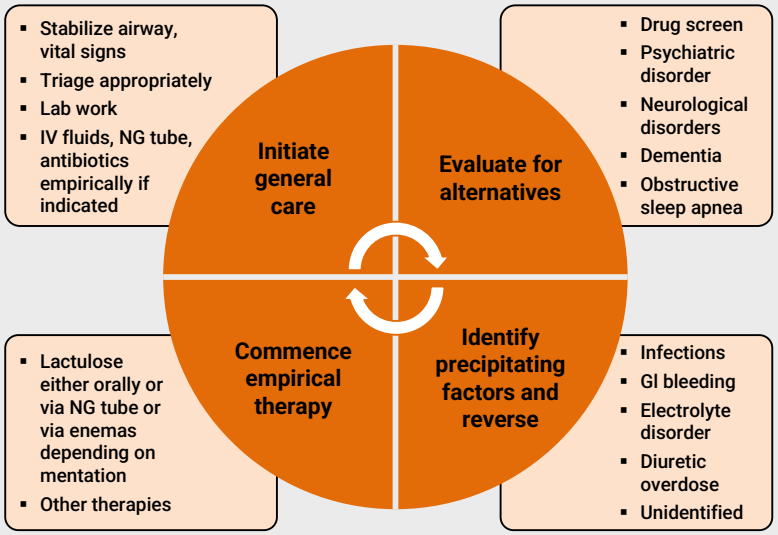
Admission serum ammonia associated with 90-day transplant-free survival in hospitalized patients with acutely decompensated cirrhosis

ULN = upper limit of normal.

Vierling JM, et al. *Clin Gastroenterol. Hepatol.*, 2016;14:903-906.e.1. Patwardhan VR, et al. *J Clin Gastroenterol*. 2016;50:345-350.

Four-Pronged Approach to HE

1. **Initiation of care** for patients with altered consciousness
2. **Alternative causes** of AMS should be sought and treated
3. Identification of **precipitating factors** and their correction
4. Commencement of **empirical HE treatment**



AMS = altered mental status; IV = intravenous. NG = nasogastric.

Vilstrup H, et al. *Hepatology.* 2014;60:715-735. Acharya C, Bajaj JS. *Am J Gastroenterol.* 2018;113:1600-1612.

FDA-Approved Treatment Options for HE

Drug name	Drug class	Mechanism of action
Lactulose	Poorly absorbed disaccharide	▪ Decreases blood ammonia concentration – Promotes elimination of NH_3 – Fermentation by bacteria acidify colon and prevent absorption – Reduces urease-producing bacteria
Rifaximin	Non-aminoglycoside semi-synthetic, nonsystemic antibiotic	▪ Decreases blood ammonia concentration – Broad spectrum antibiotic; results in a change in bowel flora – May cause downregulation of intestinal glutaminase activity

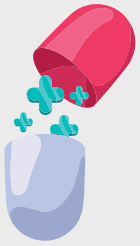
Reau, NS. *Gastroenterol Hepatol*. 2023;19:740-748. Lactulose prescribing information (PI), 4/2025 (www.drugs.com/pro/lactulose.html). Rifaximin (Xifaxan®) PI, 10/2023 (https://shared.salix.com/globalassets/pi/xifaxan550-pi.pdf). Accessed 5/22/25.

We will now watch a brief animation overviewing treatment options for HE

Mechanisms of Anti-Amyloid Therapeutics in Alzheimer's

https://youtu.be/LbXUHnPf7R4

Practical Considerations for Use of Lactulose in HE



Dosage/administration

- Administered orally by mouth or through a nasogastric tube or via retention enemas
- Initiated at 25 mL every 1–2 hours to achieve ≥2 soft or loose stools per day

Safety

- Key side effects include abdominal distension, cramping, diarrhea, electrolyte changes, and flatulence

Reau, NS. *Gastroenterol Hepatol*. 2023;19:740-748. Mullen KD, et al. *Semin Liver Dis*. 2007;27:32-48. Vilstrup H, et al. *Hepatology*. 2014;60:715-735. Patidar KR, Bajaj JS. *Clin Gastroenterol Hepatol*. 2015;13:2048-2061. Lactulose PI, 4/2025 (www.drugs.com/pro/lactulose.html). Accessed 5/22/25.

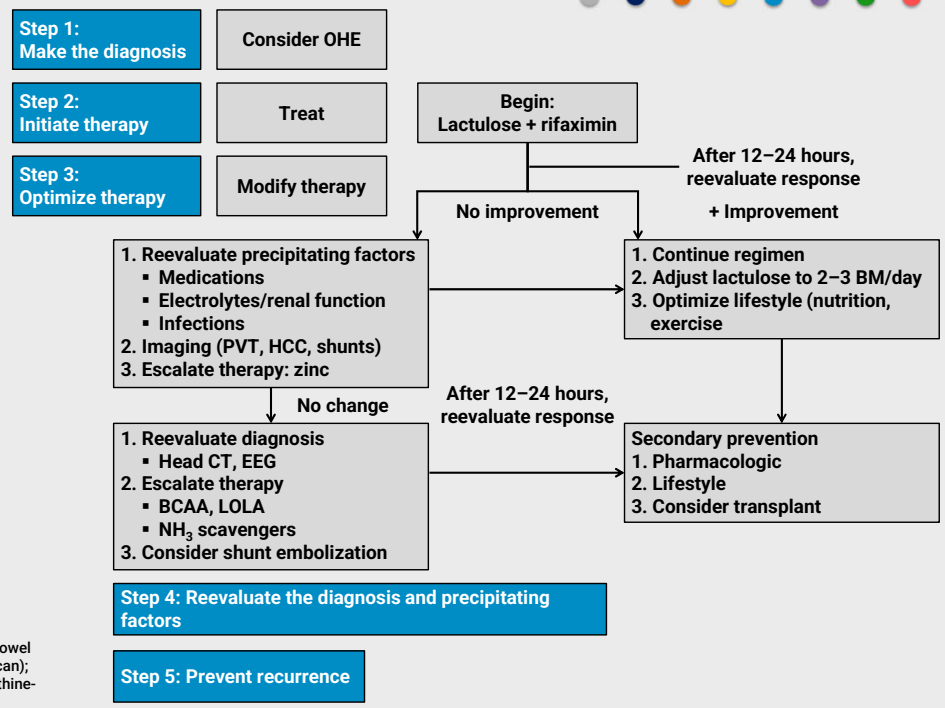
Practical Considerations for Use of Rifaximin in HE

