



CURRENT DILEMMAS  
IN THE MANAGEMENT OF  
**CIRRHOSIS**

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**HEPATOLOGY**  
Centers of  
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*Provided by:*

**CLDF**  
Chronic Liver Disease Foundation

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- This program is supported by an educational grant from Salix Pharmaceuticals.

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# Educational Objectives

- Discuss the natural history and complications of cirrhosis including management options
- Review data on the screening, diagnosis and management of chronic liver disease
- Describe the importance of linking patients with chronic liver disease into specialty care

# Case 1

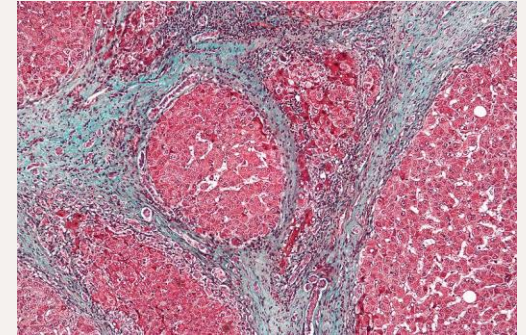
- Paul is a 62 year old black man who presents to the ER with severe abdominal pain.
- PMHx: “liver problem” years ago when drinking
  - Developed ascites but resolved with abstinence
- Exam: Diffusely tender abdomen with some guarding
- Labs:
  - CBC: WBC 7.2, Hb 10.1, Plts 71
  - CMP: Alb 3.4, TB 1.2, AST 32, ALT 25, AP 251, Cr 1.2
  - Viral hepatitis screen: negative
- CT with large heterogeneous mass

# Discussion

1. Does Paul have cirrhosis?
  - What do you suspect is the reason for his pain?
2. How do you diagnose cirrhosis?
  - Biopsy
  - Imaging
  - Non-invasive markers? And for which etiologies?
  - Transient elastography?
3. What would you do next?

# Compensated Cirrhosis May Be Difficult to Recognize

- Asymptomatic (compensated)
  - Subtle clues may be overlooked
    - Thrombocytopenia
    - Muscle wasting
    - AST>ALT without alcohol consumption
    - Liver enzymes may not be abnormal
  - Etiology may be remote
    - Prior alcohol use
    - Uncontrolled DM and obesity
- Decompensated (Symptomatic)
  - Portal hypertension: ascites, OHE, variceal bleeding
  - Hepatic failure: Jaundice, Coagulopathy







# Non-Invasive Markers

- Indirect biomarkers
  - APRI, FIB4 etc
- Direct biomarkers
  - Fibrotest, Fibrosure, etc
- Transient Elastography
- Clinically obvious cirrhosis does not require confirmation

# Prevalence of Cirrhosis

- The prevalence of cirrhosis, both worldwide and in the US, is unknown<sup>1</sup>
  - Cirrhosis is an outcome of a variety of causes; underlying cause is commonly used for surveillance purposes<sup>2</sup>
  - Compensated cirrhosis often goes undetected for prolonged periods of time<sup>1</sup>
- Experts estimate that 5.5 million people in the United States have cirrhosis<sup>3</sup>

