



CLINICAL CARE OPTIONS®
INTERNAL MEDICINE

Contemporary Issues in Medicine: Preventing Hepatic Encephalopathy in Patients With Cirrhosis



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Agenda

- **Cirrhosis**
 - The Major Risk Factor for Hepatic Encephalopathy
- **Hepatic Encephalopathy**
 - Management of Overt Hepatic Encephalopathy
 - Prevention of Recurrent Hepatic Encephalopathy
 - Prevention of Readmission for Hepatic Encephalopathy
- **Telehealth for Care of Patients With Advanced Liver Disease**

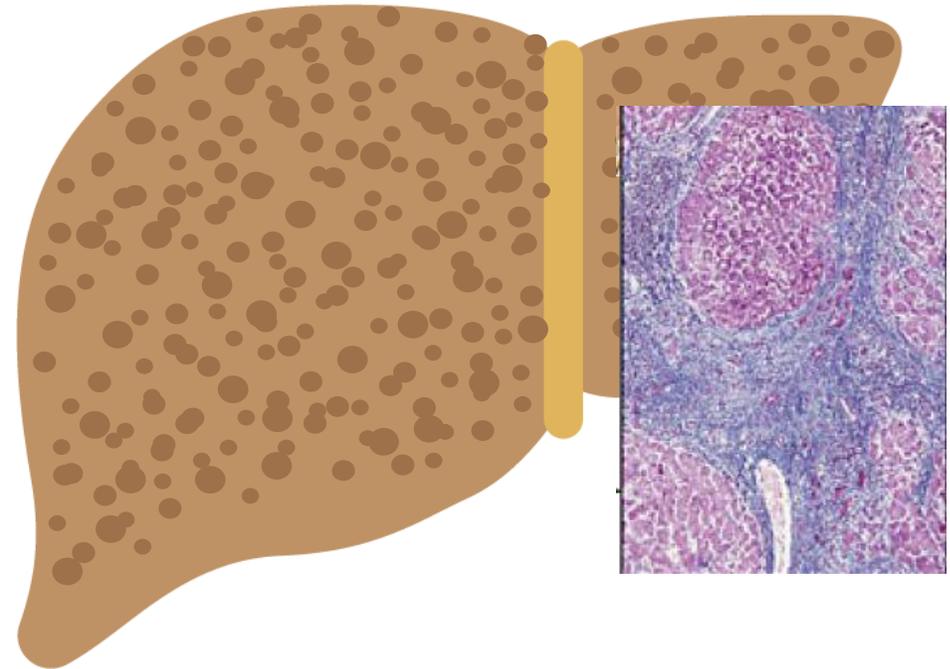


Cirrhosis: The Major Risk Factor for Hepatic Encephalopathy



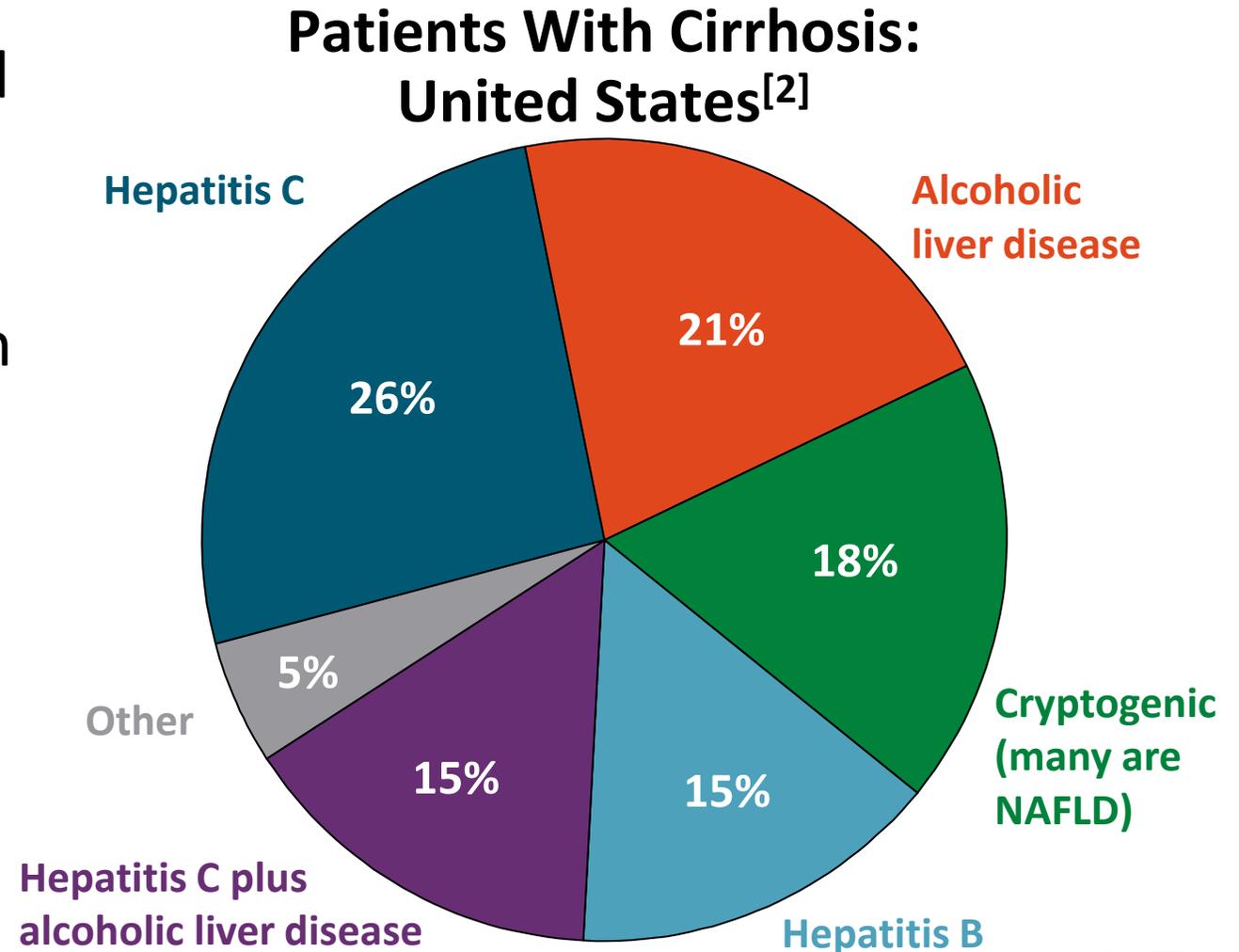
What Is Cirrhosis?

- End stage of any chronic liver disease
- Characterized histologically by regenerative nodules surrounded by fibrous tissue
- 2 clinical types:
 - Compensated
 - Decompensated