Description	Indication	Safety
▪ Minimally absorbed (<0.4%) oral antibiotic ▪ Broad-spectrum in vitro activity against aerobic and anaerobic enteric bacteria	▪ 550 mg BID for reduction in risk of OHE in patients ≥18 years of age	▪ No clinical drug interactions reported ▪ No dosing adjustment required in patients with liver disease or renal insufficiency

BID = twice daily.

Reau, NS. *Gastroenterol Hepatol*. 2023;19:740-748 . Mullen KD, et al. *Semin Liver Dis*. 2007;27:32-48. Vilstrup H, et al. *Hepatology*. 2014;60:715-735. Patidar KR, Bajaj JS. *Clin Gastroenterol Hepatol*. 2015;13:2048-2061. Rifaximin (Xifaxan®) PI, 10/2023 (https://shared.salix.com/globalassets/pi/xifaxan550-pi.pdf). Accessed 5/22/25.

Optimizing Therapy for OHE

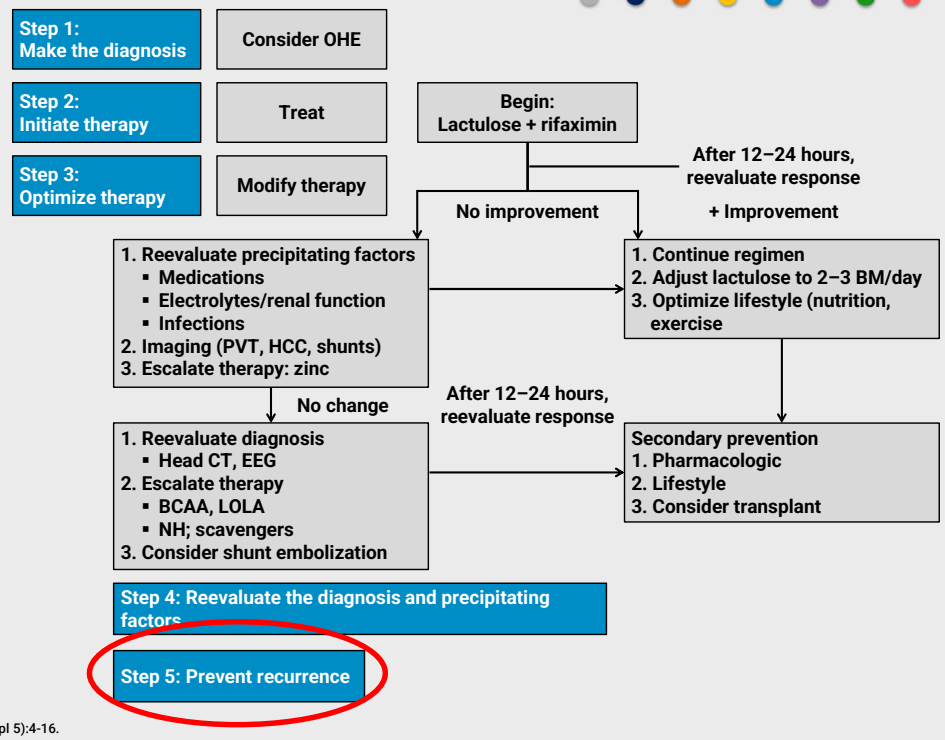


Lactulose:
20–30 gm QID—titrate to 2/3 BM
Enema: 300 mL (200 g) in 1 liter

BCAA = branched-chain amino acids; BM =bowel movements; CT = computed tomography (scan); EEG = electroencephalogram; LOLA = L-ornithine-L-aspartate; PVT = portal vein thrombosis.

Reau NS, et al. *Gastroenterol Hepatol.* 2016;12(suppl 5):4-16.

Optimizing Therapy for OHE (Continued)



Lactulose:
20–30 gm QID—titrate to 2/3 BM
Enema: 300 mL (200 g) in 1 liter

Reau NS, et al. *Gastroenterol Hepatol.* 2016;12(suppl 5):4-16.