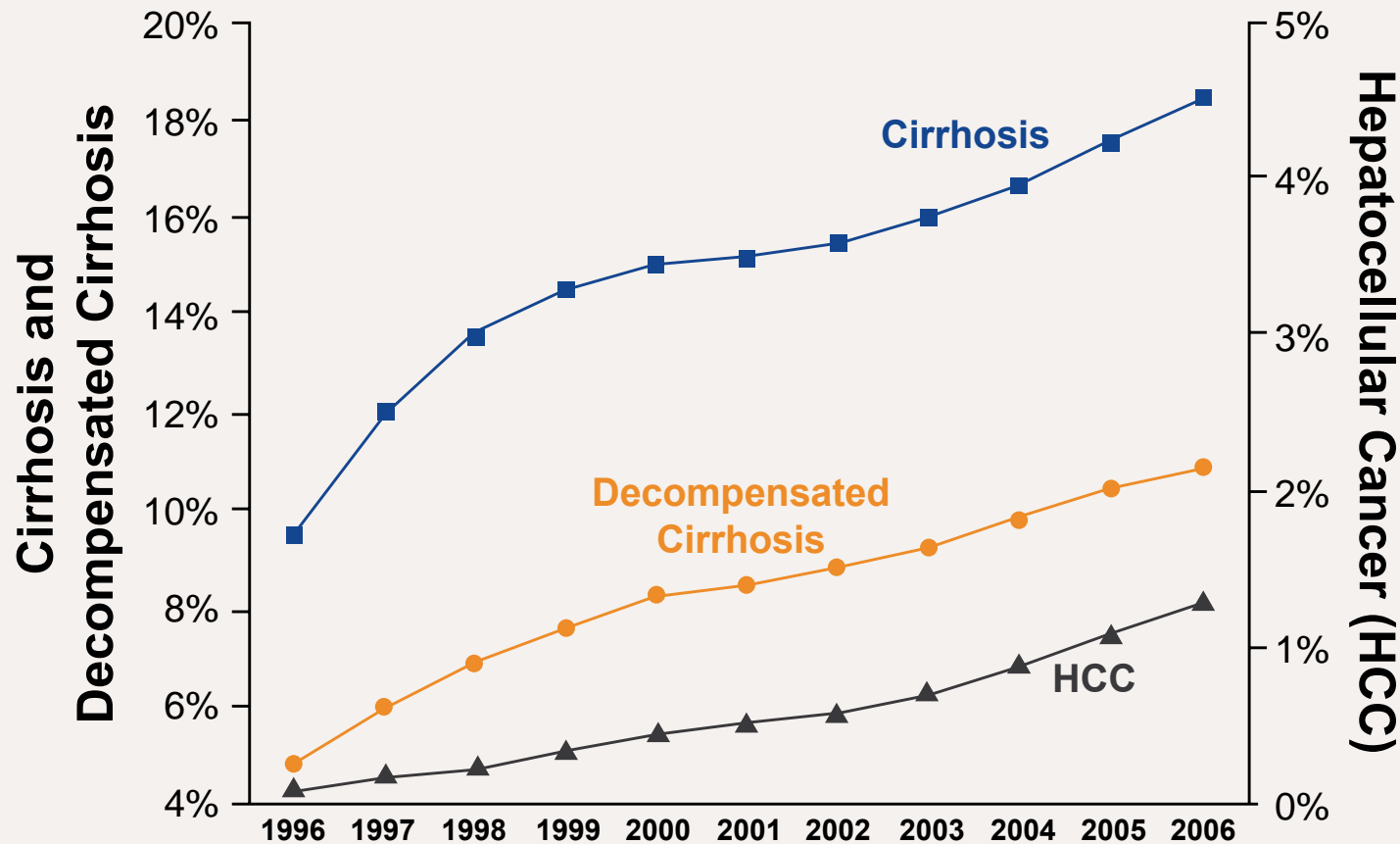
1. Schuppan D, Afdhal NH. *Lancet* 2008;371(9615):838-851.

2. Available at <http://pubs.niaaa.nih.gov/publications/surveillance83/Cirr05.htm>; Accessed February 2015.

3. Khungar V, Poordad F. *Clin Liver Dis* 2012;16:73-89.

# Progressive Increase in Incidence of HCV-Related Cirrhosis and HCC in US

Annual Prevalence Rates Between 1996 and 2006 Among HCV-Infected Veterans



# Liver Cancer Projected to Be the 3rd Leading Cause of Cancer-Related Death by 2030

## “Projecting Cancer Incidence and Deaths to 2030: The Unexpected Burden of Thyroid, Liver and Pancreas Cancers in the United States.”

- Cancer incidence/deaths projected for 2020 and 2030
- Breast, prostate, and lung cancers remain top cancer diagnoses
- Lung cancer is projected to remain top cancer killer
  - Pancreas and **liver cancers** projected to surpass breast, prostate, and colorectal cancers to become the 2<sup>nd</sup> and 3<sup>rd</sup> leading causes of cancer-related death

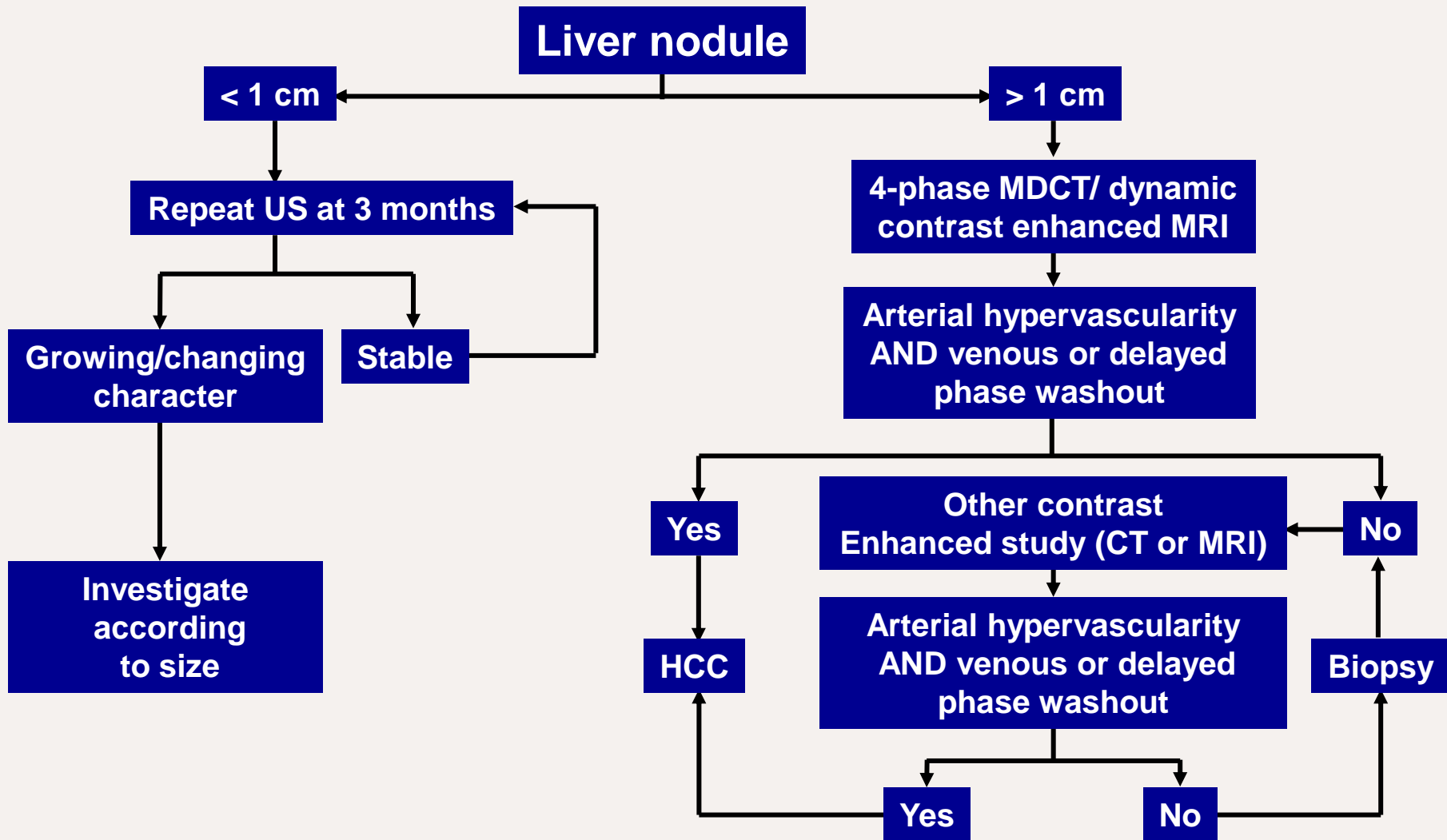
# Early Recognition Allows Preventative Measures

