Hot Topics in Liver Disease 2019

Steve Fern, D.O.

Specialists in Gastroenterology

Saint Louis, Missouri

UNECOM 1989

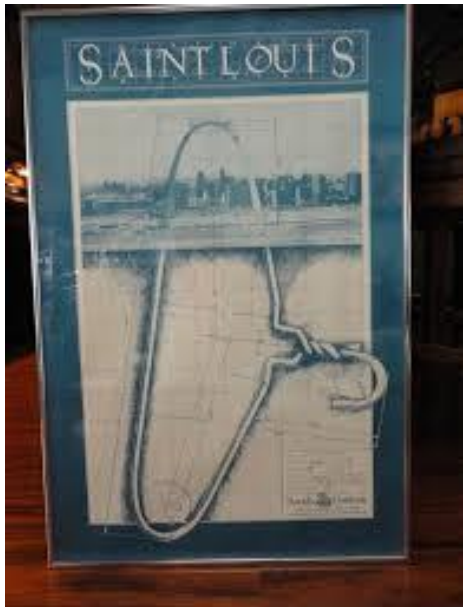
DISCLOSURES

No disclosures

Who AM I?

Cardinals™

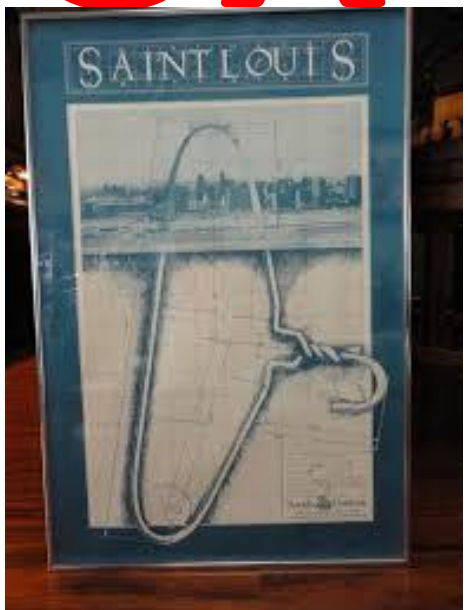
SIG
specialists in gastroenterology



CRP
Clinical
Research
Professionals

Who AM I?

DIEHARD RED SOX FAN



CRP Clinical Research Professionals

OBJECTIVES

What's New in HCV?

What about NAFLD/NASH?

What's New in Cirrhosis?

- General Evaluation
- Managing Complications
  - Varices
  - Thrombocytopenia
  - Hepatic Encephalopathy

OBJECTIVES

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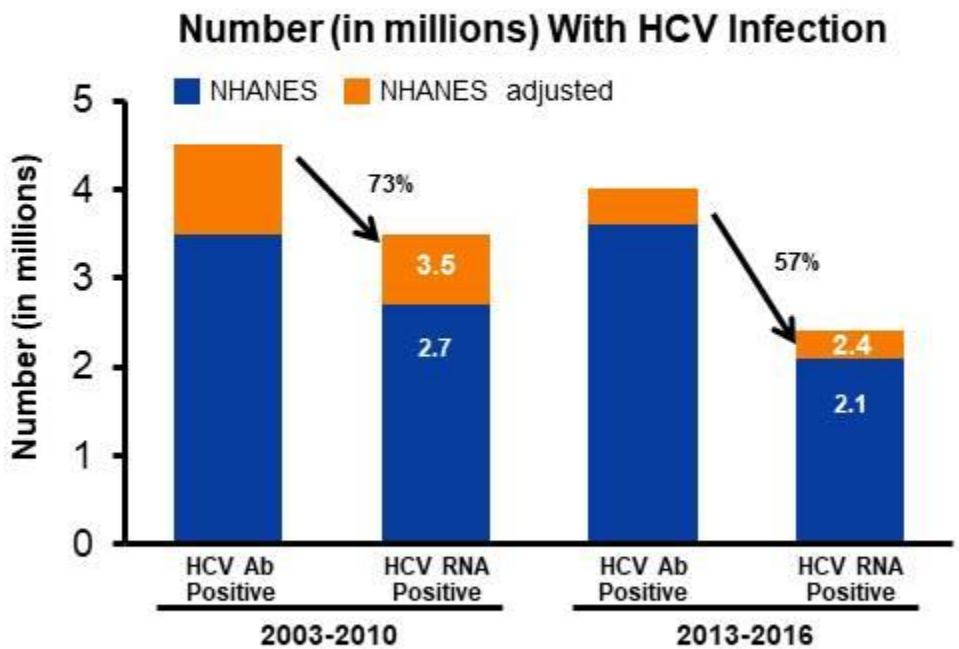
Acute Hepatitis C on the Rise

CDC (2013-2016): Estimated HCV Prevalence Among Adults in the United States

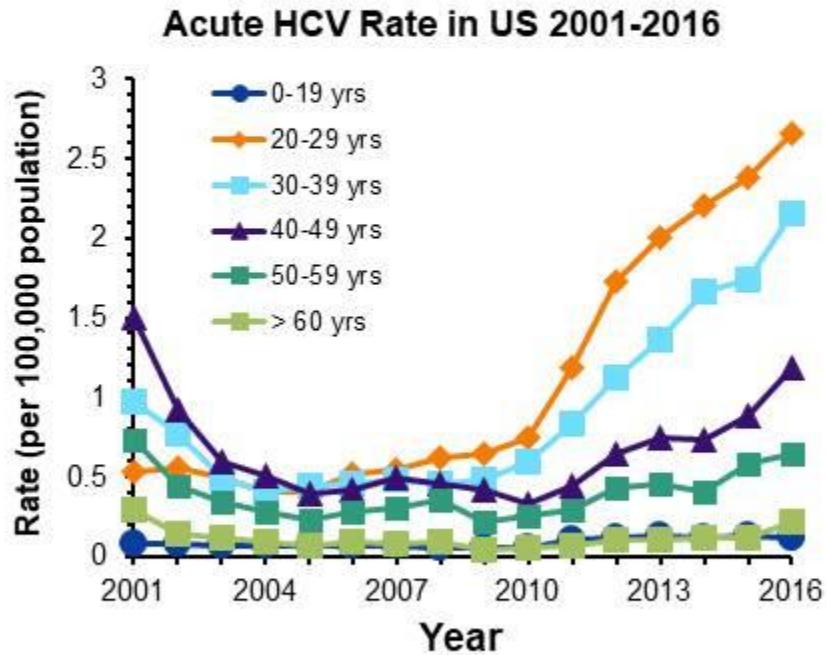
- HCV antibody positive (including past and current infection)
  - Number: 4.1 million (95% CI 3.4-4.9)
  - Prevalence: 1.7% (95% CI 1.4-2.0)
- HCV RNA positive (including current infection)
  - Number: 2.4 million (95% CI 2.0-2.8)
  - Prevalence: 1.0% (95% CI 0.8-1.1)



Estimated adult US population in 12/2016: 245 million.
Datasets analyzed: National Health and Nutrition Examination Survey (noninstitutionalized civilian population).
Combination of literature reviews and population size estimation approaches (incarcerated people, unsheltered homeless people, active-duty military personnel, and nursing home residents).
Hofmeister MG, et al. *Hepatology*. 2019 Mar;69(3):1020-1031. doi: 10.1002/hep.30297. Epub 2018 Nov 6.

Changing Trends in Acute HCV in the US (2001-2016)

- New acute HCV infection in 2016
  - Reported cases (n=2967)
  - Estimated (n=41,200, adjusted for under-ascertainment and under-reporting)
- 3.5-fold increase in new cases since 2010
  - Reflects new infections associated with rising rates of injection-drug use
- Most newly acquired acute HCV infections occurred among young, white, PWIDs, who live in non-urban areas (i.e., Appalachian, Midwestern, and New England states)



CDC. Surveillance for viral hepatitis - United States, 2016. https://www.cdc.gov/hepatitis/statistics/2016surveillance/index.htm

Populations at Risk

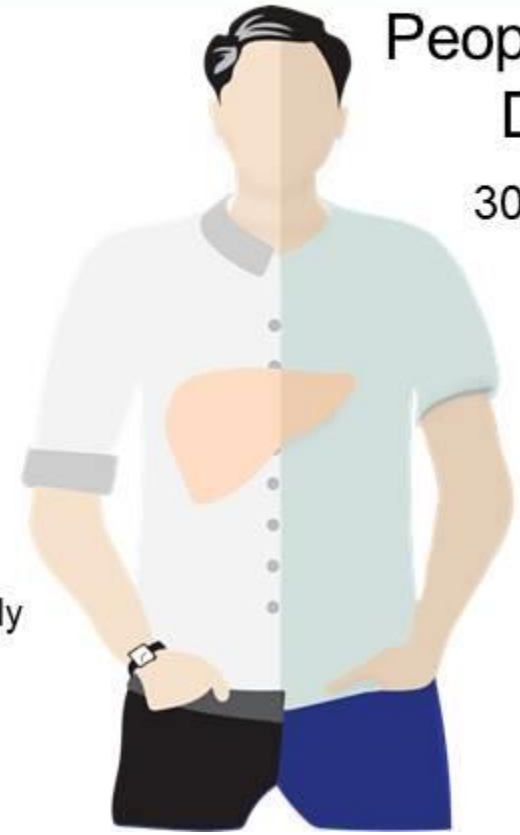
Baby Boomers (born 1945-1965)

1960s
Up to 300,000 cases of acute HCV per year; risk of exposure via blood transfusion up to 33%

1970s
Volunteer donor system reduces risk of exposure via blood transfusion

1989
HCV discovered

1992
Widespread introduction of HCV antibody testing



People Who Inject Drugs (PWID)

30-70% prevalence

Alter HJ. *Nat Med.* 2000;6:1082-1086.