Once Overt HE Occurs, Patients Have Increased Risk of Recurrence

40% risk of Overt HE recurrence at **1 year** after first episode

40% risk of **another Overt HE recurrence within 6 months**, despite lactulose treatment

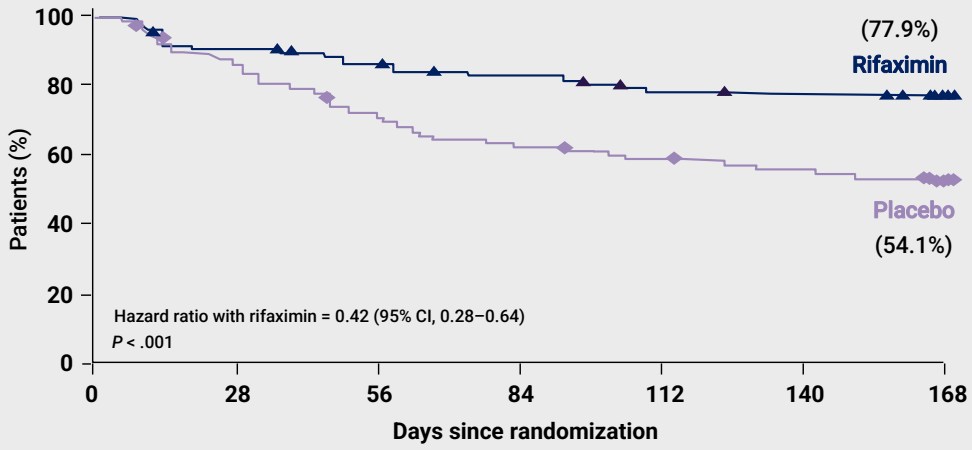
Prescribing appropriate therapy is important to help reduce the risk of HE-related readmissions

In a study that assessed continuation and initiation of appropriate therapies for reduction in risk of HE recurrence upon discharge in patients with HE

59% of patients (n = 1429/2420) were prescribed **lactulose alone or no HE therapy at discharge**

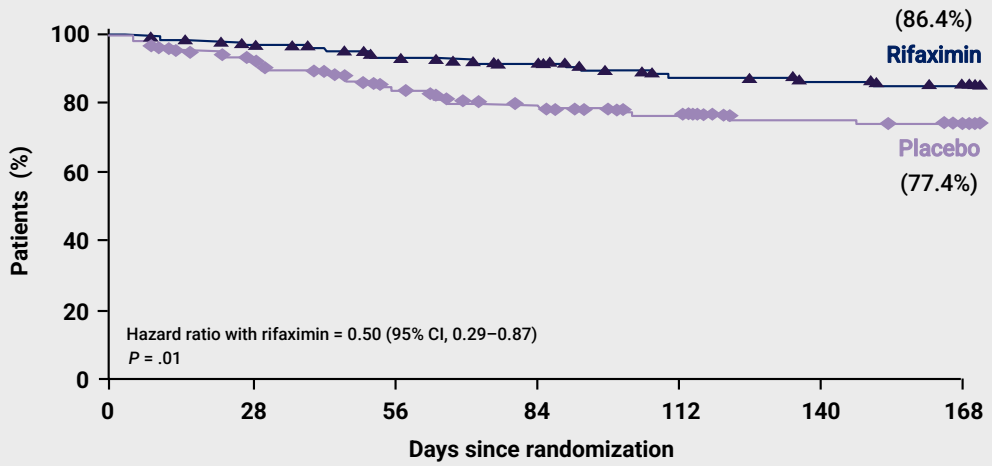
Vilstrup H, et al. *Hepatology*. 2014;60:715-735. Bajaj JS, et al. *Aliment Pharmacol Ther*. 2019;49:1518-1527.

Rifaximin Treatment in OHE: Time to First Breakthrough Episode
(Primary Endpoint)



Bass NM, et al. *N Engl J Med*. 2010;362:1071-1081.

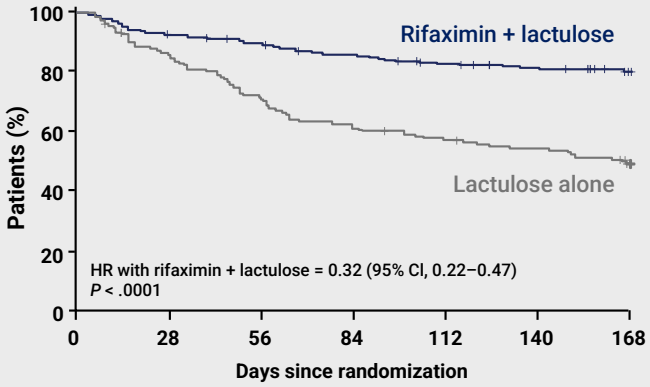
Rifaximin Treatment in OHE: Time to First HE-Related Hospitalization
(Key Secondary Endpoint)



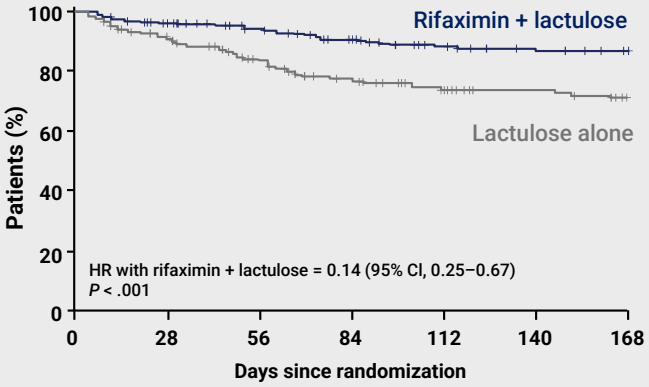
Bass NM, et al. *N Engl J Med.* 2010;362:1071-1081.

Rifaximin + Lactulose vs Lactulose Alone for Reducing Risk of HE Recurrence

Time to first breakthrough overt HE episode



Time to first HE-related hospitalization



HR = hazard ratio.

