HEPATITIS C ONLINE COURSE

Hepatic Encephalopathy

Charles Landis, MD, PhD
Assistant Professor of Medicine
Division of Gastroenterology and Hepatology
University of Washington

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Hepatitis web study

Disclosure Slide

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  - Gilead
  - Janssen Pharmaceuticals
  - Vital Therapies

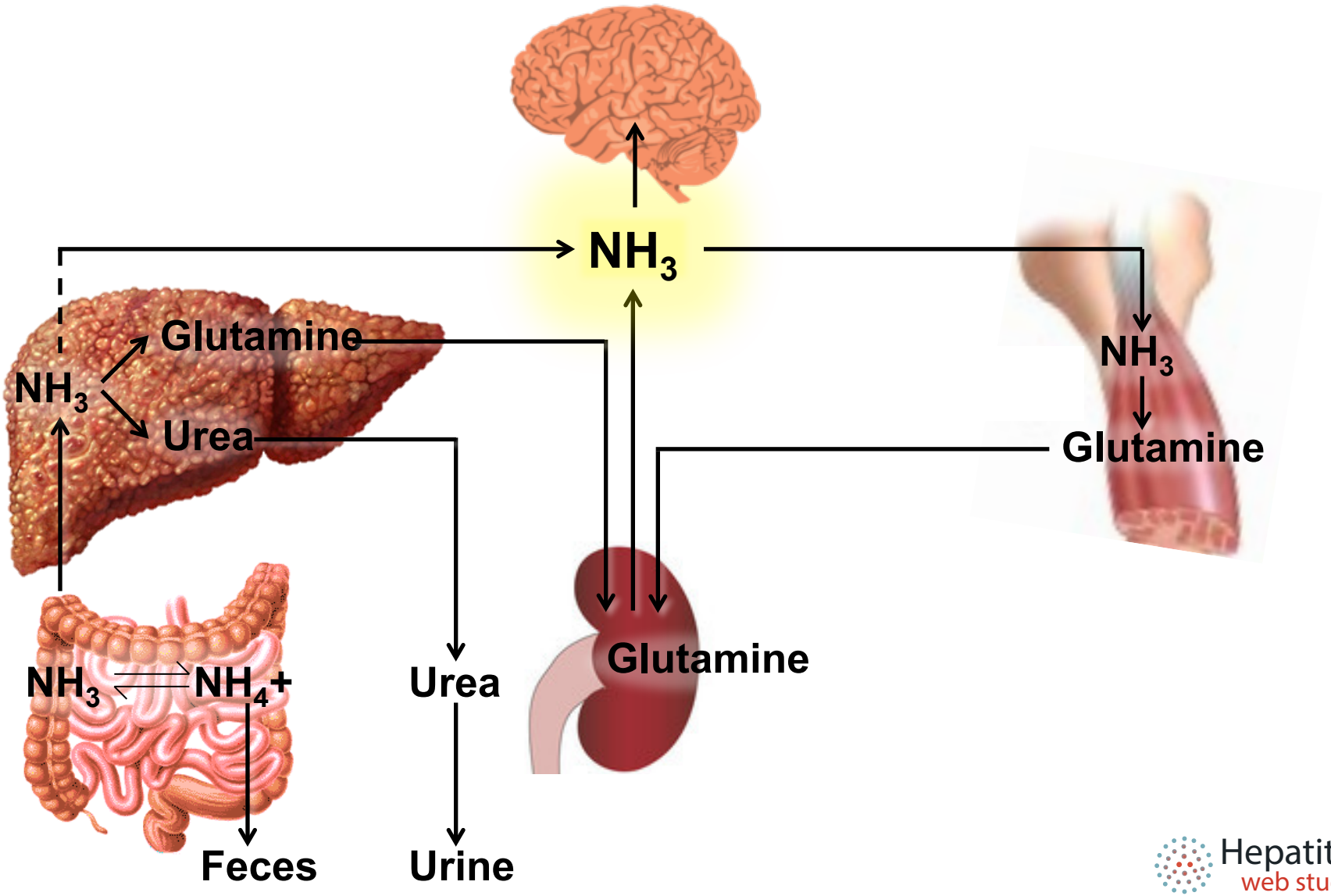
Definitions

- **Hepatic Encephalopathy**
  Potentially reversible neuropsychiatic abnormalities seen in patients with liver dysfunction or porto-systemic shunting

- **Minimal Hepatic Encephalopathy**
  Subclinical encephalopathy in patients with liver dysfunction, only detectable with specialized neuropsychiatric tests

Source: Ferenci P, et al. Hepatology. 2002;35:716-21.