- HCC screening
- Screening for varices
- Recognition of encephalopathy
- Recognition of ascites
- Life style and nutrition counseling
- Early intervention when decompensation first recognized

# HCC Screening

- HCC detected after the onset of symptoms has a very poor prognosis
  - With 0-10% survival at 5 years
- Early recognition can improve outcomes
  - Resection or liver transplantation
  - 5-year disease-free survival of greater than 50%
- Screening with Ultrasound recommended at 6 month intervals in all individuals with cirrhosis
- **MUST RECOGNIZE CIRRHOSIS**

# HCC Diagnostic Algorithm





# Case 2

- Tim is a 56 year old white man with HCV cirrhosis complicated by ascites and non-bleeding varices. He is listed for transplantation with a MELD of 17.
- His wife calls his coordinator because Tim has been sleeping all day.
- The coordinator advises her to take Tim to the nearest ER.

# How would you explain Tim's symptoms?

- Primary complications of cirrhosis include:
  - Ascites
  - Jaundice
  - Variceal hemorrhage
  - Hepatic encephalopathy
- Other complications that can occur include:
  - Hepatocellular carcinoma
  - Spontaneous bacterial peritonitis
  - Hepatic hydrothorax
  - Hepatorenal syndrome
  - Portopulmonary hypertension
  - Portal vein thrombosis
  - Hepatopulmonary syndrome

# Overt Hepatic Encephalopathy (OHE)

- Overt hepatic encephalopathy (OHE) occurs in:
  - 30% to 45% of cirrhotic patients
  - 10% to 50% of patients with TIPS
- Covert hepatic encephalopathy (CHE) affects approximately 20% to 60% of patients with liver disease
  - Has been called subclinical encephalopathy or minimal encephalopathy (MHE) in the past

# Diagnosis of OHE

- Clinical recognition of the distinctive neurologic features of HE
- Knowledge that underlying cirrhosis is present
- Exclusion of other etiologies of neurologic and/or metabolic abnormalities
- Identification of precipitating factors
- Grading the severity

Adapted from:

Mullen KD. *Semin Liver Dis.* 2007;27(suppl 2):3-9.

Lawrence KR, Klee JA. *Pharmacotherapy.* 2008;28(8):1019-1032.

# Neurologic Manifestations of OHE

Common	Less Common
<ul style="list-style-type: none"><li>• Confusion or coma</li><li>• Asterixis</li><li>• Loss of fine motor skills</li><li>• Hyper-reflexia</li></ul>	<ul style="list-style-type: none"><li>• Cognitive deficits detected by special testing</li><li>• Babinski sign</li><li>• Slow, monotonous speech</li><li>• Extrapyrarnidal-type movement disorders</li><li>• Clonus</li><li>• Decerebrate posturing</li><li>• Decorticate posturing</li><li>• Hyperventilation</li><li>• Seizures*</li></ul>

\*Seizures seen primarily in type A HE.

Mullen KD. *Semin Liver Dis.* 2007;27(suppl 2):3-9.