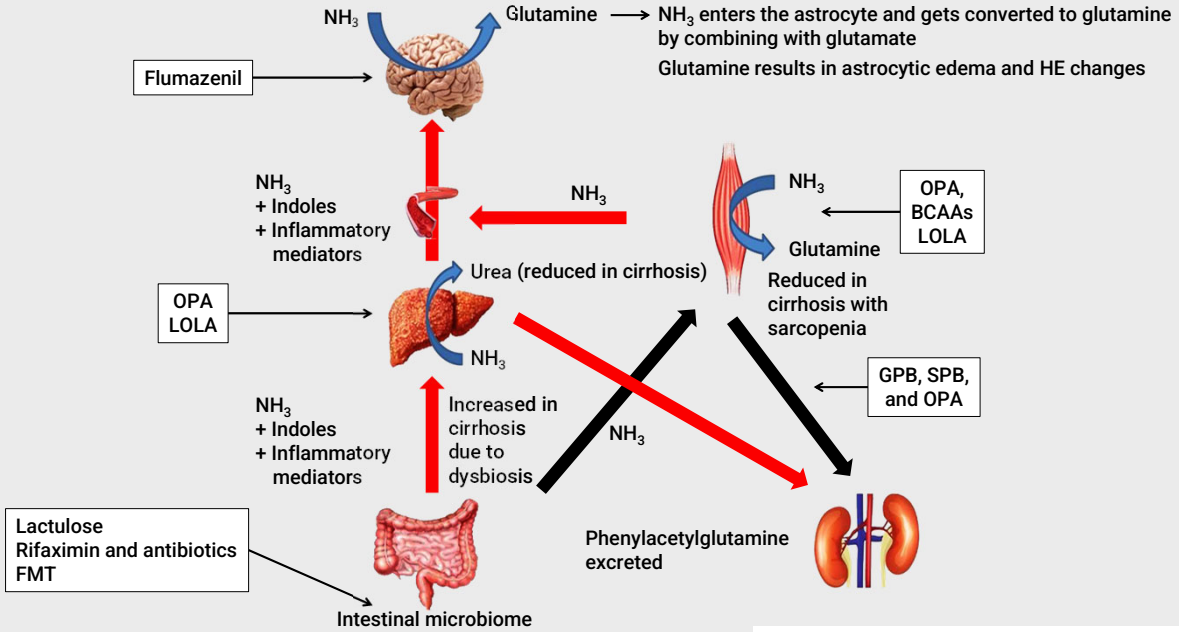
Sanyal AJ, et al. *Hepatol Commun.* 2024;8:e0436.

Rifaximin for HE: Criteria for Use in VA System

Inclusion criteria: The answers to one of the following must be fulfilled in order to meet criteria
Refractory to lactulose (Select both to be eligible)
☐ Patient has had recurrent or persistent hepatic encephalopathy despite receiving lactulose at a dose that obtains 2–3 loose stools per day.
☐ Both endpoints (recurrent or persistent symptoms of hepatic encephalopathy and number of loose stools per day) are documented in patient's medical record.
Intolerance to lactulose (Select both to be eligible)
☐ Patient being treated with lactulose for recurrent or persistent hepatic encephalopathy and experiencing ≥4 loose stools per day despite lactulose dosage reductions
☐ Both endpoints (number of loose stools per day and dosage adjustments) are documented in the patient's medical record
Nonadherence to lactulose (Select both to be eligible)
☐ Patient experiencing recurrent or persistent hepatic encephalopathy secondary to nonadherence of lactulose despite provision of patient education on more than one visit regarding the importance of adherence
☐ Both endpoints (recurrent or persistent symptoms of hepatic encephalopathy and repeated efforts in patient education) are documented in the patient's medical record

Criteria for rifaximin for treatment of chronic HE in chronic liver disease. 2016 (www.va.gov/formularyadvisor/DOC_PDF/Rifaximin_for_Hepatic_Encephalopathy.pdf). Accessed 5/22/25.

Areas of Action for Different Therapies in Cirrhosis and HE



Modified from Acharya C, Bajaj JS. *Am J Gastroenterol*. 2018;113:1600-1612.

FMT = fecal microbiota transplant; GPB = glycerol phenylbutyrate; OPA = ornithine phenylacetate; SPB = sodium phenylacetate

Case 1: Pete

Pete is a 70-year-old male veteran with cirrhosis and dementia-like symptoms

Presentation
- Pete presents to the clinic after a recent car accident
- He was evaluated in the ED and was found to be confused

Past medical history
- Pete has a history of PTSD, HTN, and HLD

Family history
- No liver disease in Pete's family

Clinical notes
- No alcohol use
- Recent PCP visit for memory loss and confusion after he was unable to find his car after shopping at Walmart with his wife

ED = emergency department; HLD = hyperlipidemia; HTN = hypertension: PCP = primary care provider; PTSD = post-traumatic stress disorder.

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Case 1: Physical Exam

Pete's physical examination is notable for the following findings

- **Skin exam:** multiple ecchymotic areas, concerning for falling
- **HEENT:** mild icterus
- **Abdomen:** no ascites, tender from seat-belt injury
- **Neuro:** mild asterixis

HEENT = head, eyes, ears, nose, throat.

Case 1: Pete's Lab Values and Test Results

WBC	3.2
Hb	11.3
PLT	119
Na	138
Total bilirubin	2.7
Albumin	3.4
INR	1.2
AST	46
ALT	32
Glucose	119
HbA1c	5.4
Creatinine	0.6
Alcohol	Negative
MELD/MELD-Na/MELD 3.0 scores	12/14/14

Urine analysis	+nitrites, +WBC

CXR	Normal

Hepatitis Bs Ag	Negative
Hepatitis C Ab	Negative

CT abdomen	Cirrhosis, PHT, no ascites, no mass
CT head	Mild cerebral atrophy

Ab = antibody; CXR = chest x-ray; Hb = hemoglobin; HbA1c = glycated hemoglobin; hepatitis BsAg = hepatitis B surface antigen; INR = International Normalized Ratio; MELD = model for end-stage liver disease; PHT = portal hypertension; PLT = platelets; WBC = white blood (cell) count.