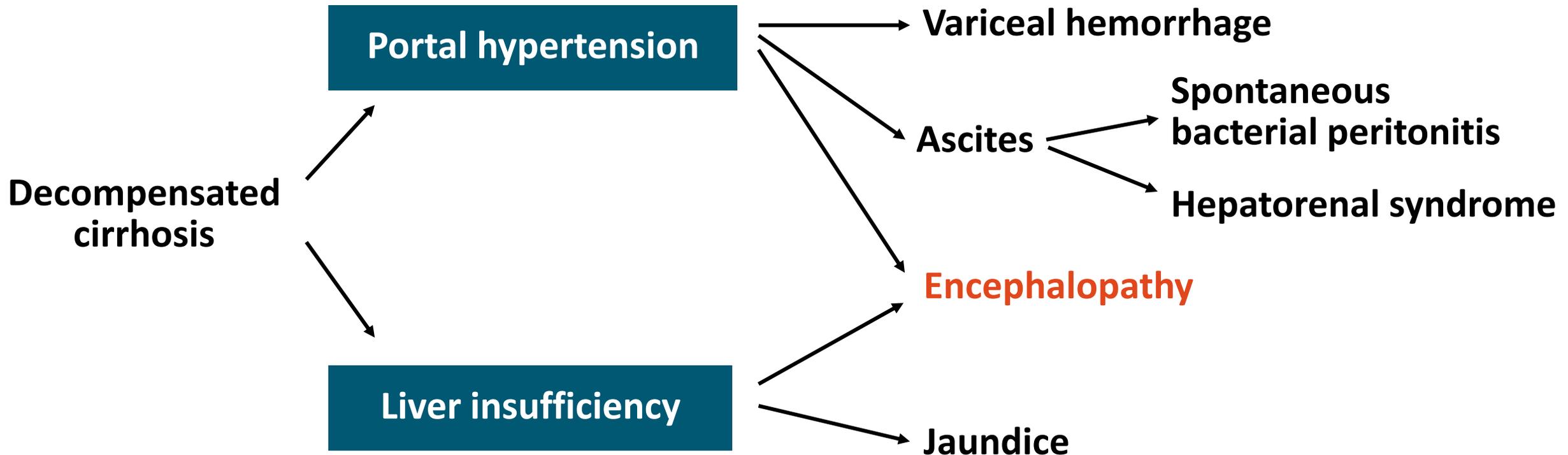


Cirrhosis: Burden of Disease

- A leading cause of morbidity and mortality in the United States^[1]
- Early readmission increases clinical/economic burden in such patients^[1]



Complications of Cirrhosis: Portal Hypertension or Liver Insufficiency



Readmission Common With Decompensated Cirrhosis

Days After Discharge	Readmission Rate
7	14%
30	Up to 37% ^[1-6]
90	53% ^[6]

← **Hepatic encephalopathy** is strongest positive predictor of early 30-day readmission^[7]

Improving management of hepatic encephalopathy improves cirrhosis-related outcomes

1. Tapper. Clin Gastroenterol Hepatol 2016;14:753. 2. Volk. Am J Gastroenterol. 2012;107:247.
3. Tapper. Hepatology. 2015;62:584. 4. Singal. Clin Gastroenterol. 2013;11:1335. 5. Ghaoui. Liver Int. 2014;34:204.
6. Bajaj. Hepatology. 2016;64:200. 7. Sood. J Clin Exp Hepatol. 2019;9:484.

Noninvasive Determination of Cirrhosis



Cirrhosis: Noninvasive Tests and Online Calculators

- APRI and FIB-4 based on AST, platelet count \pm other lab values^[1]
 - Thrombocytopenia is a common complication of liver cirrhosis^[2]

10:48

AST to Platelet Ratio Index (APRI)

Determines the likelihood of hepatic fibrosis and cirrhosis in patients with hepatitis C.

Favorite ★

When to Use ▾ Pearls/Pitfalls ▾ Why Use ▾

AST Norm: 1 - 40 U/L

AST upper limit of normal 40 U/L

Platelet count Norm: 150 - 350 $\times 10^9/L$ ↔

10:48

Fibrosis-4 (FIB-4) Index for Liver Fibrosis

Noninvasive estimate of liver scarring in HCV and HBV patients, to assess need for biopsy.

Favorite ★

When to Use ▾ Pearls/Pitfalls ▾ Why Use ▾

Age Use with caution in patients <35 or >65 years old, as the score has been shown to be less reliable in these patients. [] years

AST Aspartate aminotransferase Norm: 1 - 40 U/L

Platelet count Norm: 150 - 350 $\times 10^9/L$ ↔

ALT Alanine aminotransferase Norm: 1 - 35 U/L

Albumin Norm: 35 - 55 g/L ↔

1. Available at: <https://www.mdcalc.com>. 2. Hayashi. 2014;20:2595.



Identifying Undiagnosed Cirrhosis: Assessing Liver/Spleen Characteristics

Abdominal Ultrasound/CT/MRI

- Liver nodularity
- Spleen size

Vibration Controlled Transient Elastography (*FibroScan*)

- Limited availability
- Determines liver stiffness
 - Worsening fibrosis associated with stiffening of the liver