# Other Causes of Altered Mental Status\*

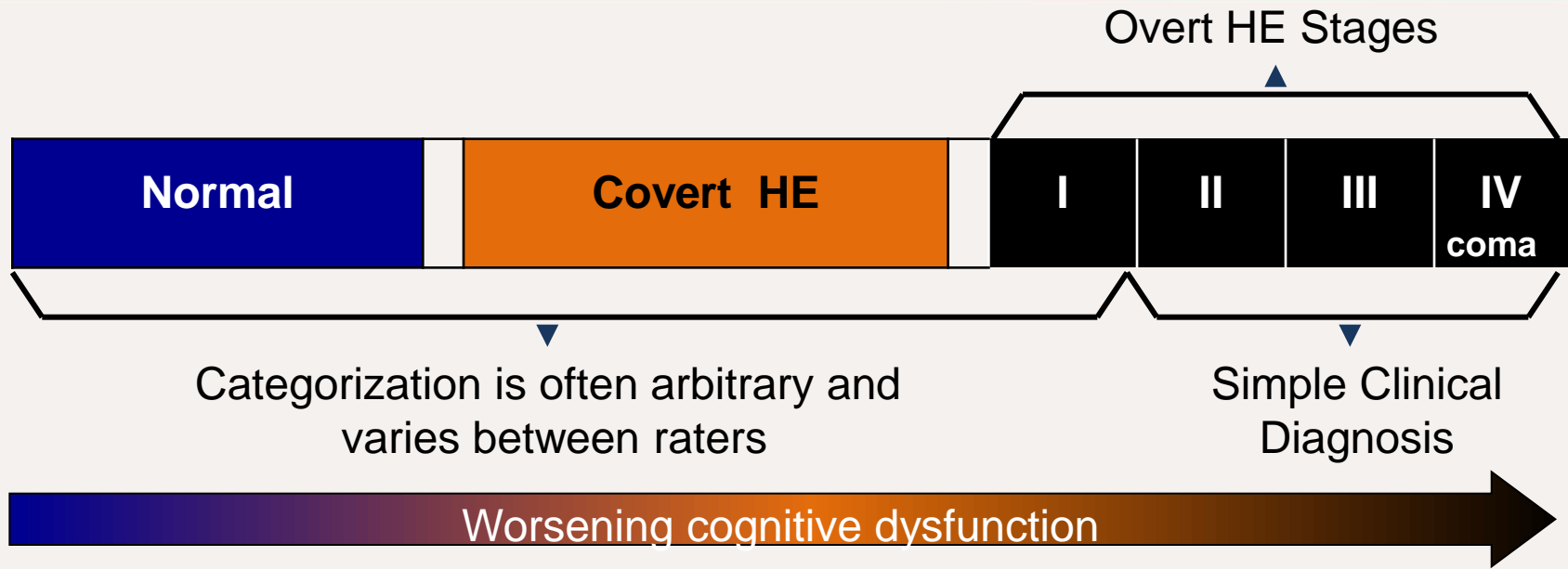
- Intracranial hematomas
- Thyroid dysfunction
- Hypoglycemia
- Hypoxia
- Hypercapnia
- Drug intoxication
- Hypoglycemia
- Hyperglycemia
- Acidosis
- Encephalitis
- Severe sepsis<sup>†</sup>
- Uremia

\*Most entities can be diagnosed by brain imaging or laboratory tests.

<sup>†</sup>Severe sepsis can cause encephalopathy or precipitate HE.

Mullen KD. *Semin Liver Dis.* 2007;27(suppl 2):3-9.

# Characterization of HE Stages



## West Haven Criteria

Grade	Features
0	No abnormalities detected
I	Trivial lack of awareness; Euphoria or anxiety; short attention span; Impairment of addition or subtraction
II	Lethargy or apathy, Disorientation for time, Obvious personality change, Inappropriate behavior
III	Somnolence to semi-stupor, Responsive to stimuli, Confused, Gross disorientation, Bizarre behavior
IV	Coma, unable to test mental state