Case 1: Question 1

Based on Pete's presentation and clinical workup, what is his likely diagnosis?

a) Alcohol use disorder
b) Multi-infarct dementia
c) Hepatic encephalopathy
d) Urinary tract infection

Case 1. Question 2

A repeat urinalysis and culture confirms that Pete has an *e. coli* urinary tract infection

In addition to treating the UTI, what do you recommend next for Pete?

a) Begin lactulose
b) Begin rifaximin
c) Refer for liver transplantation
d) Nothing other than reassess in 3 months

Case 1: Follow-Up and Question 3

- You advise Pete to begin lactulose therapy and to stop driving and schedule a return visit in 2 weeks
- On his return, Pete has stopped lactulose due to GI side effects but is now complaining of trouble sleeping at night and being tired during the day
- His wife also notes that he seems a little distracted during the day

What treatment would you consider now for Pete?

a) Resume lactulose at a lower dose
b) Resume lactulose and start rifaximin
c) Start rifaximin and stop the lactulose
d) Have Pete start a benzodiazepine for sleep

Secondary Prophylaxis

Recommendations

- Lactulose is recommended as secondary prophylaxis following a first episode of overt HE, and should be titrated to obtain 2–3 bowel movements per day **(LoE 1, strong recommendation, 96% consensus)**
- Rifaximin as an adjunct to lactulose is recommended as secondary prophylaxis following >1 additional episodes of overt HE within 6 months of the first one **(LoE 2, strong recommendation, 92% consensus)**

EASL. *J Hepatol.* 2022;77:807-824.

Secondary Prophylaxis

- In a patient with overt HE, recurrent episodes are common and therefore therapy is recommended to continue unless there is clear improvement in liver function or nutritional status or the precipitant factors is well controlled

Recommendation

- In patients with a history of overt HE with improvement of liver function and nutritional status and in whom precipitant factors have been controlled, discontinuation of anti-HE therapy should be considered on an individual basis **(LoE 5, weak recommendation, 77% consensus)**

EASL. *J Hepatol.* 2022;77:807-824.

HE and Driving Is Controversial

- Driving simulation studies and on-road driving tests show that patients with cirrhosis and HE have been shown to exhibit problems with vehicle handling, adaptation, cautiousness, lane-keeping, brake usage, and are more likely to need intervention from an instructor to avoid accidents
- **Still, stable well-controlled HE may not be a contraindication to driving**
- If patients want to resume driving, they should schedule a formal driving reassessment with the local authorities based on local regulations

Recommendation

- Patients who have had an episode of overt HE should be provided with information on the risks associated with driving and on the appropriateness of formal driving assessment with the relevant authorities **(LoE 5, strong recommendation, 100% consensus)**

EASL. *J Hepatol.* 2022;77:807-824.

Case 1: Question 4

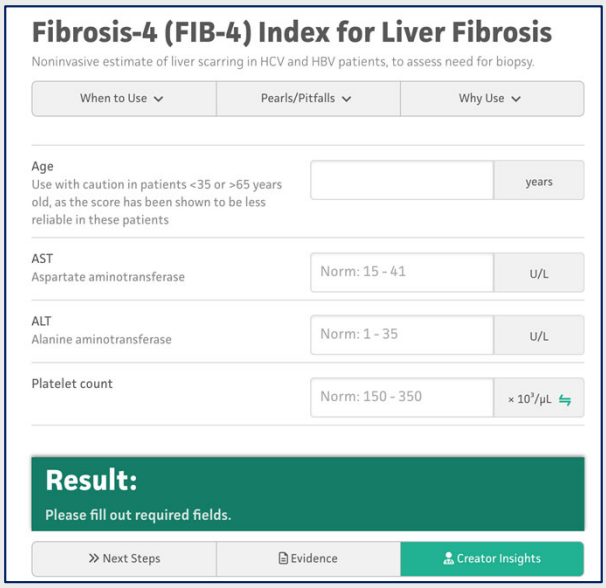
Should Pete have additional neurocognitive testing?

a) No, he clearly has cirrhosis with hepatic encephalopathy

b) The history of PTSD increases the chance that he has Wilson Disease

c) He has risk for dementia, and testing for concomitant neurocognitive disease is important

FIB-4 Can Be Used to Assess Liver Damage

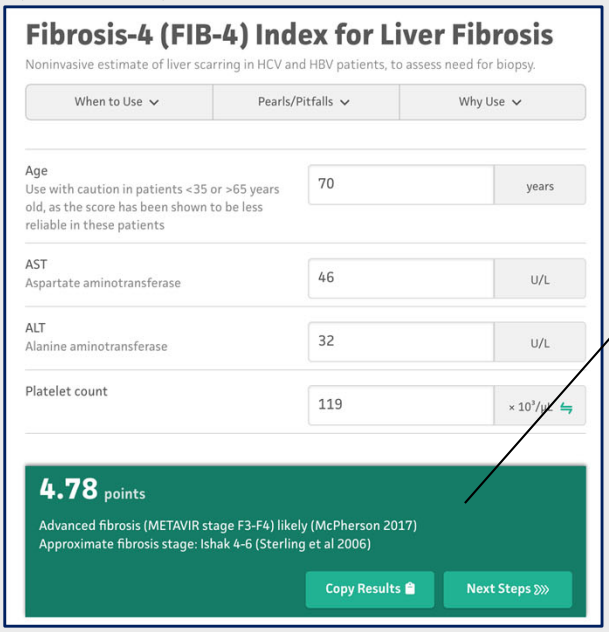


FIB-4	Approximate fibrosis	
<1.45	0–1	No referral needed
1.45–3.25	2–3	(Indeterminate) Refer
>3.25	4–6	(High) Refer

(Please note: Fib4 in patients under 35 yrs old and over 65 can be unreliable)

FIB-4 Index for liver fibrosis (www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). Accessed 5/22/25.