Pathophysiology



Pathophysiology – Other factors

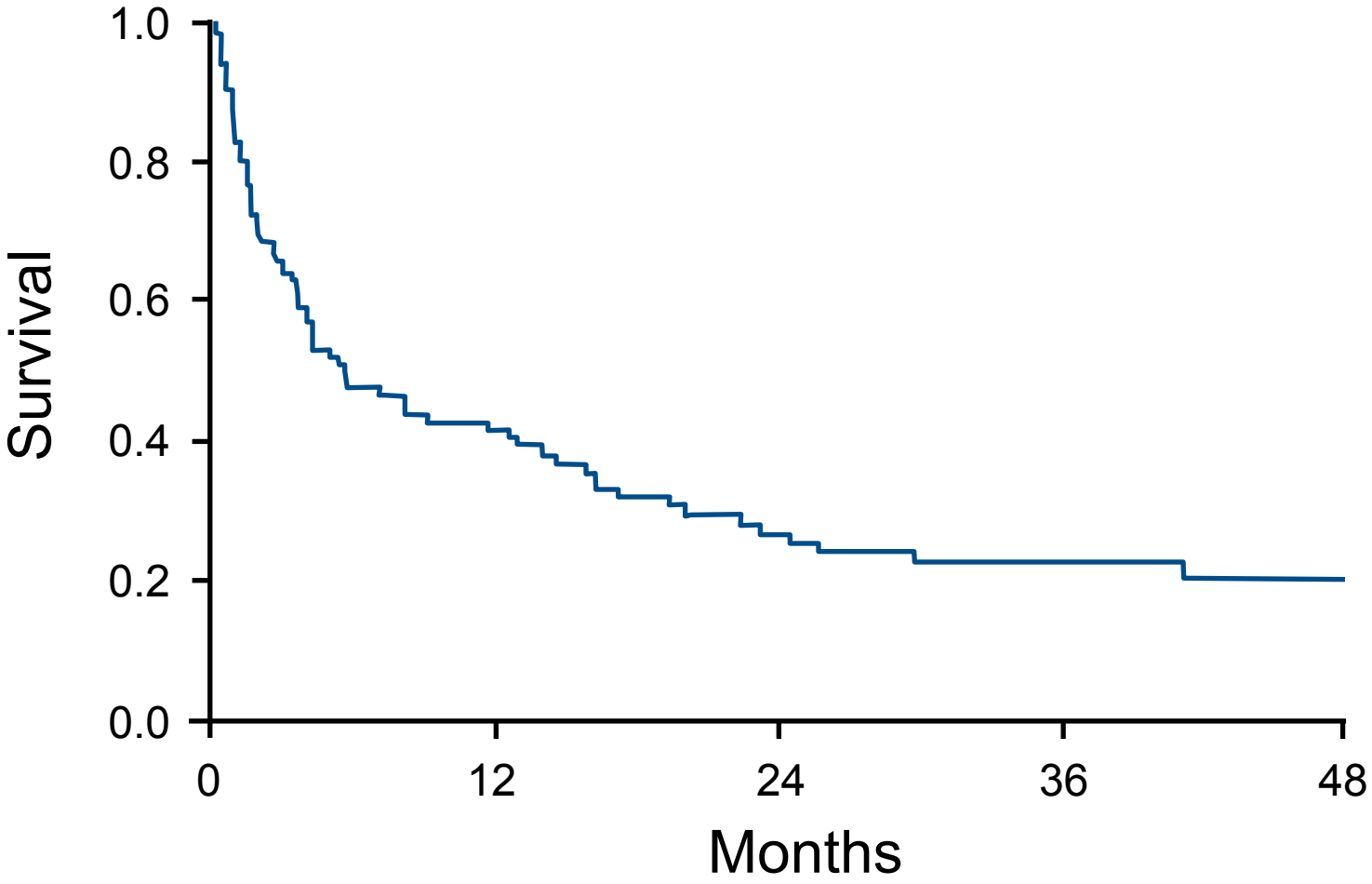
- GABA/benzodiazepine receptor complex
- Branched-chain amino acids
- Serotonin
- Zinc
- Manganese

Epidemiology

- 30-45% of patients with decompensated Cirrhosis have HE
- 20% annual risk of development in of patient with compensated cirrhosis.
- 60-80% of patients with compensated cirrhosis have evidence of minimal hepatic encephalopathy

Source: Bajaj JS. Aliment Pharmacol Ther. 2010;31:537-47.