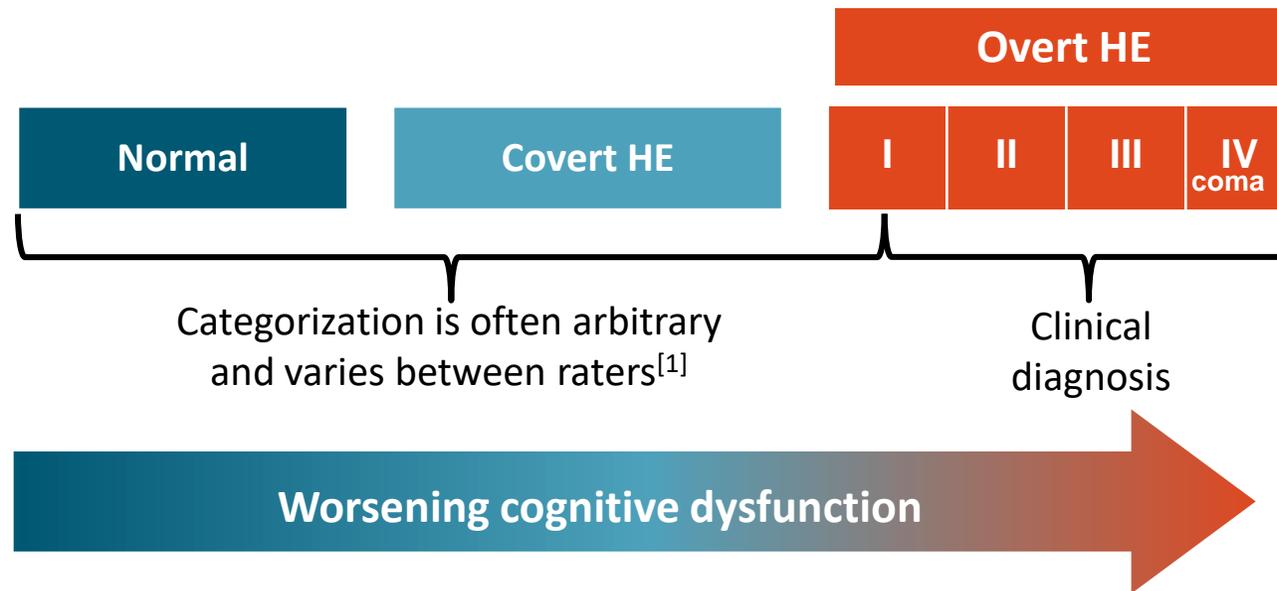
Hepatic Encephalopathy



Hepatic Encephalopathy

- Brain dysfunction caused by liver insufficiency and/or portosystemic shunting^[1]
- Wide spectrum of neurologic/psychiatric abnormalities from mild cognitive loss to confusion to coma^[1]
 - Onset may be gradual or sudden^[2]
 - May include movement problems, changes in mood, or changes in personality^[2]

Hepatic Encephalopathy: Natural History



- First episode of hepatic encephalopathy has poor prognosis,^[2-4] heralds hepatic decompensation
- Risk for recurrence within 30 days is up to 40%^[5]

Hepatic Encephalopathy: Diagnosis

Overt HE

- Patients are confused and disoriented
- Diagnosis of exclusion; rule out other causes of altered mental status

Covert HE

- Difficult to diagnose
- Use symptoms, not ammonia
 - Sophisticated psychometric tests available but not routinely used

Hepatic Encephalopathy: Pitfalls

Inappropriate ammonia testing

- High blood ammonia levels alone add **no diagnostic, staging, or prognostic value . . .** normal value calls for diagnostic re-evaluation^[1]

Polypharmacy,^[2] inappropriate medication use,^[2] disease changes in PK/PD^[3]

- Common nonadherence with diuretics, antibiotics, lactulose^[2]
 - Most nonadherence is intentional (65.3%)^[2]
- Common inappropriate use of NSAIDs (nephrotoxicity), benzodiazepines or opioids (can precipitate HE), anticholinergics^[2]

Management of Overt Hepatic Encephalopathy



Overt Hepatic Encephalopathy: 4-Pronged Approach to Management

1
Initiate care
for patients with
altered consciousness

2
Look for and treat
alternative causes
of altered mental state

3
Identify and address
precipitating factors

4
Begin
empirical treatment

Examples of Alternative Causes

- Diabetic ketoacidosis
- Pharmacotherapy (benzodiazepines, neuroleptics, opioids)
- Neurologic infections
- Electrolyte disorders
- Intracranial bleeding
- Stroke