FIB-4 Can Be Used to Assess Liver Damage
(Continued)



FIB-4	Approximate Fibrosis	
<1.45	0–1	No referral needed
1.45–3.25	2 to 3	(Indeterminate) Refer
>3.25	4 to 6	(High) Refer

(Please note: Fib4 in patients under 35 yrs old and over 65 can be unreliable)

After 65 use a cut off of > 2.0

FIB-4 Index for liver fibrosis (www.mdcalc.com/calc/2200/fibrosis-4-fib-4-index-liver-fibrosis). Accessed 5/22/25.

Case 2: Marge

Marge is a 73-year-old female veteran with HE

Presentation

- Marge was admitted to the ICU after her family was unable to wake her up to join them at breakfast

Past medical history

- Alcohol-associated cirrhosis complicated by ascites controlled with diet and diuretics
- Prior hospital admissions for hepatic encephalopathy
- Evaluated for liver transplantation but deferred due to age and frailty

Clinical notes

- No alcohol use x 5 years
- Compliant with lactulose/rifaximin/zinc
- Recent EGD G2 esophageal varices and evidence of prior banding

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EGD = esophagogastroduodenoscopy; ICU = intensive care unit.

Case 2. Physical Exam

Marge's physical examination is notable for the following findings

- **Skin exam:** spiders and palmer erythema
- **HEENT:** mild icterus
- **Abdomen:** +splenomegaly; no ascites
- **Neuro:** responds to pain only

Case 2: Marge's Lab Values and Test Results

WBC	5.4
HB	9.2
PLT	57
Na	136
Total bilirubin	1.7
Albumin	2.9
INR	1.2
AST	46
ALT	32
Glucose	97
Creatinine	1.6
Alcohol	Negative
MELD 3.0 score	17

Urine analysis	Negative
CXR	Normal
Hepatitis Bs Ag	Negative
Hepatitis C Ab	Negative
Tox screen	Negative
CT head	No bleeding
Diagnostic para	75 WBC 152 RBC

para = paracentesis; RBC = red blood (cell) count.

Case 2: Question 1

Based on Marge's presentation and clinical workup, what is the likely reason for her HE?

a) Lactulose noncompliance
b) Rifaximin noncompliance
c) Dietary protein intake
d) Portosystemic shunting

Case 2: CT Scan

Marge had a CT scan performed

- No HCC
- Extensive portosystemic collaterals

Case 2: Question 2

What should you consider next to manage Marge's HE?

a) Add sodium benzoate
b) Increase lactulose until HE is controlled
c) Supplement diet with BCAA
d) Embolization of portosystemic shunting

Spontaneous Portosystemic Shunts (SPSSs)

- SPSSs: communications among venous portal system and venous systemic circulation that bypass the liver
  - Definition is not always consistent between studies
  - Global percentage of SPSSs estimated to be between 34–42%
  - Baveno VI Cooperation Group
    - 1729 patients with liver cirrhosis
    - 60% with SPSSs and 47% of the SPSS group classified as large SPSSs (≥8 mm)
- Associated with significant reduction of hepatic reserve over 5 yrs
  - Initially a compensatory mechanism, as PH progresses, the shunt increases in size, worsening the bypass effect and contributing to the deterioration of liver function

Vidal-González J, et al. *Therap Adv Gastroenterol.* 2020;13:1756284820961287. Simón-Talero M, et al. *Gastroenterology.* 2018;154:1694-1705.e4.

EASL Clinical Practice Guidelines on Management of Hepatic Encephalopathy

Recommendation

- Obliteration of accessible portal-systemic shunts in patients with cirrhosis with recurrent or persistent HE (despite adequate medical treatment) can be considered in stable patients with a MELD score <11 **(LoE 4, weak recommendation, 100% consensus)**

EASL. *J Hepatol.* 2022;77:807-824.

SPSS Embolization

- SPSS: protective effect → decrease in the rate of ascites, varices, and gastrointestinal bleeding with large SPSSs especially with HE
- 46–71% of patients with recurrent and/or persistent HE large SPSSs

- Shunt embolization
  - 60% free of neurological symptoms 3 months post-embolization and 49–55% after 1–2 years
  - Secondary increase in PVP can worsen other PH-related complications

PVP = portal venous pressure.

Vidal-González J, et al. *Therap Adv Gastroenterol.* 2020;13:1756284820961287.