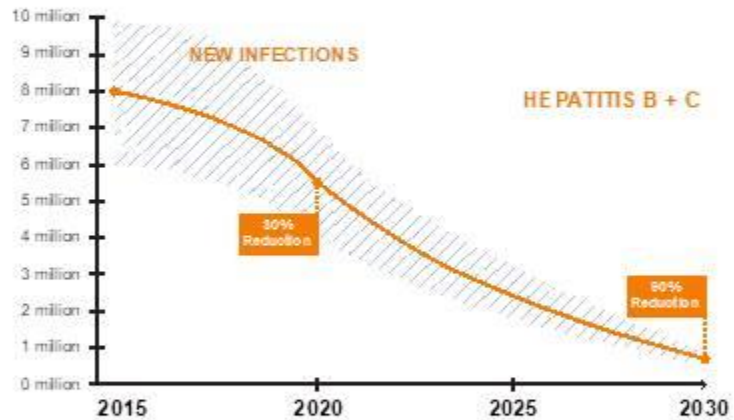
Hot Topics in Liver Disease 2019

WHO Goal: Global Elimination of Viral Hepatitis

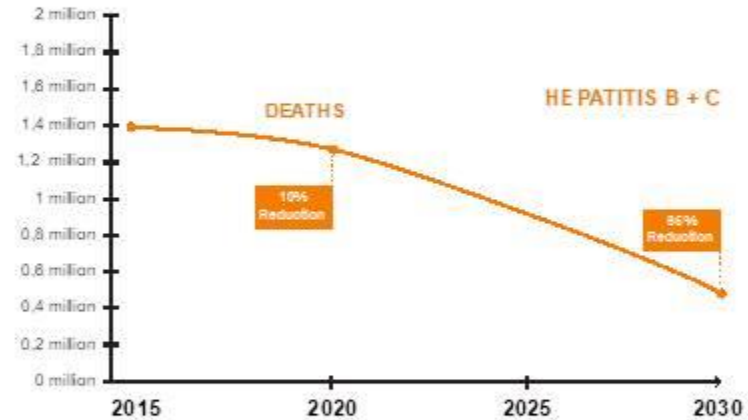
Global Health Sector Strategy: Eliminate Viral Hepatitis as a Major Public Health Threat by 2030

Impact Targets

Reduction in new infections by 90%



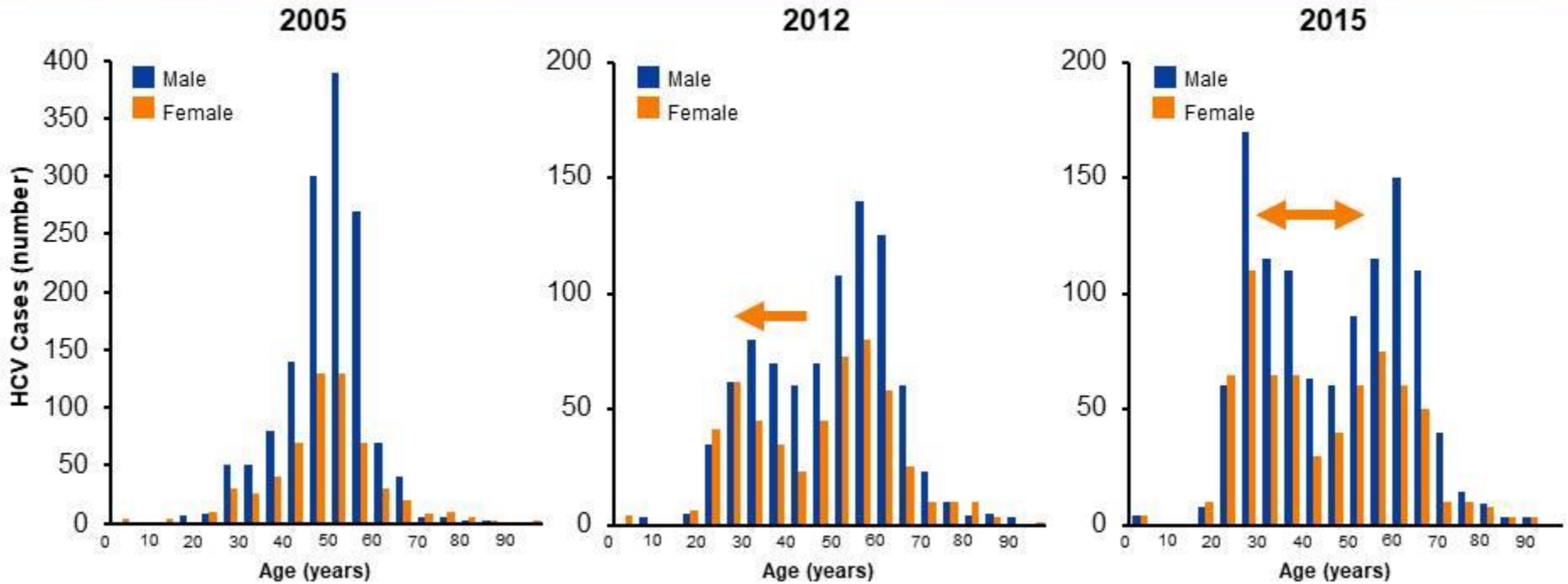
Reduction in deaths by 65%



Programmatic Targets

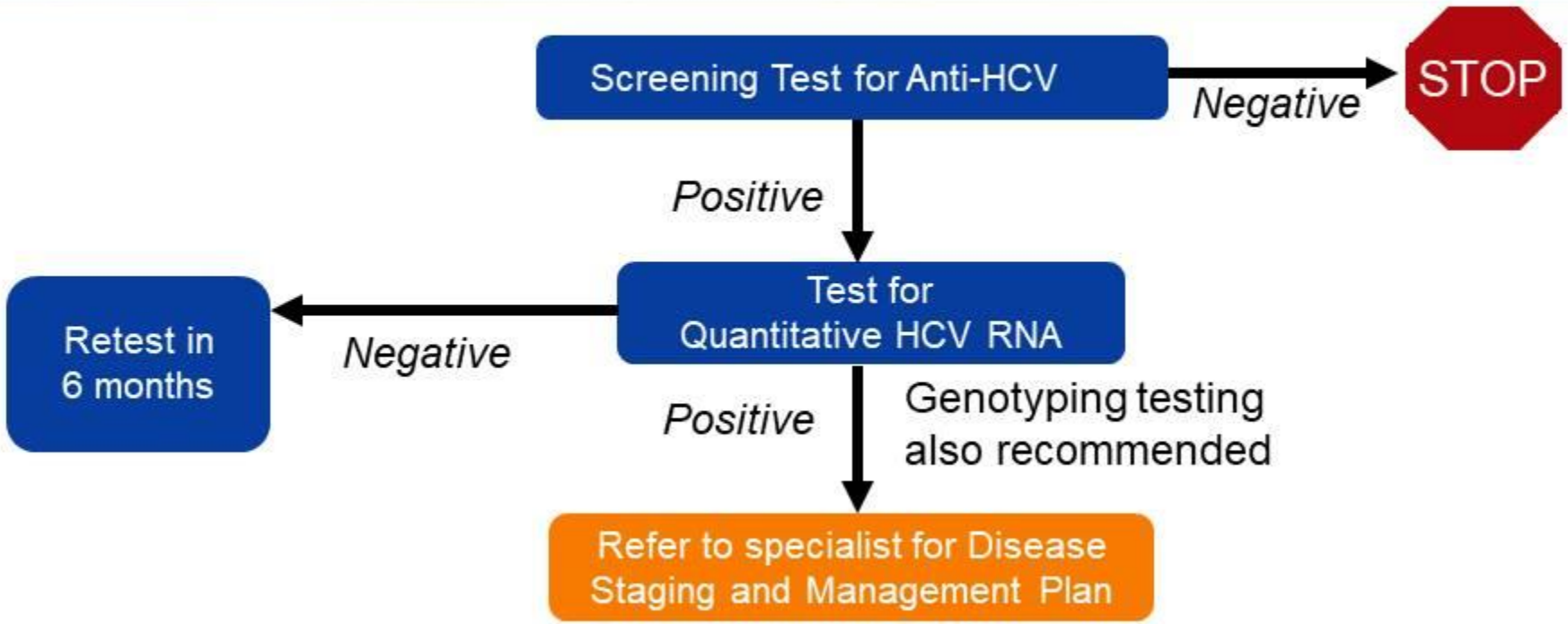
90% of people infected are diagnosed	**80%** of people diagnosed are treated	**90%** coverage of BD and B3 doses (PAHO: 95%)	**100%** of blood products are safe	**90%** of injections in health facilities are safe

HCV No Longer a Disease Limited to Baby Boomers



Data for New York State (excluding NYC).
https://www.health.ny.gov/statistics/diseases/communicable/index.htm.

HCV Screening Is Straightforward: Algorithm for Screening/Diagnosis



Modified from http://www.cdc.gov/hepatitis/HCV/PDFs/hcv_flow.pdf.
Ghany MG, et al. *Hepatology*. 2011;54(4):1433-1444.