Treatment Options for Hepatic Encephalopathy

Agent	Drug Class	Dose
Lactulose solution	Poorly absorbed disaccharide	Constipation: 15-30 mL PO QD Off-label use for HE: 30-45 mL PO TID/QID for 2-3 BM/day ^[1]
Rifaximin ^[2]	Nonaminoglycoside semisynthetic, nonsystemic antibiotic	1 tablet (550 mg) PO BID
Lactulose plus rifaximin ^[3]		Varies; increased efficacy and reduced mortality vs lactulose alone
Metronidazole, neomycin, vancomycin ^[4]	Antibiotic	Not recommended

Addressing Precipitating Factors of HE

- Most patients with HE present with concurrent precipitating factors that must be managed acutely^[1]
 - GI bleeding
 - Infection (especially spontaneous bacterial peritonitis)
 - Hypokalemic alkalosis/electrolyte imbalance^[2]
 - Constipation
 - Hypoxia
 - Sedatives/tranquilizers

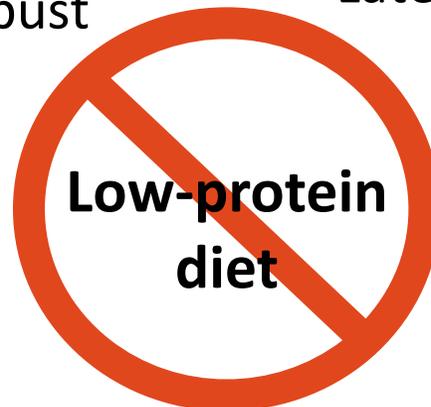
Importance of Malnutrition as a Contributor to Hepatic Encephalopathy

Problem

- Modulation of nitrogen metabolism is crucial to HE management
- ~ 75% of patients with HE have from moderate to severe protein-calorie malnutrition, resulting in loss of muscle and energy depots
- 10% of clinicians continue to order low-protein diets instead of ordering robust nutritional assessments

Targets

- Daily energy intake: 35-40 kcal/kg ideal body weight
- Daily protein intake: 1.2-1.5 g/kg/day
- Small meals or liquid nutritional supplements should be evenly distributed throughout the day
- Late-night snack should be offered