Conclusion

- Hepatic encephalopathy is a key sign of end-stage liver disease
- Ammonia measurement should be used when diagnosis is questionable
- HE is readily treatable, and active interventions can improve quality of life and decrease hospital admission rates
- Rifaximin, combined with lactulose, is first line in OHE management
- Continue therapy that controlled OHE for secondary prophylaxis

Overview of Hepatic Encephalopathy

Resource	Address
Adejumo A, Noll A, Rogal SS, et al. Dementia frequently coexists with hepatic encephalopathy but not other cirrhosis complications in US Veterans. *Am J. Gastroenterol*. 2023;118:475-480.	https://pubmed.ncbi.nlm.nih.gov/36649134/
Bajaj JS, Silvey SG, Rogal S, et al. Undiagnosed cirrhosis and hepatic encephalopathy in a national cohort of veterans with dementia. *JAMA Netw Open*. 2024;7:e2353965.	https://pubmed.ncbi.nlm.nih.gov/38294815/
Bloom PP. The misdiagnosis and underdiagnosis of hepatic encephalopathy. *Clin Transl Gastroenterol*. 2025;16:e00784.	https://pubmed.ncbi.nlm.nih.gov/39635997/
CDC/National Center for Health Statistics. FastStats: Chronic Liver Disease and Cirrhosis. Last Reviewed: November 6, 2023	https://www.cdc.gov/nchs/fastats/liver-disease.htm
D'Amico G, Morabito A, D'Amico M, et al. Clinical states of cirrhosis and competing risks. *J Hepatol*. 2018;68:563-576.	https://pubmed.ncbi.nlm.nih.gov/29111320/
Deutsch-Link S, Curtis B, Singal AK, et al. Covid-19 and alcohol associated liver disease. *Dig Liver Dis.* 2022;54:1459-1468.	https://pubmed.ncbi.nlm.nih.gov/35933291/
Dounel J, Lamorte C, Patton H, et al. Screening high-risk Veterans for cirrhosis: Taking a stepwise population health approach. *BMC Health Serv Res.* 2025;25:168.	https://pubmed.ncbi.nlm.nih.gov/39875981/
Hanson C, Goacher EK. Hepatic encephalopathy in patients with cirrhosis: Key clinical considerations for the nurse practitioner and physician assistant. *J Am Assoc Nurse Pract*. 2025;37:173-181.	https://pubmed.ncbi.nlm.nih.gov/39932441/
Hirode G, Saab S, Wong RJ. Trends in the burden of chronic liver disease among hospitalized US adults. *JAMA Netw Open*. 2020;3:e201997.	https://pubmed.ncbi.nlm.nih.gov/32239220/
Kaplan DE, Ripoll C, Thiele M, et al. AASLD practice guidance on risk stratification and management of portal hypertension and varices in cirrhosis. *Hepatology*. 2024;79:1180-1211.	https://pubmed.ncbi.nlm.nih.gov/37870298/
Manikat R, Ahmed A, Kim D. Current epidemiology of chronic liver disease. *Gastroenterol Rep.* 2024;12goae069.	https://pmc.ncbi.nlm.nih.gov/articles/PMC11194530/
Marcellin P, Kutala BK. Liver diseases: A major, neglected global public health problem requiring urgent actions and large-scale screening. *Liver Int.* 2018;38(suppl 1):2-6.	https://pubmed.ncbi.nlm.nih.gov/29427496/
Scaglione S, Kliethermes S, Cao G, et al. The epidemiology of cirrhosis in the United States: A population-based study. *J Clin Gastroenterol.* 2015;49:690-696.	https://pubmed.ncbi.nlm.nih.gov/25291348/
Silvey S, Sterling RK, French E, et al. A possible reversible cause of cognitive impairment: Undiagnosed cirrhosis and potential hepatic encephalopathy in patients with dementia. *Am J Med*. 2024;137:1082-1087.e1.	https://www.amjmed.com/article/S0002-9343(24)00398-X/fulltext

Thrift AP, Nguyen TH, Pham C, et al. The prevalence and determinants of NAFLD and MAFLD and their severity in the VA primary care setting. *Clin Gastroenterol Hepatol*. 2023;21:1252-1260.e5.	https://pubmed.ncbi.nlm.nih.gov/35811043/
Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet.* 2014;383:1749-1761.	https://pubmed.ncbi.nlm.nih.gov/24480518/

Management of HE (Diagnosis and Treatment)

Resource	Address
Acharya, Chathur, and Jasmohan S Bajaj. Current Management of Hepatic Encephalopathy. *Am J Gastroenterol*. 2018;113:1600-1612.	https://pubmed.ncbi.nlm.nih.gov/30002466/
American Association for the Study of Liver Diseases; European Association for the Study of the Liver. Hepatic encephalopathy in chronic liver disease: 2014 practice guideline by the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases. *J Hepatol*. 2014;61:642-659.	https://pubmed.ncbi.nlm.nih.gov/25015420/
Bajaj JS, Schubert CM, Heuman DM, et al. Persistence of cognitive impairment after resolution of overt hepatic encephalopathy. *Gastroenterology*. 2010;138:2332-2340.	https://pubmed.ncbi.nlm.nih.gov/20178797/
Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med*. 2010;362:1071-1081.	https://pubmed.ncbi.nlm.nih.gov/20335583/
Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. *Hepatology*. 2007;46:1844-1852.	https://pubmed.ncbi.nlm.nih.gov/17685471/
Conn HO, Bircher J, eds. *Hepatic Encephalopathy: Syndromes and Therapies.* Medi-Ed Press;1994.	https://search.worldcat.org/title/28891629
European Association for the Study of the Liver. EASL Clinical Practice Guidelines on the management of hepatic encephalopathy. *J Hepatol*. 2022;77: 807-824.	https://pubmed.ncbi.nlm.nih.gov/35724930/
Faccioli J, Nardelli S, Gioia S, Riggio O, Ridola L. Nutrition assessment and management in patients with cirrhosis and cognitive impairment: A comprehensive review of literature. *J Clin Med.* 2022;11:2842.	https://pubmed.ncbi.nlm.nih.gov/35628968/
Frenette CT, Levy C, Saab S. Hepatic encephalopathy-related hospitalizations in cirrhosis: Transition of care and closing the revolving door. *Dig Dis Sci.* 2022;67:1994-2004.	https://pubmed.ncbi.nlm.nih.gov/34169435/
Guevara M, Baccaro ME, Torre A, et al. Hyponatremia is a risk factor of hepatic encephalopathy in patients with cirrhosis: A prospective study with time-dependent analysis. *Am J Gastroenterol*. 2009;104:1382-1389.	https://pubmed.ncbi.nlm.nih.gov/19455124/
Kaplan, A. Why do we use lactulose and rifaximin for hepatic encephalopathy? American Academy for the Study of Liver Diseases (AASLD). July 6, 2021.	https://www.aasld.org/liver-fellow-network/core-series/why-series/why-do-we-use-lactulose-and-rifaximin-hepatic
Mas A. Hepatic encephalopathy: From pathophysiology to treatment. *Digestion*. 2006;73(suppl 1):86-93.	https://pubmed.ncbi.nlm.nih.gov/16498256/