OBJECTIVES

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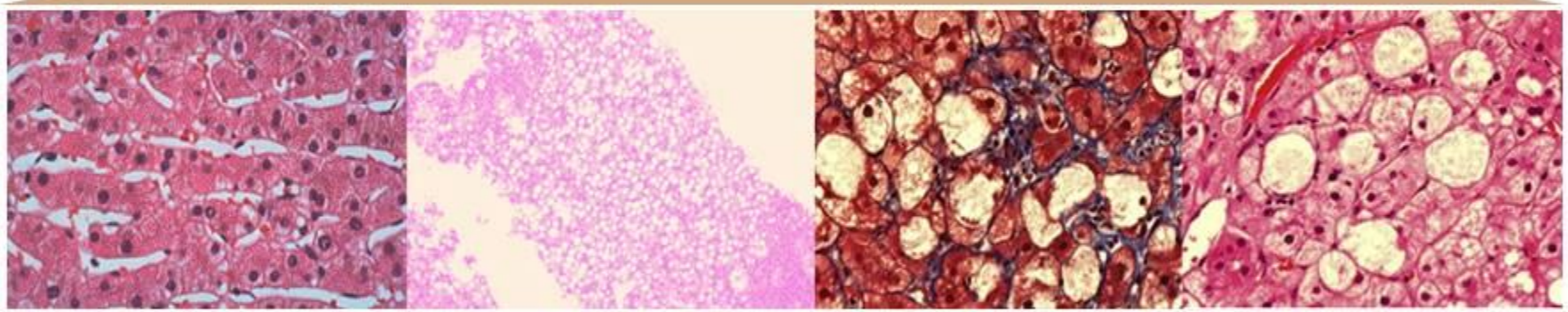
- Thrombocytopenia
- Hepatorenal Syndrome
- Hepatic Encephalopathy

NAFLD Encompasses the Entire Spectrum of Fatty Liver Disease

NAFLD

Disease of hepatic fat accumulation absent alcohol consumption, hereditary disorders, or steatogenic medication use



Normal

NAFL

- >5% hepatic steatosis
- No evidence of hepatocyte injury (ballooning) or fibrosis

NASH

- Progressive type of NAFLD
- >5% hepatic steatosis ± inflammation with hepatocyte injury (ballooning) ± fibrosis

NASH Cirrhosis

Cirrhosis + current or previous histological evidence of steatosois

Chalasani N et al. *Hepatology*. 2018;67(1):328-357.

NAFLD in the United States

30% to 40%
of Americans have NAFLD[1]

3% to 12%
of Americans have NASH[1]

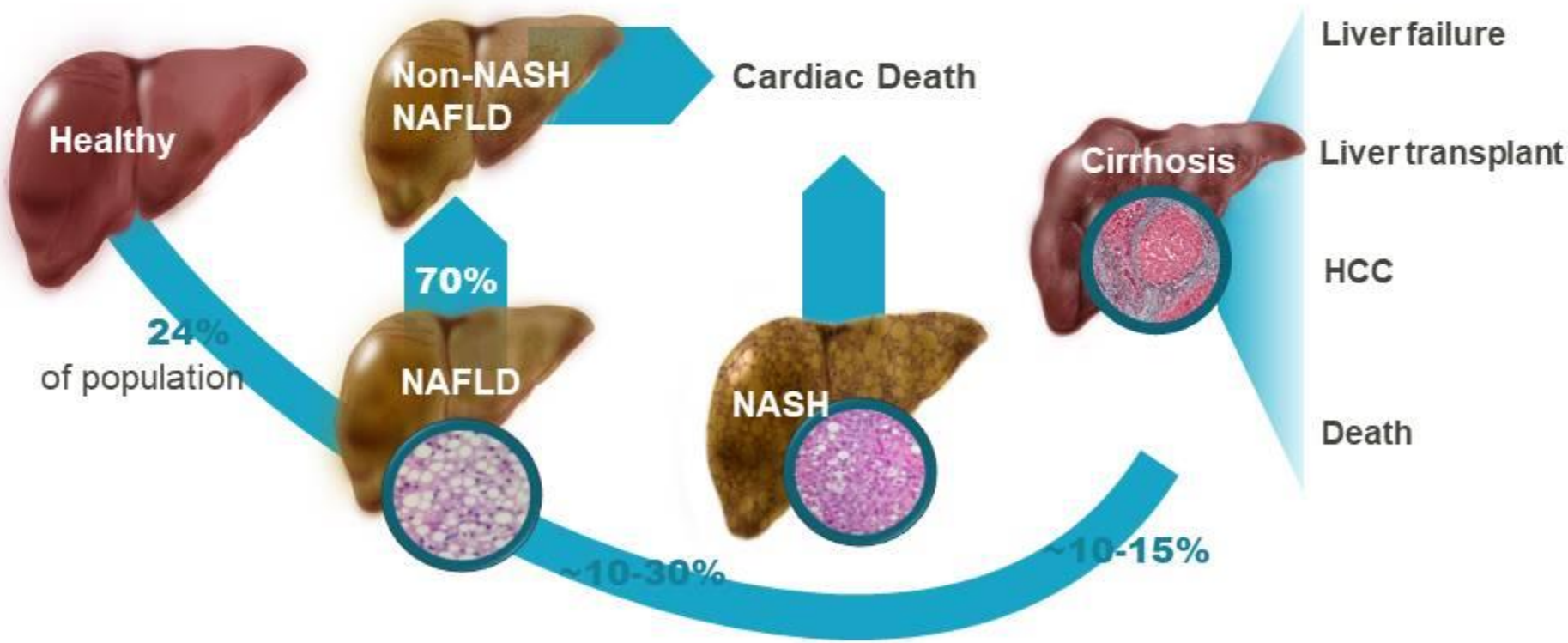
#2
leading indication for liver transplantation in the US after HCV[2]

#3
most common cause of HCC in the US[3]

$103 billion
estimated annual direct costs of NAFLD[4]

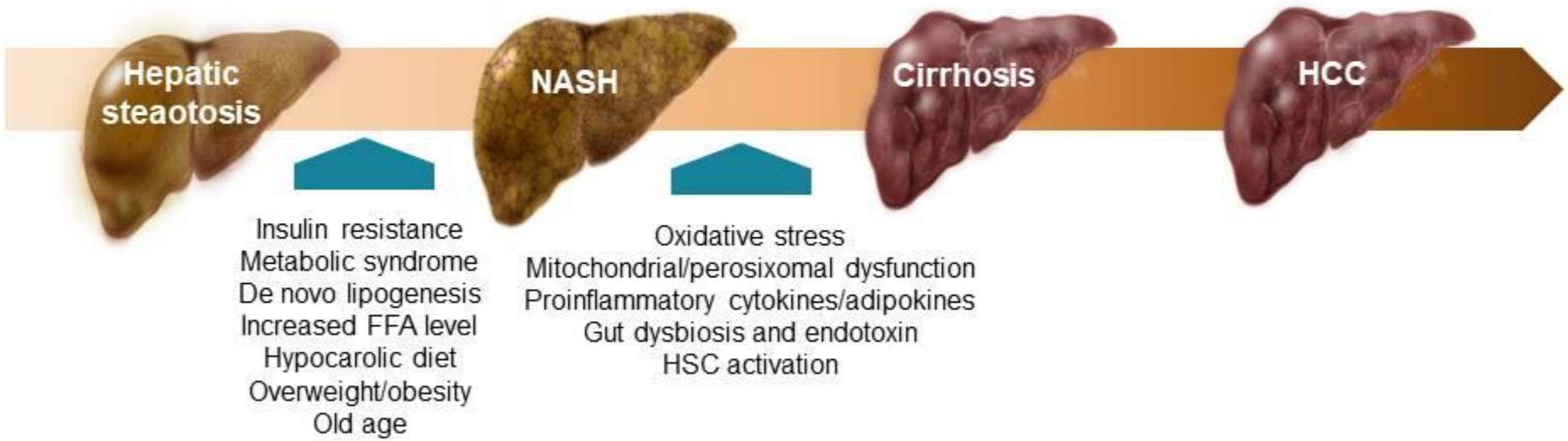
1. NIDDKD. Available at https://www.niddk.nih.gov/health-information/liver-disease/nafld-nash/definition-facts. Accessed May 18, 2018.
2. Wong RJ et al. *Gastroenterology*. 2015;148:547-555.
3. Mohamad B et al. *Hepatol Int*. 2016;10:632-639. **4.** Younossi ZM et al. *Hepatology*. 2016;64(5):1577-1586.

Natural History of NAFD and NASH



1. Younossi Z. *Clin Liver Dis.* 2018;11(4):92-94. **2.** Rinella ME. *JAMA.* 2015;313(22):2263-2273.

Disease Progression in NAFLD Attributed to Multiple Hits



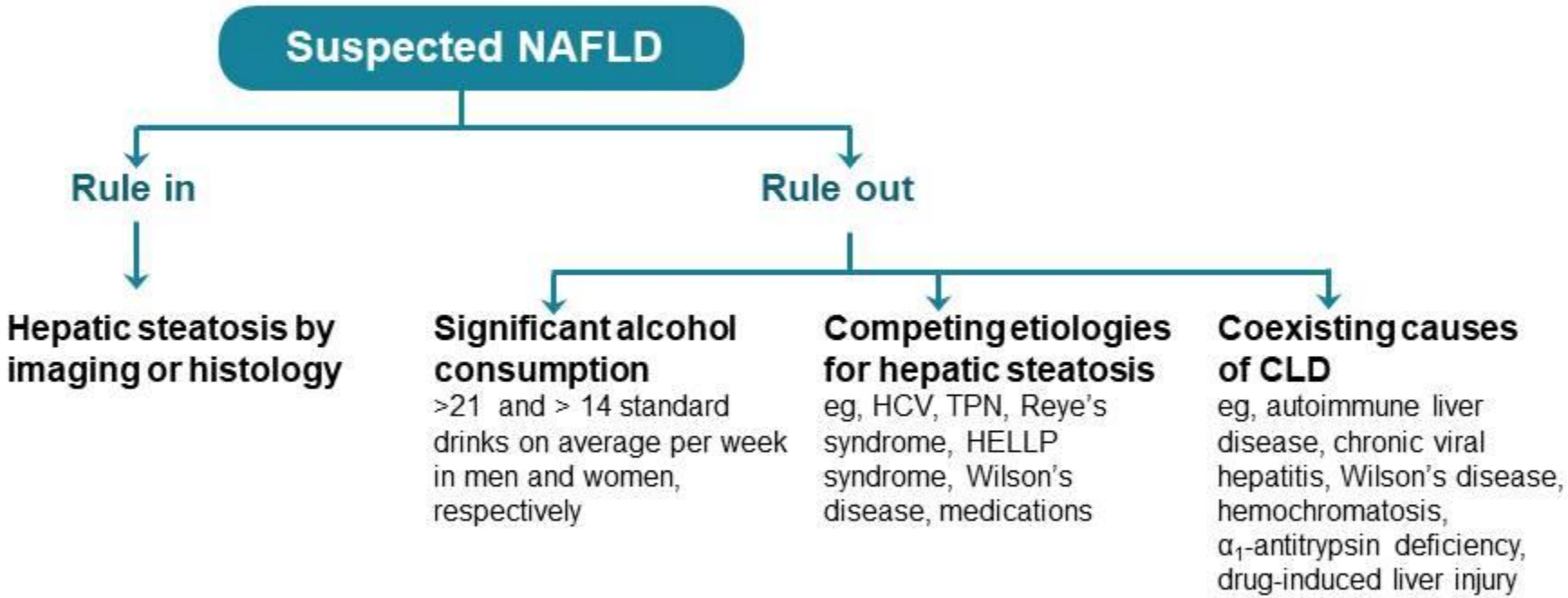
Fierbinteanu-Braticevici C et al. *Cell Biol Toxicol*. 2017;33:5-14.