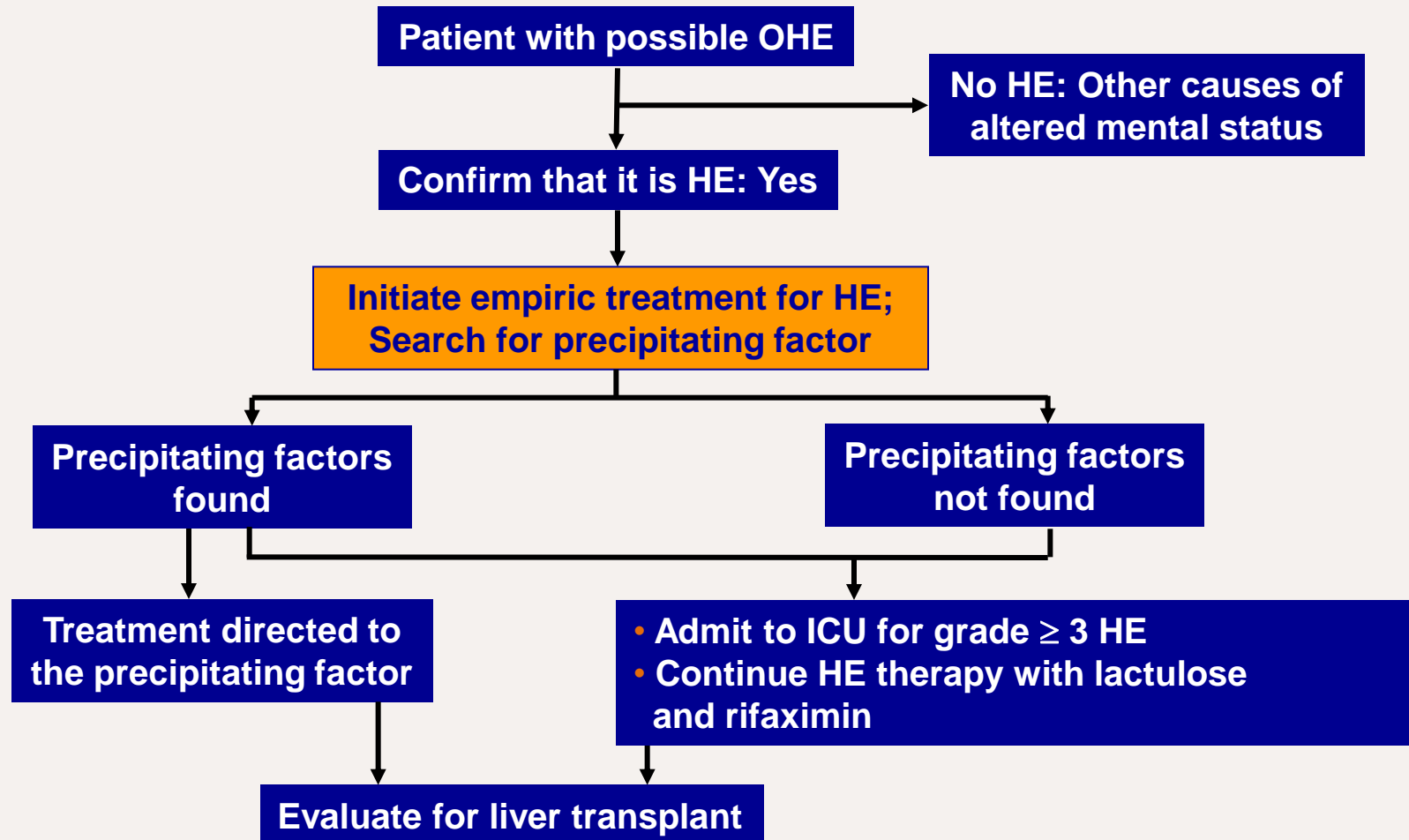
# Measuring Serum Ammonia Level in Patients with Altered Mental Status

- One's clinical impression is the main guide to diagnosing hepatic encephalopathy (HE)
- A normal or modestly elevated blood ammonia level does not rule out a diagnosis of HE
- Blood ammonia testing may be helpful if there is no clear evidence of underlying chronic liver disease
  - An increased blood ammonia level may have prognostic value (e.g., acute liver failure) or may be the basis for further evaluation for uncommon metabolic disorders (e.g., urea cycle disorders)



How would you manage Tim?

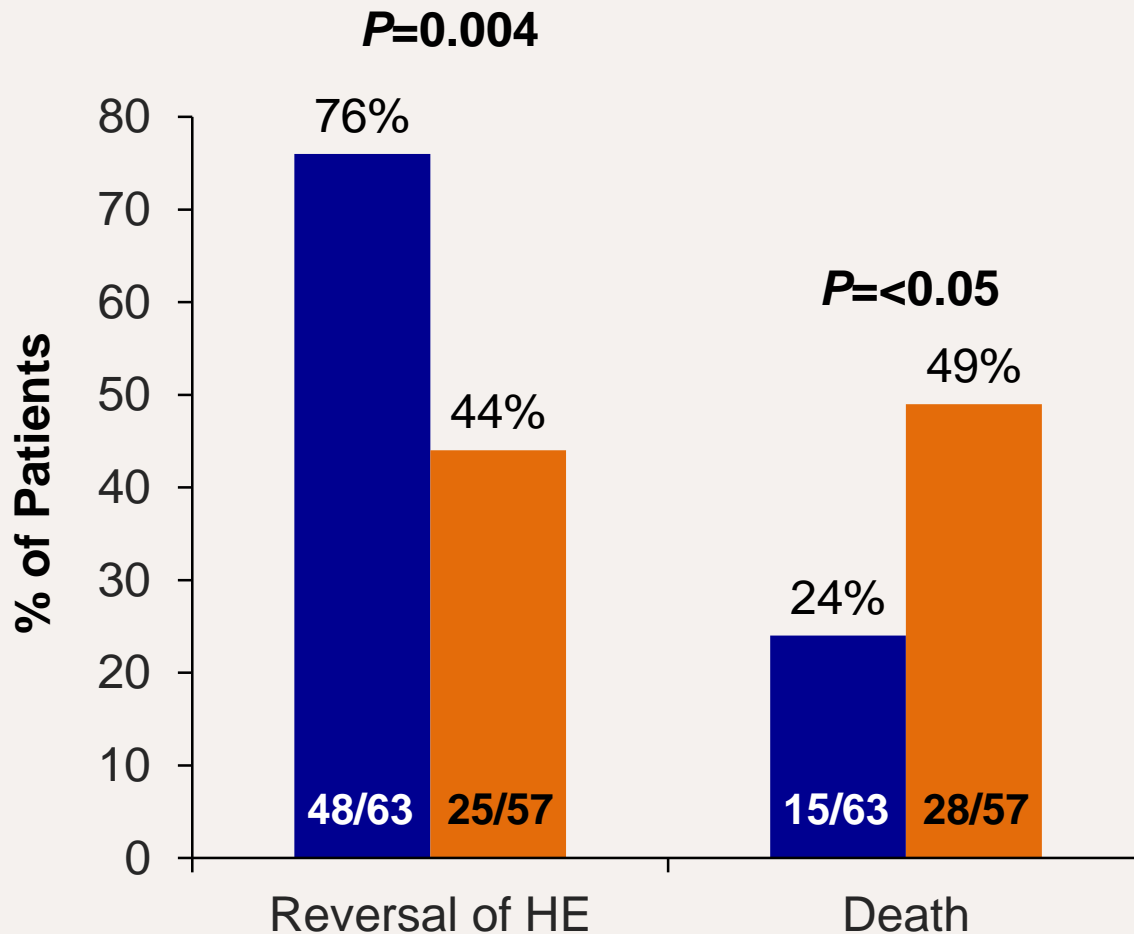
# Proposed Algorithm for Inpatient OHE Management