Survival after First Episode of Hepatic Encephalopathy



Source: Bustamante J, et al. J Hepatol. 1999;30:890-5.

Impact of Hepatic Encephalopathy

- 111,000 hospitalizations per year
- Average length of stay for hospitalization with HE is 8.5 days
- Total $ for hospitalizations with HE estimated to be $7.254 billion nationwide (2009)

Source: Stepanova M, et al. Clin Gastroenterol Hepatol. 2012;10:1034-41.

Hepatic Encephalopathy
Nomenclature

Type	Description	Example
Type A	Encephalopathy associated with acute liver failure	Fulminate liver failure due to Acetaminophen overdose
Type B	Encephalopathy with porto-systemic bypass and no intrinsic hepatocellular disease	TIPSS in absence of cirrhosis
Type C	Encephalopathy associated with cirrhosis and/or portal hypertension	Decompensated cirrhosis

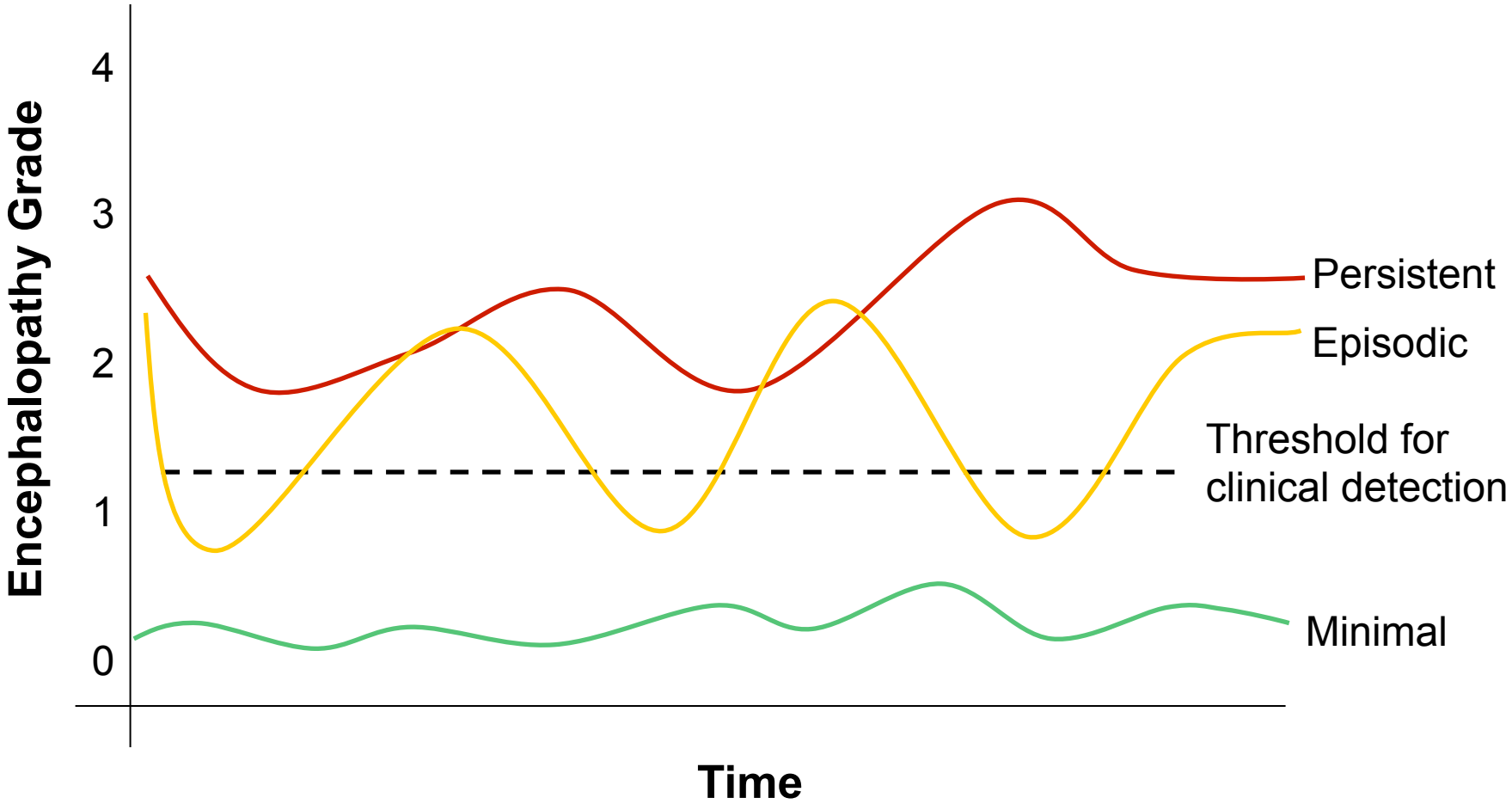
Source: Bajaj JS. Aliment Pharmacol Ther. 2010;31:537-47.