Risk Factors Associated with NAFLD

Common conditions with established association	Other conditions associated with NAFLD
Obesity	Hypothyroidism
T2DM	Obstructive sleep apnea
Dyslipidemia	Hypopituitarism
Metabolic Syndrome	Hypogonadism
Polycystic ovarian syndrome	Pancreatoduodenal resection
	Psoriasis

Chalasani N et al. *Hepatology*. 2018;67(1):328-357.

AASLD Requirements for Diagnosing NAFLD



CLD, chronic liver disease; HCV, hepatitis C virus; TPN, total parenteral nutrition; HELLP, .
Chalasani N et al. *Hepatology*. 2018;67(1):328-357.

AASLD Guidance for Noninvasive Identification of Patients At High Risk for NASH

Decision Aids

Metabolic syndrome	Predicts the presence of SH and useful in targeting patients for liver biopsy
NFS **FIB-4 index** **ELF**	Useful for identifying NAFLD patients with higher likelihood of bridging fibrosis (stage 3) or cirrhosis (stage 4)

Imaging

VCTE Vibration-controlled Transient Elastography **MRE** Magnetic Resonance Elastography	Useful for identifying advanced fibrosis in patients with NAFLD

Chalasani N et al. *Hepatology*. 2018;67(1):328-357.

Other Causes of Hepatic Steatosis

Examples of other causes of fatty liver

- Excessive alcohol consumption
- Malnutrition
- Medications
- Parenteral nutrition

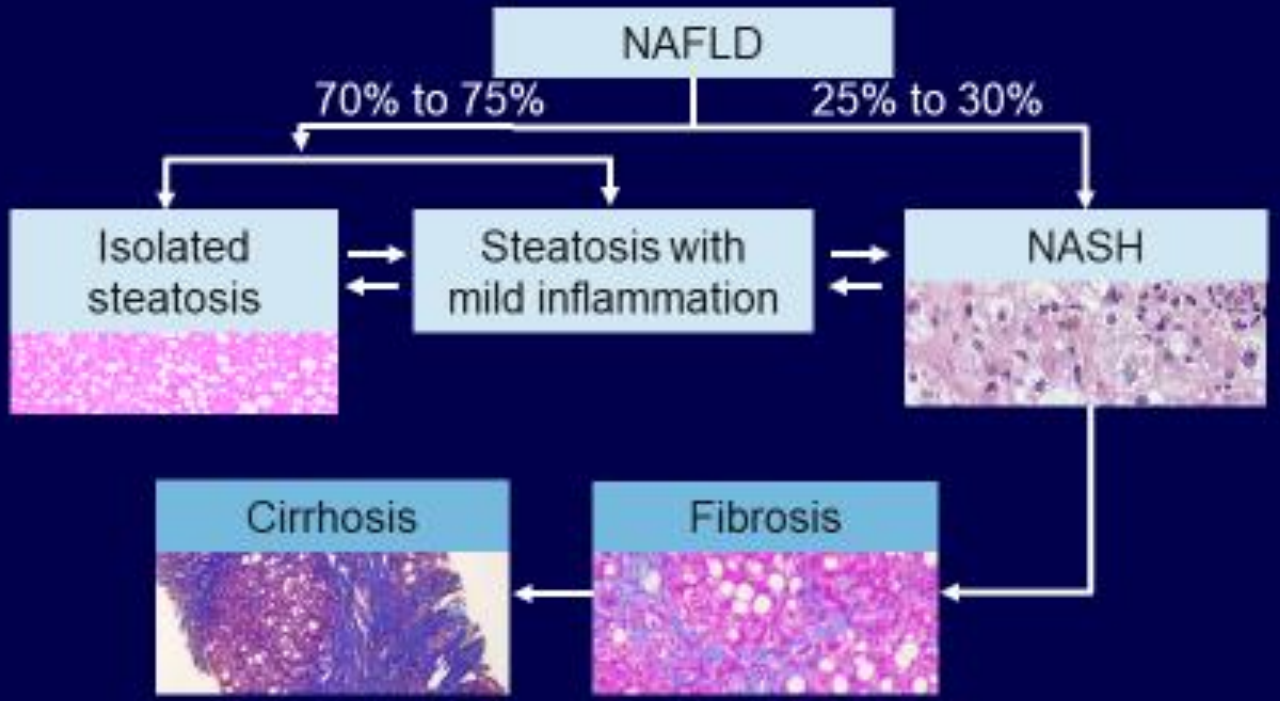
Examples of other liver diseases that can present with steatosis

- Hepatitis C, acute hepatitis D
- Wilson disease
- Hemachromatosis
- Lipodystrophy
- Lysosomal acid lipase deficiency

Angulo P, et al. Hepatology. 2007;45:846-854.
Brunt EM, et al. Nat Rev Dis Primers. 2015;1:15080.

NAFLD Disease Progression

Histological Subtypes[1,2]



Change in Fibrosis*[3,4]

Regression: 18%-22%

Stable: 40%-43%

Progression: 34-42%

*N = 108 pts with NAFL/NASH and median 6.6 yrs follow-up (data from serial biopsies).

1. Ludwig J, et al. Mayo Clin Proc. 1980;55(7):434-438.
2. Kleiner DE, et al. Hepatology. 2005;41(6):1313-1321.
3. McPherson S, et al. J Hepatol. 2015;62:1148-1155.
4. Singh S, et al. Clin Gastroenterol Hepatol. 2015 Apr;13(4):643-54

Noninvasive Diagnosis of Liver Fibrosis in NAFLD

Clinical or Laboratory Tests		Imaging
Simple	**Complex**	**Elastography**
▪ AST/platelet ratio index ▪ FIB-4 index ▪ NAFLD fibrosis score ▪ BARD score	▪ NASH *FibroSure* ▪ ELF ▪ HepaScore	▪ VCTE *FibroScan* ▪ MR elastography ▪ ARFI

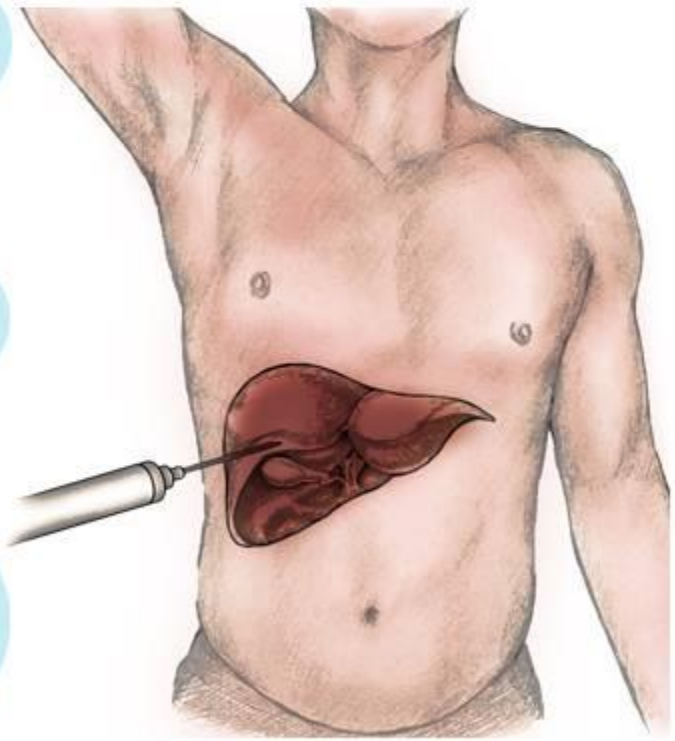
Slide credit: clinicaloptions.com

Liver Biopsy Is the Gold Standard for Characterizing Liver Histological Alterations in NAFLD

AASLD Recommendation for When to Obtain Livery Biopsy in NAFLD

NAFLD +

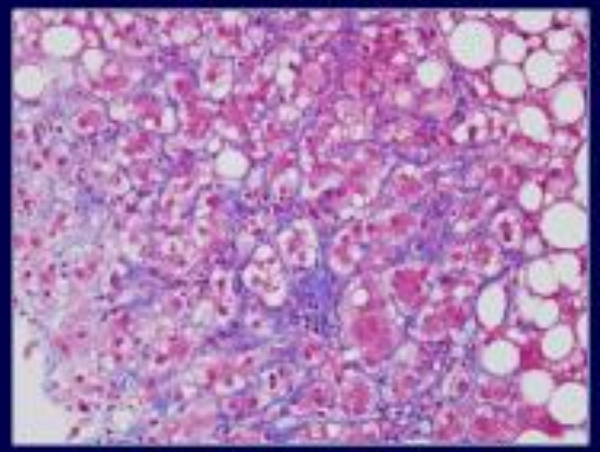
- ↑ risk for steatohepatitis and/or advanced fibrosis
- Metabolic syndrome and elevated LFTs
- Competing etiologies for hepatic steatosis and inability to exclude/assess severity of coexisting CLD without biopsy