Nabi E, Bajaj JS. Useful tests for hepatic encephalopathy in clinical practice. *Curr Gastroenterol Rep*. 2014;16:362.	https://pmc.ncbi.nlm.nih.gov/articles/PMC3918211/
O'Malley KA, Vinson L, Pless Kaiser A, Sager Z, Hinrichs K. Mental health and aging veterans: How the Veterans Health Administration meets the needs of aging veterans. *Public Policy Aging Rep*. 2020;30:19-23.	https://pubmed.ncbi.nlm.nih.gov/36570679/
Patidar KR, Bajaj JS. Covert and overt hepatic encephalopathy: Diagnosis and management. *Clin Gastroenterol Hepatol*. 2015;13:2048-2061.	https://pubmed.ncbi.nlm.nih.gov/26164219/
Reau NS. The importance of making an accurate diagnosis for hepatic encephalopathy. *Gastroenterol Hepatol*. 2023;19: 740-748.	https://pmc.ncbi.nlm.nih.gov/articles/PMC10885427/
Riordan SM, Williams R. Treatment of hepatic encephalopathy. *N Engl J Med*. 1997;337:473-479.	https://www.nejm.org/doi/full/10.1056/NEJM199708143370707
Sanyal A, Younossi ZM, Bass NM, et al. Randomised clinical trial: Rifaximin improves health-related quality of life in cirrhotic patients with hepatic encephalopathy – a double-blind placebo-controlled study. *Aliment Pharmacol Ther.* 2011;34:853-861.	https://pubmed.ncbi.nlm.nih.gov/21848797/
Sanyal AJ, Kowdley KV, Reau NS, et al. Rifaximin plus lactulose versus lactulose alone for reducing the risk of HE recurrence. *Hepatol Commun*. 2024;8:e0436.	https://pubmed.ncbi.nlm.nih.gov/38727685/
Serper M, Kaplan DE, Shults J, et al. Quality measures, all-cause mortality, and health care use in a national cohort of veterans with cirrhosis. *Hepatology*. 2019;70:2062-2074.	https://pubmed.ncbi.nlm.nih.gov/31107967/
Silvey S, Sterling RK, French E, et al. A possible cause of cognitive impairment: Undiagnosed cirrhosis and potential hepatic encephalopathy in patients with dementia. *Am J Med*. 2024;137:1082-1087.	https://pubmed.ncbi.nlm.nih.gov/38942345/
Simón-Talero M, Roccarina D, Martínez J, et al. Association between portosystemic shunts and increased complications and mortality in patients with cirrhosis. *Gastroenterology*. 2018;154:1694-1705.e4.	https://pubmed.ncbi.nlm.nih.gov/29360462/
U.S. Department of Veterans Affairs. Rifaximin for Treatment of Chronic Hepatic Encephalopathy in Chronic Liver Disease. Criteria for Use. November 2016.	https://www.va.gov/formularyadvisor/DOC_PDF/Rifaximin_for_Hepatic_Encephalopathy.pdf
Vierling JM, Mokhtarani M, Brown RS Jr, et al. *Clin Gastroenterol. Hepatol*. 2016;14:903-906.e1.	https://www.sciencedirect.com/science/article/abs/pii/S1542356515016560
Vilstrup H, Amodio P, Bajaj J, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. *Hepatology*. 2014;60:715-735.	https://pubmed.ncbi.nlm.nih.gov/25042402/
Zhang Y, Cao C, Li C, et al. Physical exercise in liver diseases. *Hepatology*. Published online June 5, 2024. doi:10.1097/HEP.0000000000000941	https://pubmed.ncbi.nlm.nih.gov/38836646/

Additional Resources

Resource	Address
Green EW, Mitra A. Diagnosis and management of hepatic encephalopathy: a summary for patients. *Clin Liver Dis (Hoboken)*. 2022;20:90-92.	https://journals.lww.com/cld/fulltext/2022/09000/diagnosis_and_management_of_hepatic.4.aspx
U.S. Department of Veterans Affairs. Cirrhosis for Patients. Last updated May 7, 2019.	https://www.hepatitis.va.gov/cirrhosis/patient/index.asp
U.S. Department of Veterans Affairs. Hepatic Encephalopathy. March 2018.	https://www.hepatitis.va.gov/pdf/HE-fact-sheet.pdf
U.S. Department of Veterans Affairs. Viral Hepatitis and Liver Disease. Last updated May 13, 2024.	https://www.hepatitis.va.gov/

All URLs accessed June 5, 2025