Clinical Features of Hepatic Encephalopathy
West Haven Criteria

Grade	Consciousness	Intellect and Behavior	Neurological Findings
0	Normal	Normal	Normal examination or impaired psychomotor testing (MHE)
1	Mild lack of awareness	Shortened attention span; impaired addition or subtraction	Mild asterixis or tremor
2	Lethargic	Disoriented; inappropriate behaviour	Obvious asterixis; slurred speech
3	Somnolent but arousable	Gross disorientation; bizarre behaviour	Muscular rigidity and clonus; Hyper-reflexia
4	Coma	Coma	Decerebrate posturing

Source: Bajaj JS. Aliment Pharmacol Ther. 2010;31:537-47.

Subcategories of Hepatic Encephalopathy
Type C



Source: Bajaj JS. Aliment Pharmacol Ther. 2010;31:537-47.

Diagnosis

- Diagnosis is clinical based on the presence of cirrhosis or portosystemic shunt with symptoms of encephalopathy
- Rare alternate diagnoses include meningitis, infectious encephalitis, Wernicke's encephalopathy and Wilson disease

Clinical Evaluation

- NH_3 elevated in 90% of all HE but also at least marginally elevated in 90% of all patients with cirrhosis
- NH_3 levels correlate (poorly) with HE Grade
- EEG not used routinely
  - Normal for stage 0 or MHE
  - Triphasic waves over frontal lobes that oscillate at 5 Hz for stage I,II,III
  - Slow delta wave activity in stage IV
- MRI/CT typically only show findings in Type A (fulminate liver failure) and Grade 4 HE

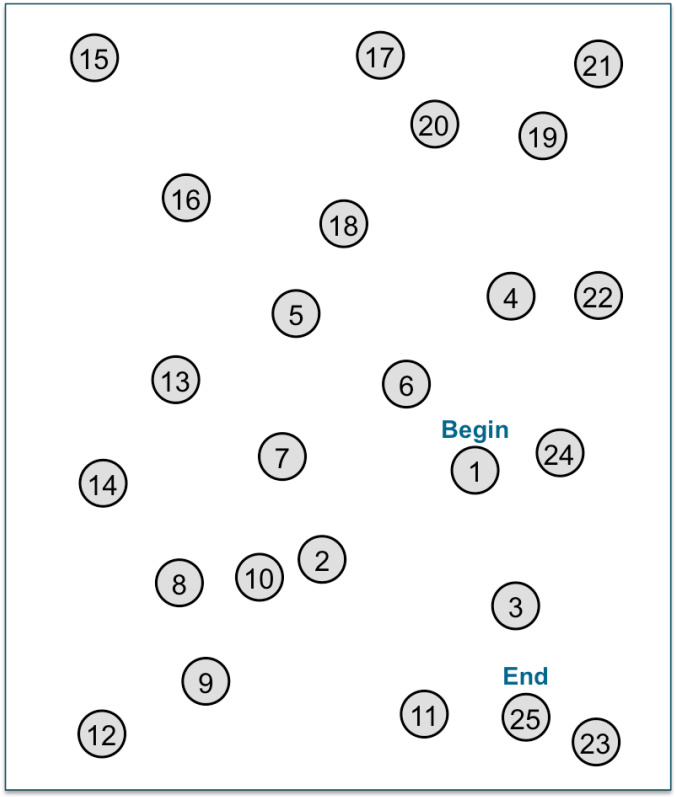
Source: Ong JP, et al. Am J Med. 2003;114:188-93.