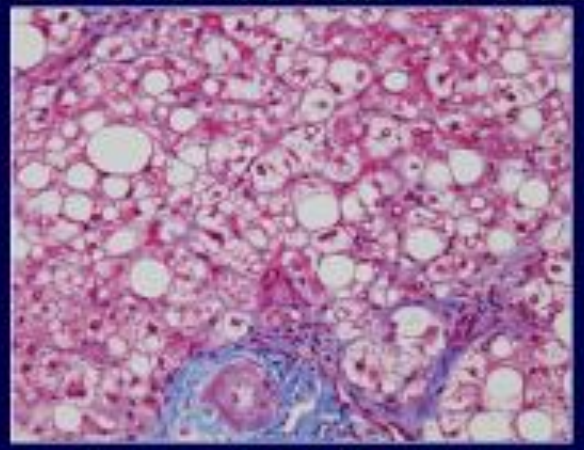
Chalasani N et al. *Hepatology*. 2018;67(1):328-357.

Fibrosis Staging in NASH

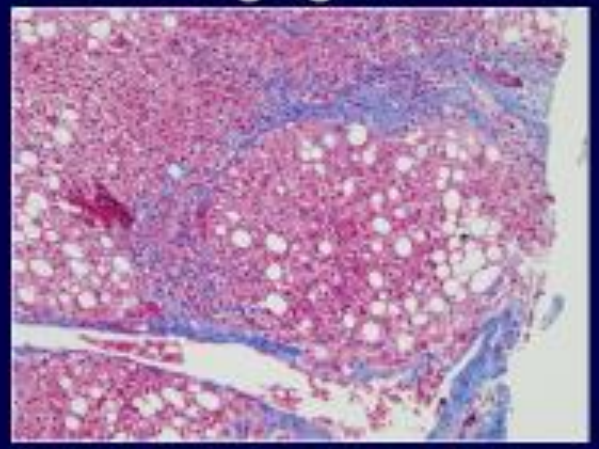
F1: Perisinusoidal



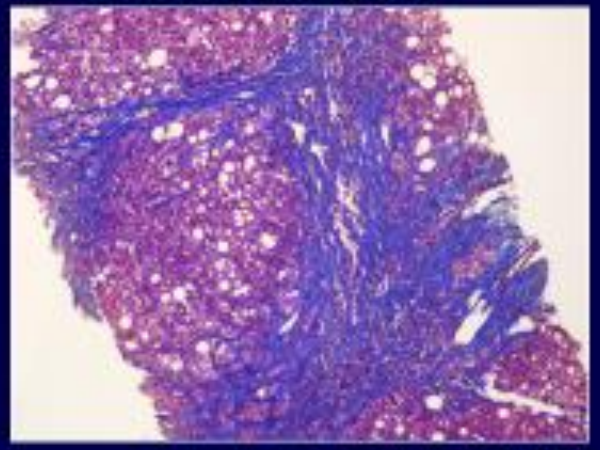
F2: Perisinusoidal + Portal



F3: Bridging Fibrosis



F4: Cirrhosis



Slide credit: clinicaloptions.com

Outline

- Current Best Practices in NASH Management
  - Lifestyle Changes
  - Pharmacologic
  - Surgical Management Strategies
- Investigational Therapies
  - Phase III
  - Phase II

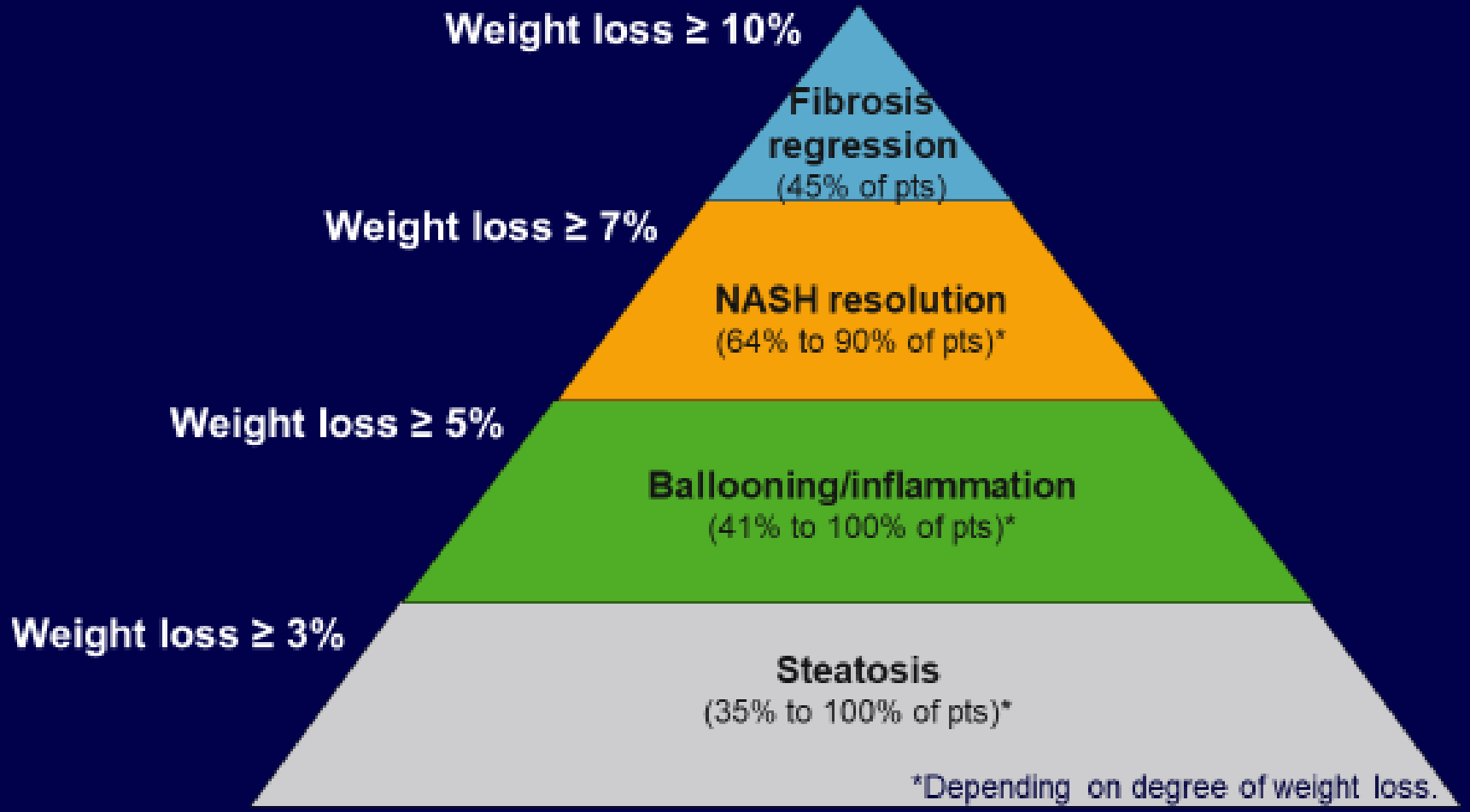
Effect of Diet in NAFLD

- Limiting total caloric intake is ideal and more important than aiming for a specific nutrient composition
- My diet recommendation: limit processed carbs!
  - White/brown bread, rice
  - White/orange potatoes
  - Flour/corn tortillas
  - Pizza/pasta
  - Chips
  - Fructose-containing sodas and juices

Hannah WN, et al. Dig Dis Sci. 2016;61:1365-1374.

Percentage of Weight Loss Associated With Histological Improvement in NAFLD

- Analysis of data from 4 randomized studies



*Depending on degree of weight loss.

Hannah WN, et al. Clin Liver Dis. 2016;20:339-350.

Slide credit: clinicaloptions.com

Effect of Exercise on NAFLD

- Physical inactivity linked to
  - Increased body weight
  - Central adiposity
  - Insulin resistance
  - Increased risk of metabolic syndrome
  - NAFLD
  - Severity of NASH

Hannah WN, et al. Dig Dis Sci. 2016;61:1365-1374.

Lifestyle Recommendations for Treating NASH

Caloric intake reduction
≥30% or
~750-1,000 kcal/day
improved insulin resistance
and hepatic steatosis

Weight loss
of 3% to 5% can improve steatosis, but 6% to 10% is needed to improve NASH/fibrosis

Exercise
alone may reduce steatosis, but effect on other histologic features unknown

No heavy alcohol consumption
Insufficient data to guide recommendations regarding nonheavy alcohol consumption

Chalasani N et al. *Hepatology*. 2018;67(1):328-357.