# Treatment Approach for Acute Overt Hepatic Encephalopathy

- Precipitating factors:
  - GI bleeding
  - Infection
  - Sedating medications
  - Electrolyte abnormalities
  - Constipation
  - Renal Failure

# Treatment Approach for Acute Overt Hepatic Encephalopathy: Lactulose + Rifaximin vs. Lactulose



■ Lactulose + Rifaximin  
■ Lactulose + Placebo

- Treatment was given through nasogastric tube and continued until recovery of HE or a maximum of 10 days
- Hospital stay was shorter with lactulose + rifaximin than with lactulose + placebo (5.8±3.4 vs. 8.2±4.6 days,  $P=0.001$ )

# Treatment Approach for Acute Overt Hepatic Encephalopathy

## General supportive and nutritional interventions

General supportive care	<ul style="list-style-type: none"><li>• Fall precautions in disoriented patients</li><li>• Prevention of infections--changing IV lines, prevent aspiration pneumonia, isolation</li></ul>
Nutritional support	<ul style="list-style-type: none"><li>• Regular protein diets are recommended</li><li>• Consider addition of branched-chain amino acids (valine, leucine, and isoleucine) and zinc; consider eliminating wheat and milk proteins</li></ul>

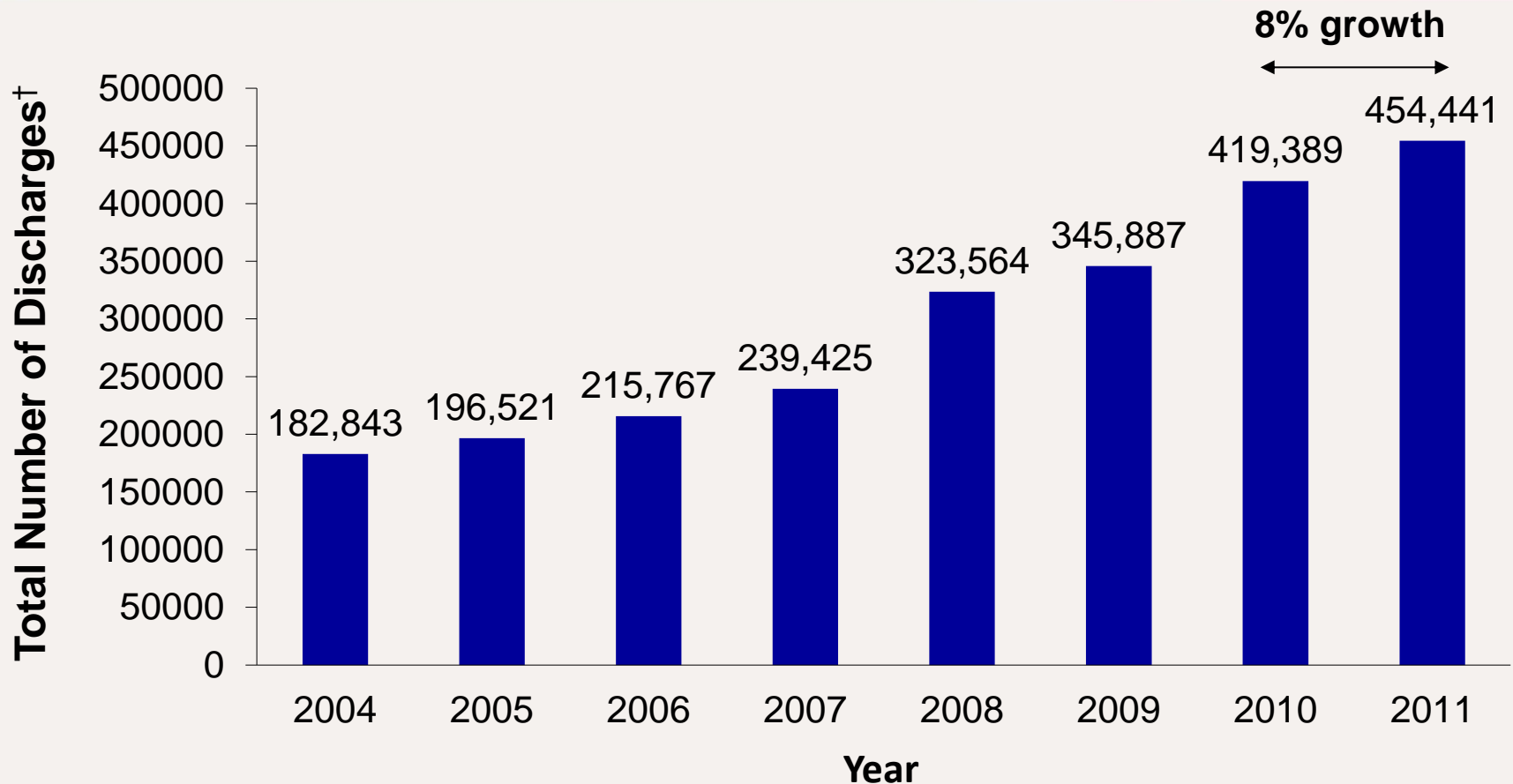
# Outpatient Management after an Episode of OHE