Prevention of Recurrent Hepatic Encephalopathy

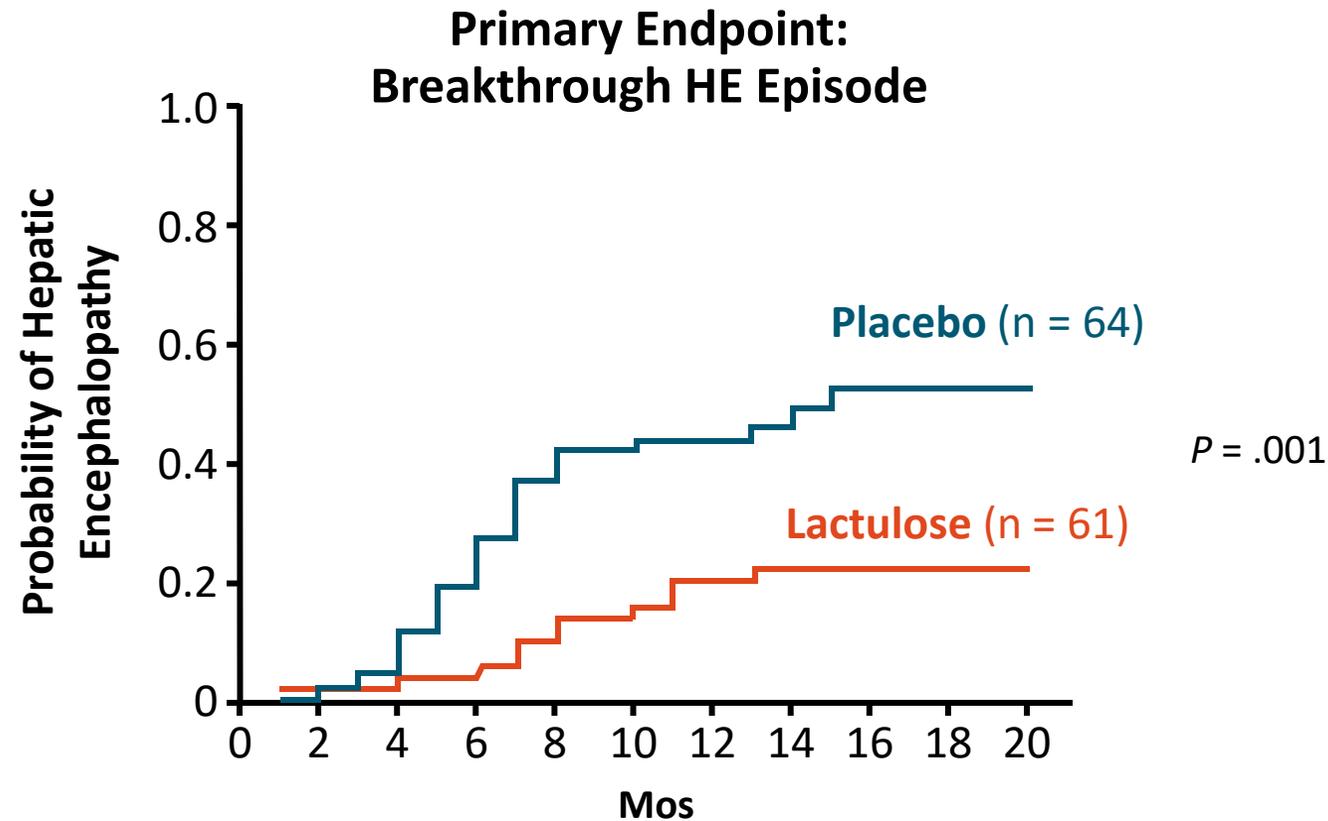


Prevention of Recurrent Hepatic Encephalopathy

- Initial episode: **lactulose**
- Second episode: **lactulose + rifaximin**
 - Routine use of **lactulose + rifaximin** therapy decreased 30-day readmission by 40%^[2]
- Therapy may be discontinued if either^[1]:
 - Precipitating factors are well controlled (eg, infections and variceal bleeding) or
 - Liver function or nutritional status has improved
- Routine prophylactic therapy (lactulose or rifaximin) not recommended for prevention of post-TIPS episodes

Lactulose in Hepatic Encephalopathy

- Randomized, placebo-controlled trial of patients in remission from hepatic encephalopathy (N = 125) followed for median 14 mos