My Recommendation

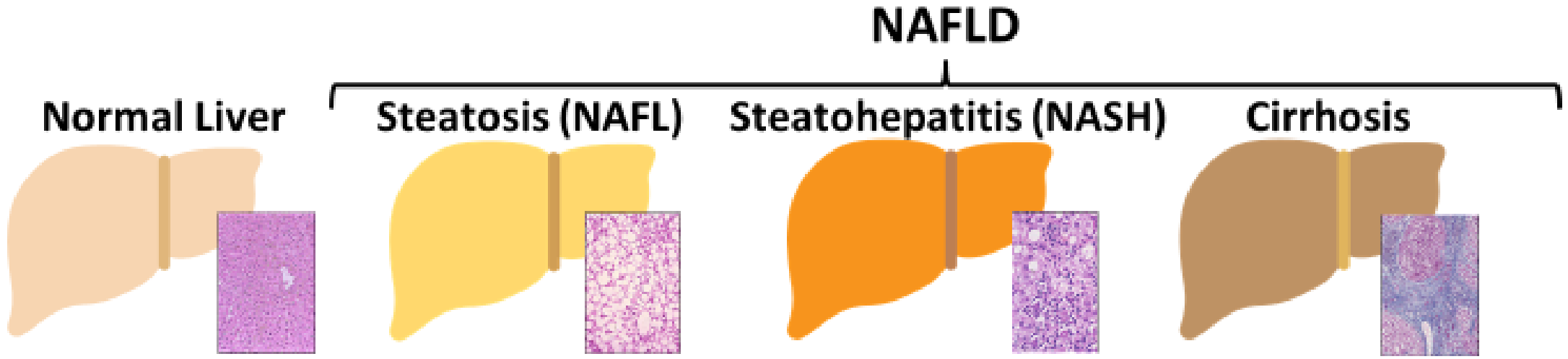
Slide credit: clinicaloptions.com

Current Status of Pharmacologic Treatments for NASH

- No FDA-approved therapies for NASH
- Currently available therapeutics with proven efficacy
  - Vitamin E
  - Pioglitazone
- More limited data
  - Pentoxifylline
  - Liraglutide

Slide credit: clinicaloptions.com

Targeting Pathophysiologic Processes



Targets related to insulin resistance and/or lipid metabolism

- PPARγ: Pioglitazone
- GLP-1: Liraglutide, Semaglutide
- ACC: GS-0976
- SCD1: Aramchol
- FGF21: BMS-986036
- THR-β: MGL-3196, VK 2807

Targets related to lipotoxicity and oxidative stress

- PPARα/δ: Elafibranor
- FXR: OCA, GS-9674, Tropifexor
- FGF19: NGM282
- Vitamin E

Targets related to inflammation and immune activation

- CCR2/5: Cenicriviroc
- TLR4: JKB-121

Targets related to cell death (apoptosis and necrosis)

- ASK1: Selonsertib

Targets related to fibrogenesis and collagen turnover

- Galectin: GR-MD-02

Slide credit: clinicaloptions.com

NASH Treatments Currently in Phase III Investigations

Agent	MoA	Trial	N	Primary Endpoint(s)	Time Point
Cenicriviroc	CCR2/5 antagonist	AURORA[1]	2000	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Elafibranor	PPARα/σ agonist	RESOLVE-IT[2]	2000	Resolution of NASH with no fibrosis worsening	72 wks
Obeticholic acid	FXR agonist	REGENERATE[3]	2370	≥ 1 stage fibrosis improvement with no NASH worsening; resolution of NASH with no fibrosis worsening	18 mos
		REVERSE[4]	540	≥ 1 stage fibrosis improvement with no NASH worsening	12 mos
Selonsertib	ASK1 inhibitor	STELLAR 3[5]	808	≥ 1 stage fibrosis improvement with no NASH worsening; event-free survival	48 wks
		STELLAR 4[6]	883	NASH with compensated cirrhosis	240 wks

Phase III/IV studies use adaptive design

- Histologic endpoints for Subpart H conditional approval
- Clinical endpoints for full approval

1. NCT03028740. 2. NCT02704403. 3. NCT02548351. 4. NCT03439254. 5. NCT03053050. 6. NCT03053063.

Slide credit: clinicaloptions.com

Bariatric Surgery Improves Clinical Parameters

- Prospective study following bariatric surgery in pts who are severely obese (N = 381) with ≥ 1 comorbidity, no excessive drinking < 2 yrs, no chronic liver diseases
  - Liver biopsies assessed by 2 blinded reviewers for fibrosis (F0-4), NAFLD scoring to determine NASH (≥ 3, probable or definite; ≥ 5, definite)

Parameter	Before Surgery	After 5 Yrs	*P* Value
Diabetes mellitus, n (%)	94 (24.8)	24 (10.8)	.00001
Arterial hypertension, n (%)	185 (48.8)	85 (37.0)	.0005
Serum triglycerides, mean (g/L)	1.67	1.06	.00001
Fasting glucose, mean (g/L)	1.18	0.94	.00001
Insulin resistance index, mean	3.2	2.83	.00001
ALT, mean (IU/L)	30.1	22.8	.00003
GGT, mean (IU/L)	39.9	29.2	.00001

Mathurin P, et al. Gastroenterology. 2009;137:532-540.

Slide credit: clinicaloptions.com

Take-Home Points

- Lifestyle changes are the foundation of any treatment plan
  - Weight loss ≥ 3% to 10% associated with histologic improvement in NAFLD
- AASLD guidance cites evidence for vitamin E (NASH without diabetes), pioglitazone (NASH with or without diabetes), bariatric surgery
- Preliminary evidence for improvement in fibrosis with some investigational therapies

Slide credit: clinicaloptions.com

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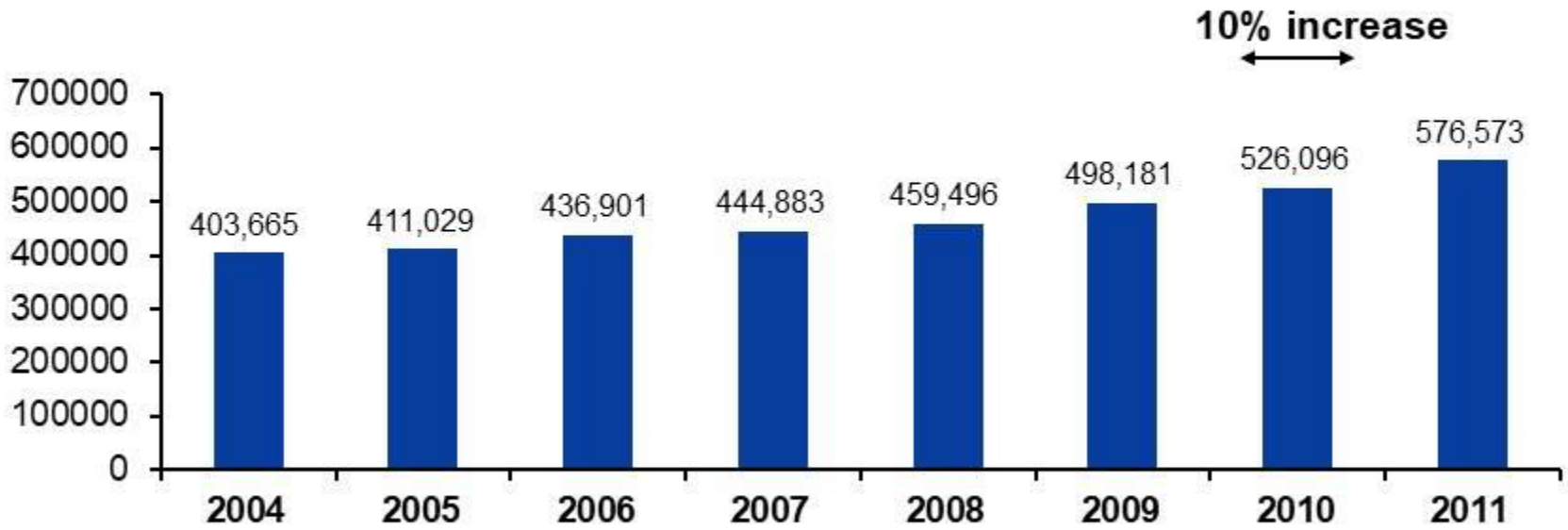
US Hospital Discharges Due to Cirrhosis Are Increasing



*ICD-9-CM diagnosis codes 571.2. 571.5, 571.6; all listed diagnoses.
HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. http://hcupnet.ahrq.gov. Accessed January 2014.

Cirrhosis Is the Final Pathway for Most Chronic Liver Diseases

Accumulation of collagen deposition= fibrosis → cirrhosis

Decompensation/ liver failure

Hepatocellular carcinoma

Liver transplantation

Histology image obtained from http://en.wikipedia.org/wiki/Cirrhosis. Accessed March 26, 2018.
Ge PS, Runyon BA. *N Engl J Med*. 2016;375:767-777.

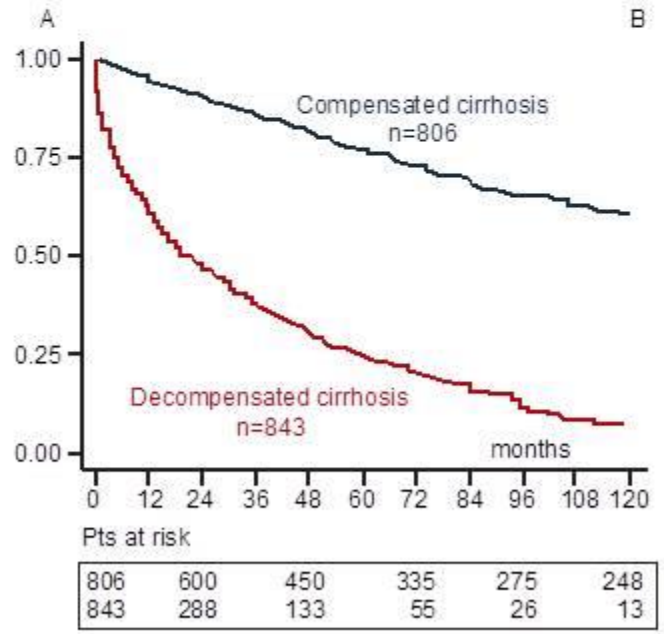
Compensated Cirrhosis May Be Difficult to Recognize

- Most patients remain asymptomatic until decompensation occurs
- Clues may be overlooked
  - Thrombocytopenia
  - Muscle wasting
  - AST>ALT without alcohol consumption
  - Liver enzymes are frequently normal
- Etiology may be remoted or subtle
  - Prior alcohol use
  - Uncontrolled diabetes mellitus and obesity

Tsochatzis EA et al. *Lancet*. 2014;383:1749-1761; Heidelbaugh JJ, Bruderly M. *Am Fam Phys*. 2006;74:756-762.