Number Connection Test

- Used for > 50 years to assess mental performance
- Simple, readily available
- Results influenced by age and level of education

Time required	HE Grade
≤30 seconds	None-Minimal
31-50 seconds	Minimal - I
51 to 80 seconds	I - II
81 – 120 seconds	II - III
Forced termination	III

Number Connection Test	
Patient's Name	
Date	
Completion Time	
Testers Initials	
Patient's Signature	



Source: Weissenborn et al. J Hepatology May 2011

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Minimal Hepatic Encephalopathy

- By definition, requires neuropsychological or neurophysiological testing
- Impairs daily functioning and quality of life
- Associated with impaired driving skills and increased risk of motor vehicle accidents
- Currently no guidelines address the testing and treatment
- Most reliable testing is difficult to use routinely in the clinic

Source: Bajaj JS, et al. Hepatology. 2012;55:1164-71.

Management of Hepatic Encephalopathy

- Stage III-IV may require endotracheal intubation and ICU care
- HE in the setting of acute liver failure prompts higher level of care and liver transplant evaluation
- Thorough evaluation for precipitating factors is essential

Precipitating Factors

- Gastrointestinal bleeding
- Infection
- Spontaneous bacterial Peritonitis
- Large volume paracentesis
- Excess dietary intake of protein
- Portal or hepatic vein thrombosis
- Benzodiazepines
- Narcotics
- Alcohol
- Hypokalemia
- Constipation

Source: Bajaj JS, et al. Hepatology. 2012;55:1164-71.

Dietary Considerations

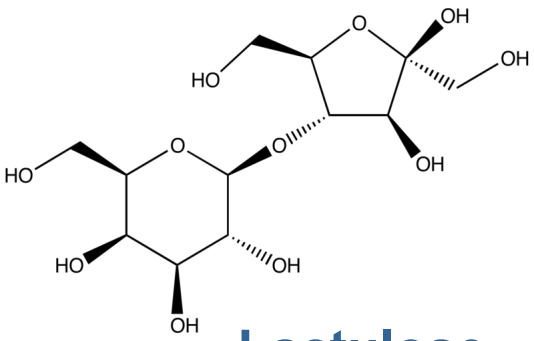
- Normal to high protein intake recommended (1.2 to 1.5 g/kg/day)
- Increased vegetable proteins intake may be helpful for patients whose symptoms worsen with protein intake
- Branched-chain amino acids supplementation can be used in severely protein-intolerant patients
- Probiotic supplementation or yogurt may be beneficial, especially for minimal hepatic encephalopathy

Therapy

- Medical Therapy
  - Nonabsorbable disaccharides
  - Nonabsorbable antibiotics
- Surgical Therapy
  - TIPSS reversal
  - Liver transplantation

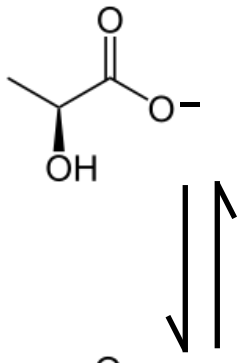
Lactulose

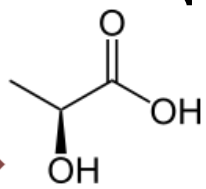
- Metabolized by colon bacterial flora to short chain fatty acids altering luminal pH



Lactulose

Intestinal Flora





Lactic Acid

NH_4^+

NH_3

Excreted in feces

Guidelines for Using Lactulose

- Lactulose 45 ml PO or via NG tube, every hour until bowel movement occurs
- Dosing is adjusted to achieve 2-3 soft bowel movements per day
- Typically 2-3 times daily dosing is required
- Lactulose retention enema may be used patients who cannot tolerate oral or NG ingestion

Rifaximin

- Semisynthetic antibiotic based on rifamycin
- Poor bioavailability - confined to the gut
- Mechanism thought be through intestinal flora alteration
- Similar efficacy to nonabsorbable disaccharides
- Due to cost, reserved for patients who cannot tolerate or do not respond to disaccharides
- Neomycin is a less costly alternative, but association with ototoxicity and nephrotoxicity limit use

Summary

- HE is commonly seen in patients with cirrhosis
- Reduced ammonia detoxification due to liver dysfunction and/or porto-systemic shunting
- HE is a clinical diagnosis
- Protein restriction is not recommend
- Any acute episode of HE warrants a thorough evaluation for precipitating factors
- Nonabsorbable disaccharides and antibiotics are mainstays of treatment

End

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