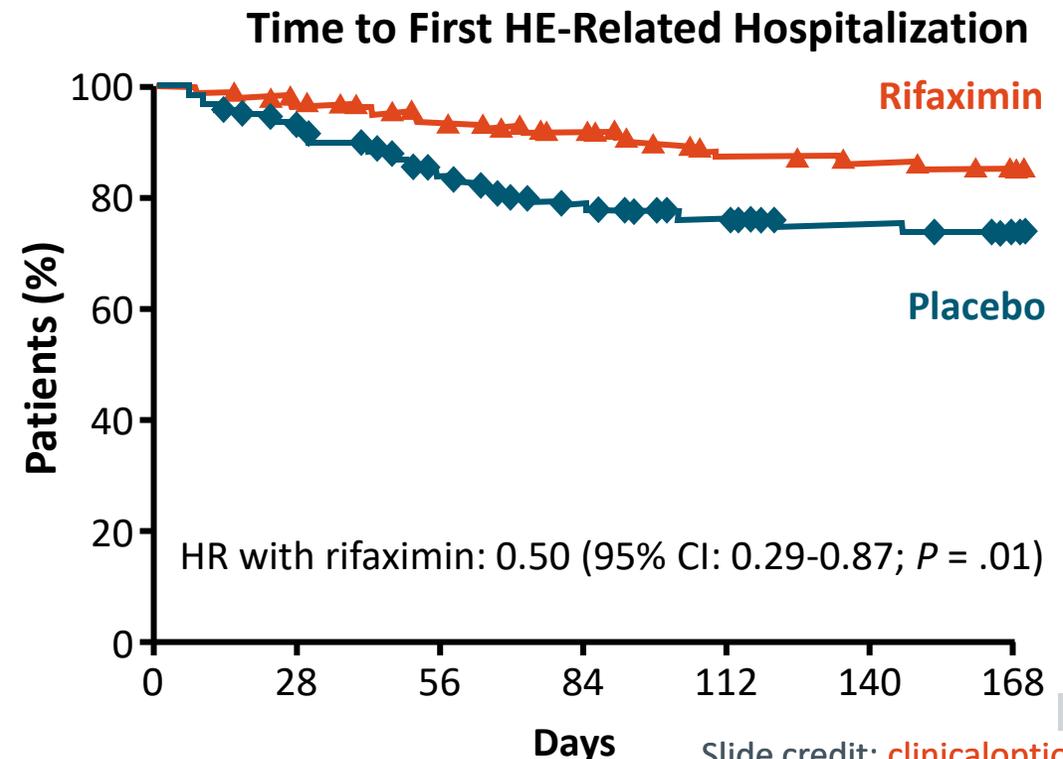
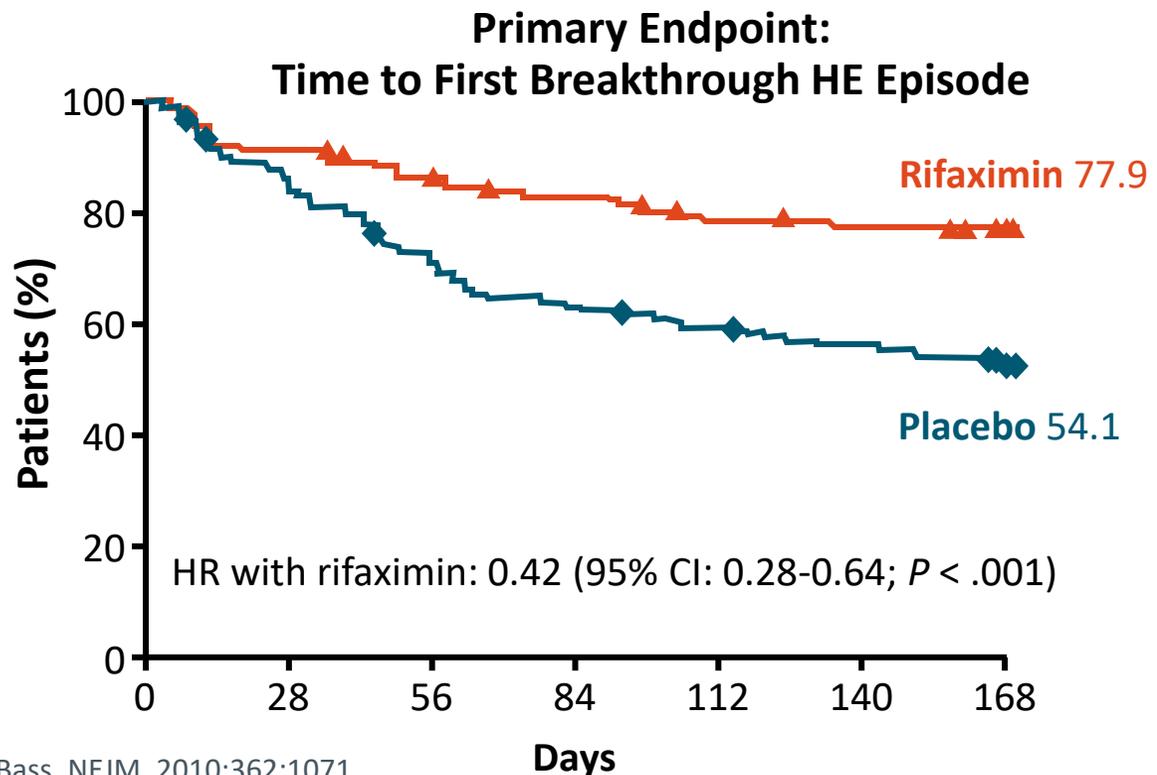
Long-term Pharmacotherapy Considerations

Treatment success depends on adherence,
which depends on tolerability

- In a retrospective analysis of N = 137 patients receiving **lactulose** for hepatic encephalopathy, **38% of those with recurrence were nonadherent**^[1]
 - **Most common reason for nonadherence:** GI tolerability (unpredictable diarrhea, abdominal pain, bloating)
- Lower incidence of adverse events when **rifaximin** used as substitute or added to lower dose of **lactulose**^[1]
- Such use of rifaximin can significantly reduce healthcare resource utilization^[2]