Survival Is Significantly Longer in Compensated Cirrhosis Compared with Decompensated Cirrhosis

Survival According to Decompensation At Diagnosis



>12 year median survival
in patients with compensated cirrhosis

D'Amico G et al. *J Hepatol*. 2006;44:217-231.

Child-Pugh Score: A Prognostic Score in Cirrhosis

	Points		
	1	2	3
Encephalopathy	None	Precipitant	Recurrent
Ascites	None	Controlled	Refractory
PT (sec prolonged) or INR	<4 <1.7	4-6 1.7-2.3	>6 >2.3
Bilirubin	<2	2-3	>3
Albumin	>3.5	3.0-3.5	<3.0

Child A: **5-6** pts — **Compensated**

Child B: **7-9** pts — **Start transplant evaluation**

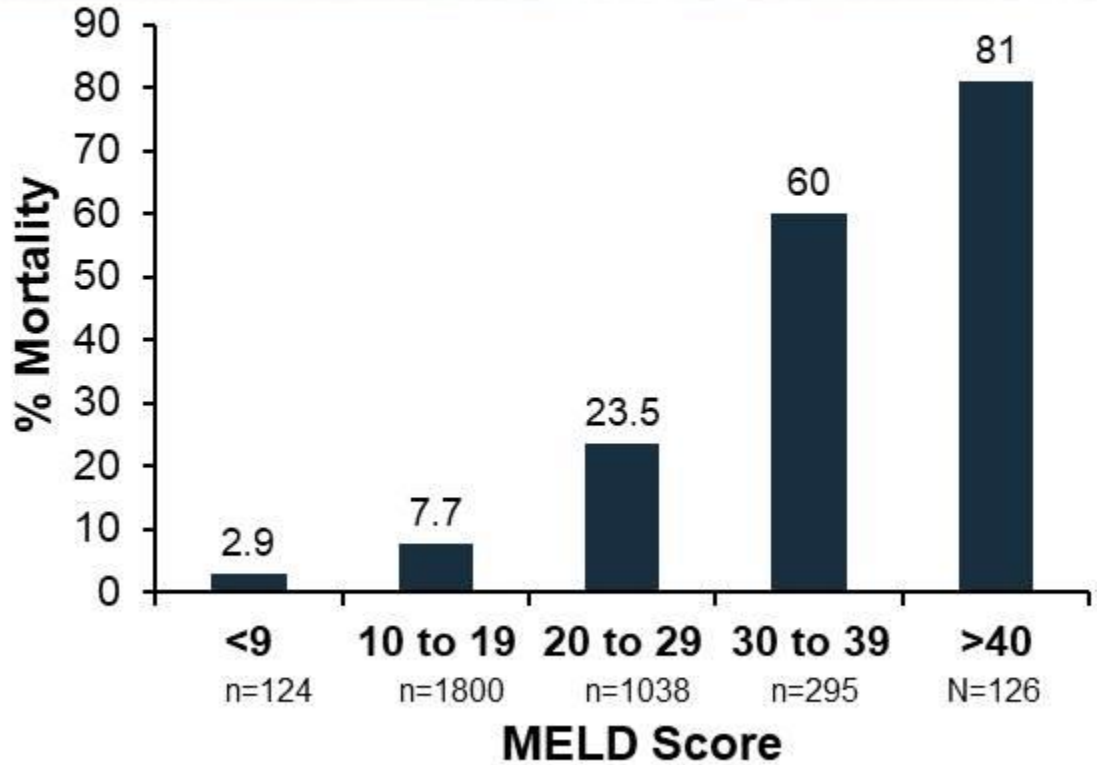
Child C: **10-15** pts

Classification of Cirrhosis Severity Model for End Stage Liver Disease Score

- Calculated from 3 variables:
  - International normalized ratio (INR; calculated from prothrombin time)
  - Bilirubin
  - Serum creatinine
- The MELD score equation:
  - [9.57 x log creatinine mg/dL + 3.78 x log bilirubin mg/dL + 11.20 x log INR + 6.43 (constant for liver disease etiology)]
- Eliminates subjectivity of encephalopathy and ascites evaluation used in Child Pugh Score

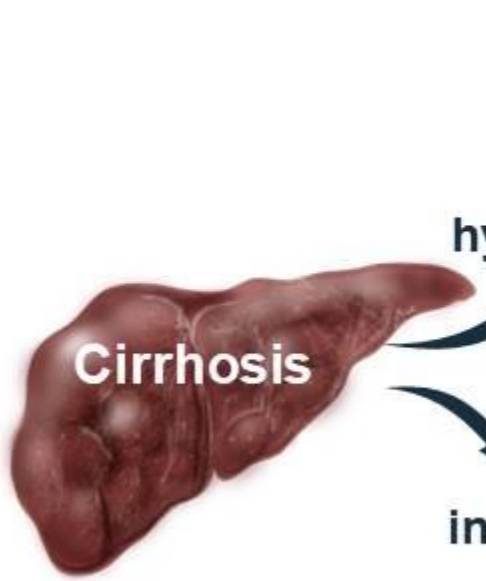
Murray KF, Carithers RL. *Hepatology*. 2005;41:1-26; Wiesner R et al. *Gastroenterology*. 2003;124:91-96.

3 Month Mortality Risk Based on MELD Score



Murray KF, Carithers RL. *Hepatology*. 2005;41:1-26; Wiesner R et al. *Gastroenterology*. 2003;124:91-96.

Complications of Cirrhosis: Decompensated Cirrhosis



Portal hypertension

- Hepatopulmonary syndrome
  Portopulmonary hypertension
- Variceal hemorrhage
- Ascites
  Hydrothorax
  - Spontaneous bacterial peritonitis
  - Hepatorenal syndrome
- **Encephalopathy**
  30-40% of cirrhotic patients

Liver insufficiency

- "Coagulopathy"
  Jaundice
  Hypoalbuminemia

Amodio P et al. *J Hepatol.* 2001;35:37-45

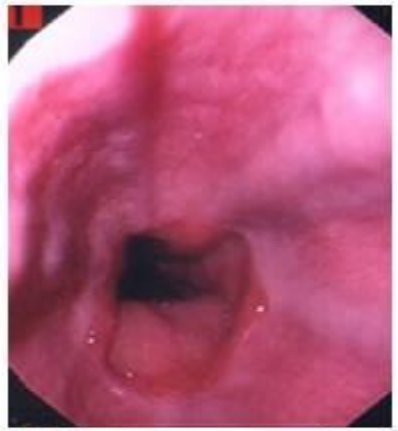
History of Present Illness – June 2018

47 year old male with decompensated alcohol-related cirrhosis

HISTORY & PE | MEDICATIONS | LABS | PROGRESS NOTES | OTHER

- 47 year old gentleman with decompensated alcohol-related cirrhosis returns to clinic after being recently admitted and banded for bleeding esophageal varices.
  - Pertinent admission labs:
    - HB 5.2, PLT 32, INR 1.4, TB 1.2
  - Required 6 bands.
  - Transfused PRBCs and Platelets
- Follow up outpatient endoscopy with additional banding recommended.

Esophageal Varices



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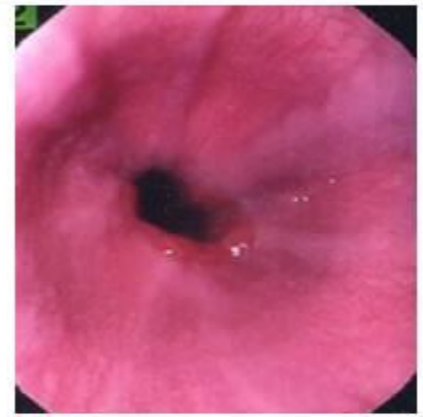

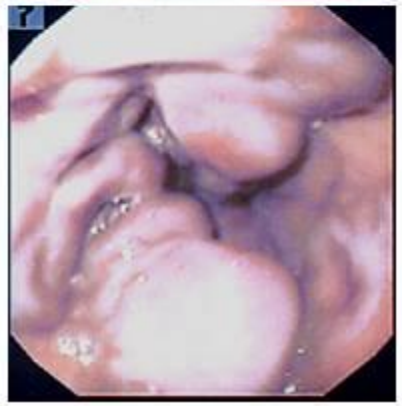

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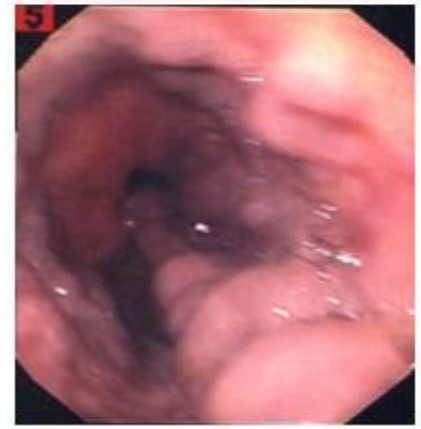