- Treatment goals
  - Prevention of recurrent episodes of HE
  - Improvement of daily functioning
  - Evaluation for liver transplant

# Prophylactic Treatment of HE

- Treating patients with covert HE to prevent development of a first episode is referred to as **primary prophylaxis** of HE
- Preventing recurrence of HE in patients who had a previous episode of HE is referred to as **secondary prophylaxis** of HE

# US Hospital Discharges Associated with Hepatic Encephalopathy\* Are Increasing



HE = hepatic encephalopathy; ICD = International Classification of Diseases.

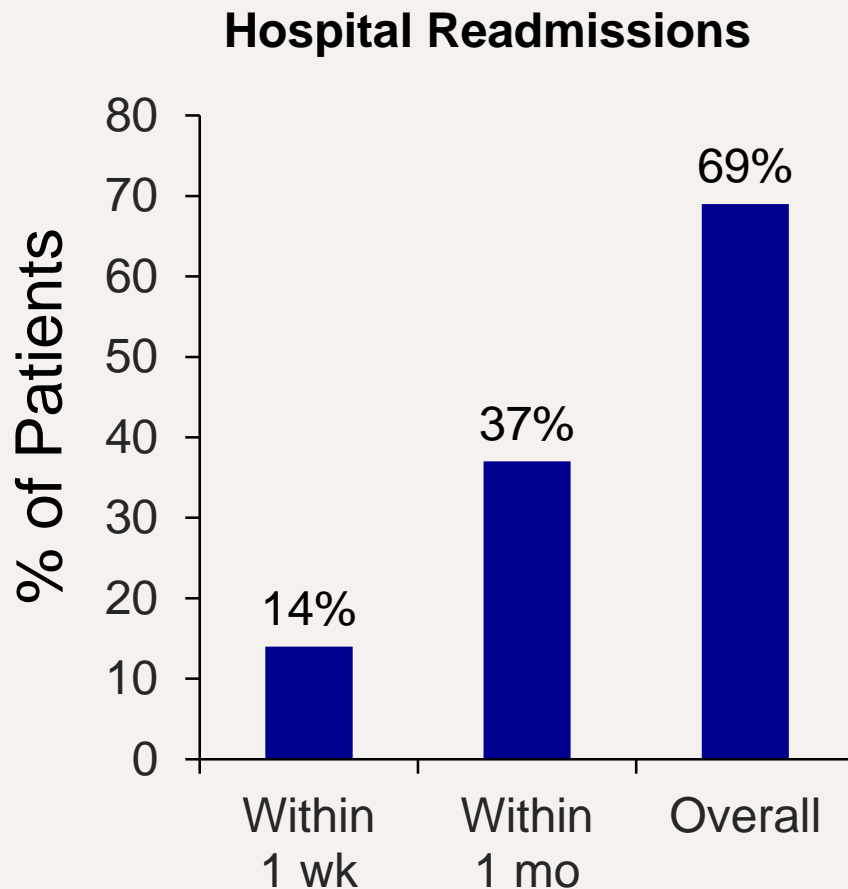
\*Data calculated using ICD-9-CM codes 291.2 (alcoholic dementia, not elsewhere classified), 348.30 (encephalopathy, not otherwise specified), and 572.2 (hepatic coma). †Includes all listed discharge diagnoses.

HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD.

<http://hcupnet.ahrq.gov>. Accessed January 2014.