Rifaximin in Hepatic Encephalopathy

- Randomized, double-blind, placebo-controlled trial of patients in remission from recurrent hepatic encephalopathy (N = 299) followed for 6 mos
 - In each arm, 91% were receiving lactulose at baseline



Rifaximin in Hepatic Encephalopathy: Safety

- Adverse events did not differ significantly between treatment arms^[1]
 - Safety profile of rifaximin appeared superior to systemic antibiotics, especially in patients with liver disease^[2]

Adverse Event > 10% in Either Arm, n (%)	Rifaximin (n = 140)	Placebo (n = 159)
Nausea	20 (14.3)	21 (13.2)
Diarrhea	15 (10.7)	21 (13.2)
Fatigue	17 (12.1)	18 (11.3)
Peripheral edema	21 (15.0)	13 (8.2)
Ascites	16 (11.4)	15 (9.4)
Dizziness	18 (12.9)	13 (8.2)
Headache	14 (10.0)	17 (10.7)

Prevention of Readmission



Factors Associated With Readmission in Cirrhosis

Patient Factors	Medical Factors	System Factors
Frailty Malnutrition Home situation Communication issues Transplant candidacy	Polypharmacy Psychological Comorbidities	Inpatient care Goals of care Discharge instructions Outpatient care Multidisciplinary management

30-Day and 90-Day Readmission Rates: Complications

- The greater the number of cirrhotic complications, the higher the 30-day and 90-day readmission rate

Cirrhotic Complication	30-Day Readmission Rate, %	90-Day Readmission Rate, %
Ascites	13.8	21.0
Variceal hemorrhage	16.5	28.5
Hepatic encephalopathy	18.1	28.8
Hepatorenal syndrome	19.2	27.5
Hepatocellular carcinoma	15.2	27.3

Most Patients With Overt Hepatic Encephalopathy Do Not Receive Proper Prophylactic Therapy at Discharge

Problem

- > 60% of patients did not receive ongoing prophylactic therapy at discharge^[1]
 - To reduce risk of recurrence, critical to **meet with family** and **ensure access to medication**

Consequence

- Undertreatment results in preventable HE recurrences and hospitalizations^[2]
 - HE accounts for 41% of critical care cirrhosis-related hospitalizations^[3]
 - Prognosis is poor: 1-yr survival 40-50%, 3-yr survival ~ 20%^[4,5]
 - Although mortality has stabilized, prevalence of major and extreme severity of disease has increased (2005-2009)^[6]

Telehealth for Care of Patients With Liver Disease



Telehealth in the Care of Cirrhosis

- Growing need for **specialty consultation** in hepatology^[1]
 - ~ 600 board-certified hepatologists (~ 1 for every 550,000 persons)^[2]
 - Majority of medical care falls to primary care physicians and gastroenterologists
- **Telemedicine/mobile health** can effectively address unmet needs by:
 - Improving screening and preventive care
 - Expanding access to best practice care in rural, underserved, and disadvantaged communities^[3]

Telehealth Models in the Care of Liver Disease

Virtual Consultations

- Direct interactions between primary care provider and specialist
 - **Extension for Community Healthcare Outcome (ECHO):** telementoring via videoconferencing of specialists and multiple primary providers^[1]
 - **Electronic consultations (eConsults):** close, collaborative care between physician and specialist, access to hepatology care^[2]

Impact

- **Specialty Access Network-ECHO (SCAN-ECHO),** implemented by VHA^[2]
 - Improved access to specialty care^[1]
 - Significantly improved survival in veterans^[2]

Key Points: Preventing Recurrence of HE

- Hepatic encephalopathy is an important cause of hospital readmission in patients with advanced liver disease
- Ammonia testing has no diagnostic, staging, or prognostic value
- Most patients do not receive prophylactic therapy upon discharge
- Lactulose and/or rifaximin are important for secondary prophylaxis of hepatic encephalopathy
- Reinforce adherence to patient/family/caregiver to reduce morbidity and potentially mortality



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