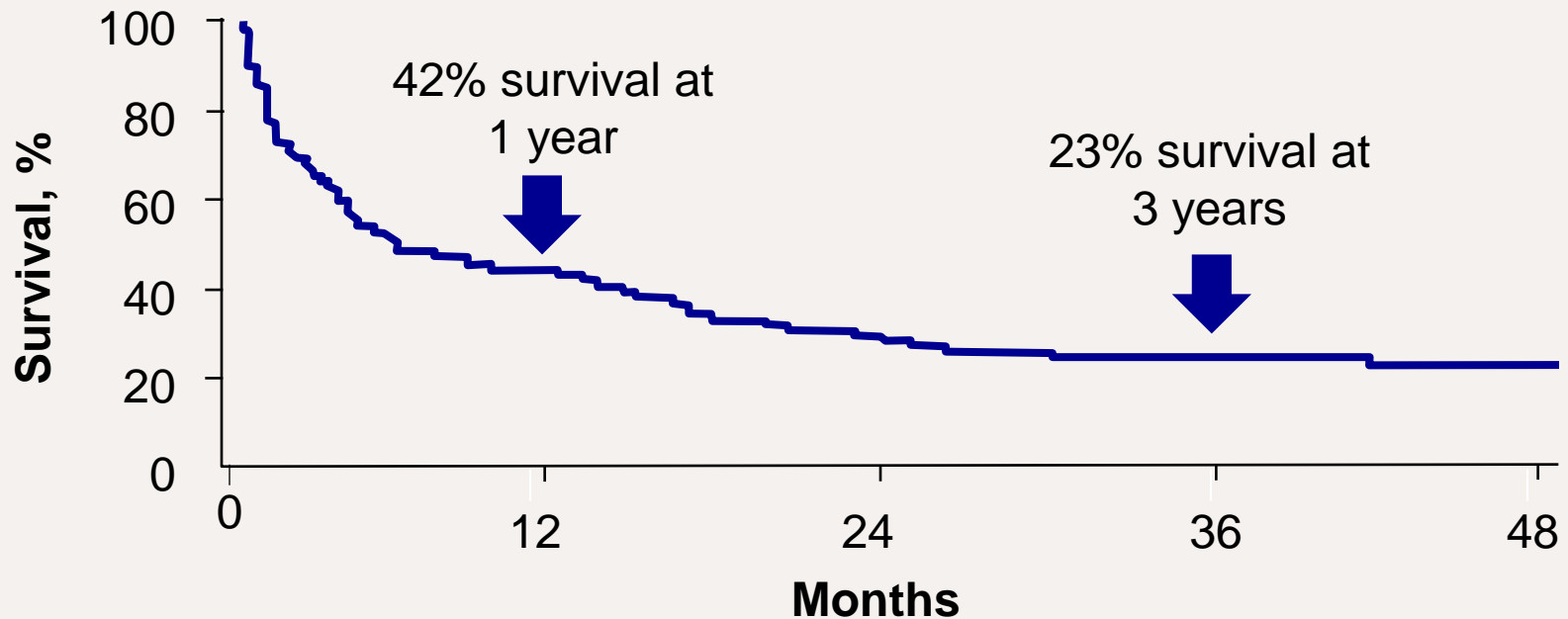
# Hospital Readmissions Among Patients with Decompensated Cirrhosis are Common



- Retrospective study of 402 patients from an academic transplant center
- Follow-up time censored at death, elective admissions such as transplant or post-procedure observation, or the date of last clinic note; median follow-up was 203 days
- Population included cirrhotic patients hospitalized for ascites, spontaneous bacterial peritonitis, renal failure, hepatic encephalopathy, or variceal hemorrhage
- Median time to first readmission was 67 days
- Median number of readmissions was 2 (range 0-40); overall rate was 3 hospitalizations/person-years

# Overt HE Is Associated with a Poor Prognosis

- <50% survival at 1 year after diagnosis of HE;  
<25% survival at 3 years



# Other Management Concerns

- Tim's OHE is well controlled on medical therapy. He returns after his hospitalization for follow-up to pre-transplant clinic.
- On review on his medication list his MD sees that he is on a beta-blocker as primary prophylaxis.
- Would you continue this medication?

# Background

- Non-selective beta-blockers (NSBBs) prevent portal hypertensive bleeding in patients with cirrhosis.
- But studies suggest NSBB use is associated with decreased survival in patients with refractory ascites.
  - NSBBs may reduce perfusion of vital organs

# NSBBs Increase AKI

- Nested case-control of liver transplant waitlist registrants at Mayo clinic
  - Cases developed AKI (2-3 fold increase in serum Cr)
  - Matched by MELD-Na score, age at registration, baseline creatinine, and follow-up duration
- Impact of NSBB on AKI incidence was different according to the presence of ascites:
  - NSBB use with ascites was associated with development of AKI (hazard ratio [HR], 2.79; 95% confidence interval [CI], 1.40-5.54),
  - Without ascites, NSBB was protected (HR, 0.19; 95% CI, 0.06-0.60)

# Conclusions

- Cirrhosis can be asymptomatic
- Screening and surveillance of life threatening complications can allow early recognition and preventative strategies
- Individuals with symptomatic cirrhosis and liver cancer should be considered for liver transplantation
  - Linkage to experienced providers is instrumental