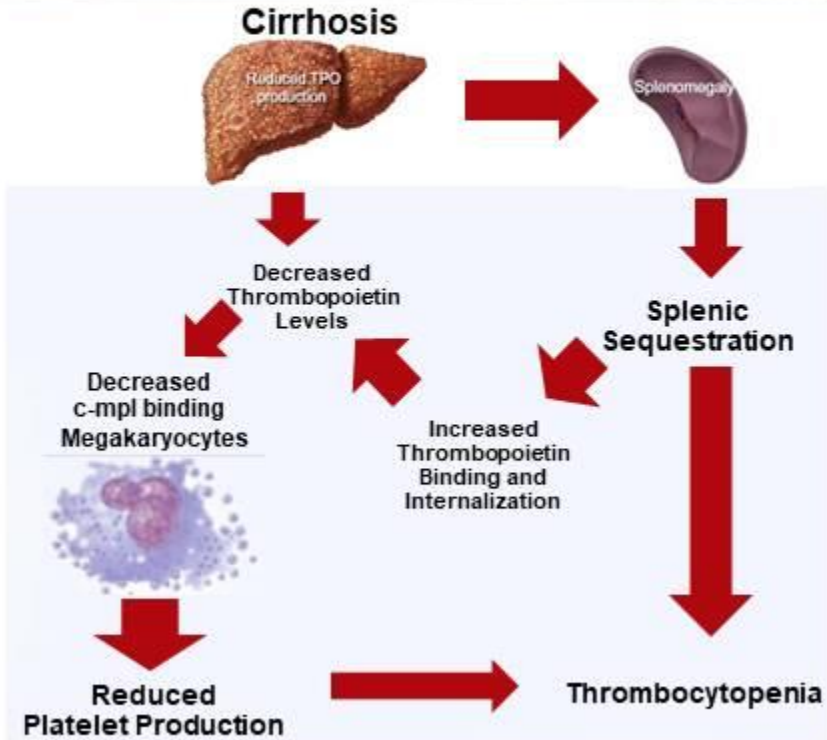
Management of Acute Hemorrhage

- Patients with suspected acute variceal hemorrhage require intensive-care unit setting for resuscitation and management
- Acute GI hemorrhage requires:
  - Intravascular volume support
  - Blood transfusions
  - Maintaining hemoglobin of ~7 g/dL
- Institute short-term (7-day) antibiotic prophylaxis
  - Ceftriaxone 1 gm/d is preferred
- Initiate therapy with octreotide (or its analogs) (2-5 days)
- Perform EGD within 12 hours; treat with endoscopic band ligation
- Rescue therapy: Emergent TIPS, balloon tamponade, esophageal stent placement

Garcia-Tsao et al. *Hepatol*. 2017.

Thrombocytopenia in Cirrhosis

- Be suspicious when platelet count <100,000 x 10^9/L
- Decreased hepatic production of thrombopoietin is a critical factor in the development of thrombocytopenia in cirrhosis
- Prevalence and severity of thrombocytopenia correlate with and parallel the severity of underlying liver disease, particularly, the extent of fibrosis



Varghese LN, et al. *Front Endocrinol.* 2017;8:59; Peck-Radosavljevic M. *Liver Int.* 2016;37:778-793; Mitchell O, et al. *Hepat Med.* 2016;8:39-50.

Thrombocytopenia in CLD

- Thrombocytopenia is a common problem in patients with cirrhosis (platelets <100,000)
  - Estimated to affect up to 70% of CLD patients
  - Extent worsens with severity of portal hypertension and disease
  - Patients may be ineligible for elective surgical or diagnostic procedures due to risk of bleeding
  - Increases risk of mortality
  - Increases risk of poor clinical outcomes

Mitchell O, et al. *Hepatic Medicine: Evidence and Research*. 2016;8:39-50; Maan, et al. *Drugs*. 2015;75(17):1981-92; Giannini EG. *Aliment Pharmacol Ther*. 2006;23:1055-65.

Relative Bleeding Risk Associated with Common Medical Procedures Performed in Patients with Chronic Liver Disease

Low

- Thoracentesis
- Paracentesis
- Endoscopy
- Upper GI endoscopy
  - ± biopsy
  - ± variceal banding ± sclerotherapy
- Colonoscopy ± polypectomy biopsy

Medium

- Liver biopsy
- Bronchoscopy ± biopsy
- Ethanol ablation
- Chemoembolization for HCC

High

- Biliary interventions
- Dental procedures
- Transjugular intrahepatic portosystemic shunt
- Laparoscopic interventions
- Nephrostomy tube placement
- Radiofrequency ablation
- Renal biopsy
- Vascular catheterization

Terrault N, et al. *Hepatology*. 2017;66(suppl S1):124A-125A. Abstract 217.

Guideline Recommendations for Appropriate Platelet Levels Based on Procedure

Guideline	Year	Transfusion Recommendations and Cited Evidence
American Association of Study of Liver Diseases (AASLD)	2009	• Platelet transfusion should be considered when levels are less than 50-60x10^9/L (this applies whether one is attempting **liver biopsy transcutaneously or transvenously)**
American Society of Gastrointestinal Endoscopy (ASGE) [Gastroenterologist]	2012	• Platelet threshold 20x10^9/L for **diagnostic endoscopy**; 50x10^9/L if **biopsies** performed

Rockey et al. *Hepatology*. 2009;49(3):1017-1044; Ben-Menachem et al. *Gastrointest Endosc*. 2012.

Current Landscape in Patients with Thrombocytopenia and CLD

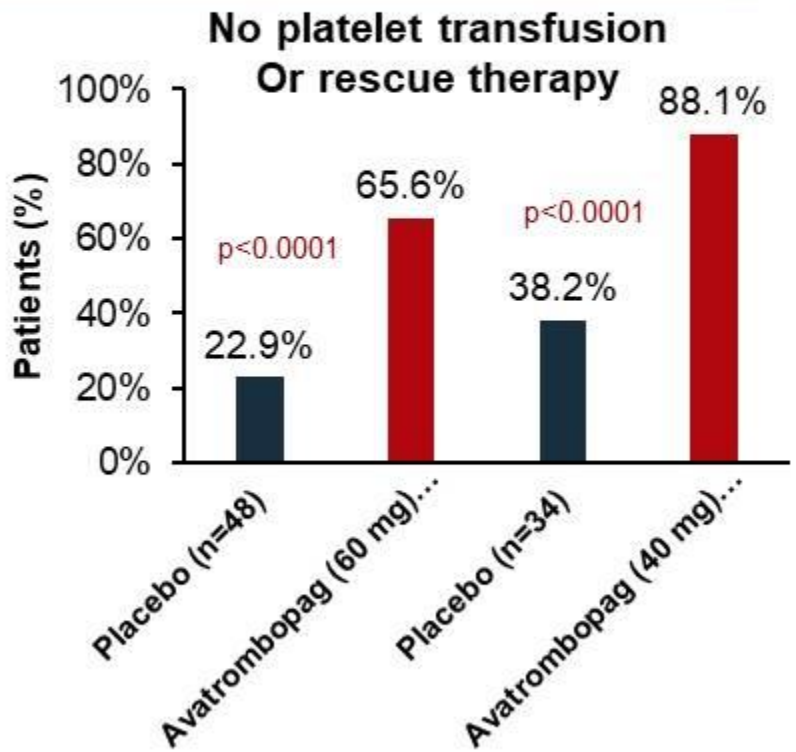
- Patients require 1-3 procedures annually
- Different procedures are associated with different risks of bleeding
  - Procedures are required to clinically manage patients with CLD
  - Thrombocytopenia can lead to serious uncontrolled bleeding in these patients negatively impacting clinical care
    - Prolonged hospitalizations
    - Serious complications
    - Poor clinical outcomes
- Historically, the only treatment option was platelet transfusion

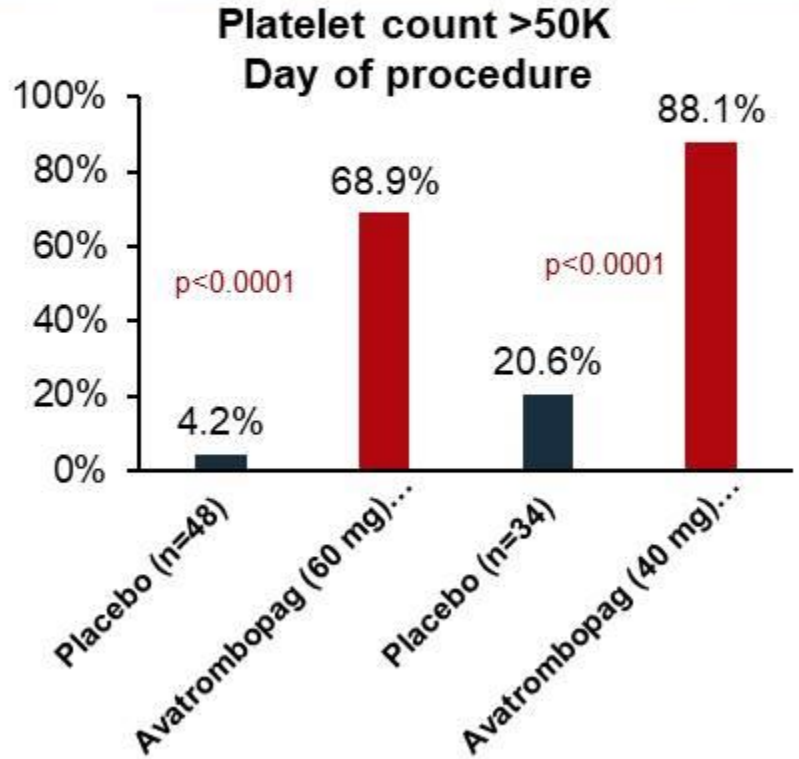
Szczepiorkowski ZM and Dunbar NM. *Hematology Am Soc Hematol Educ Program*. 2013;2013:638-44;
Lin Y and Foltz LM. *BCMJ*. 2005;47(5):245-248.

Treatment Options for Severe Thrombocytopenia in Chronic Liver Disease

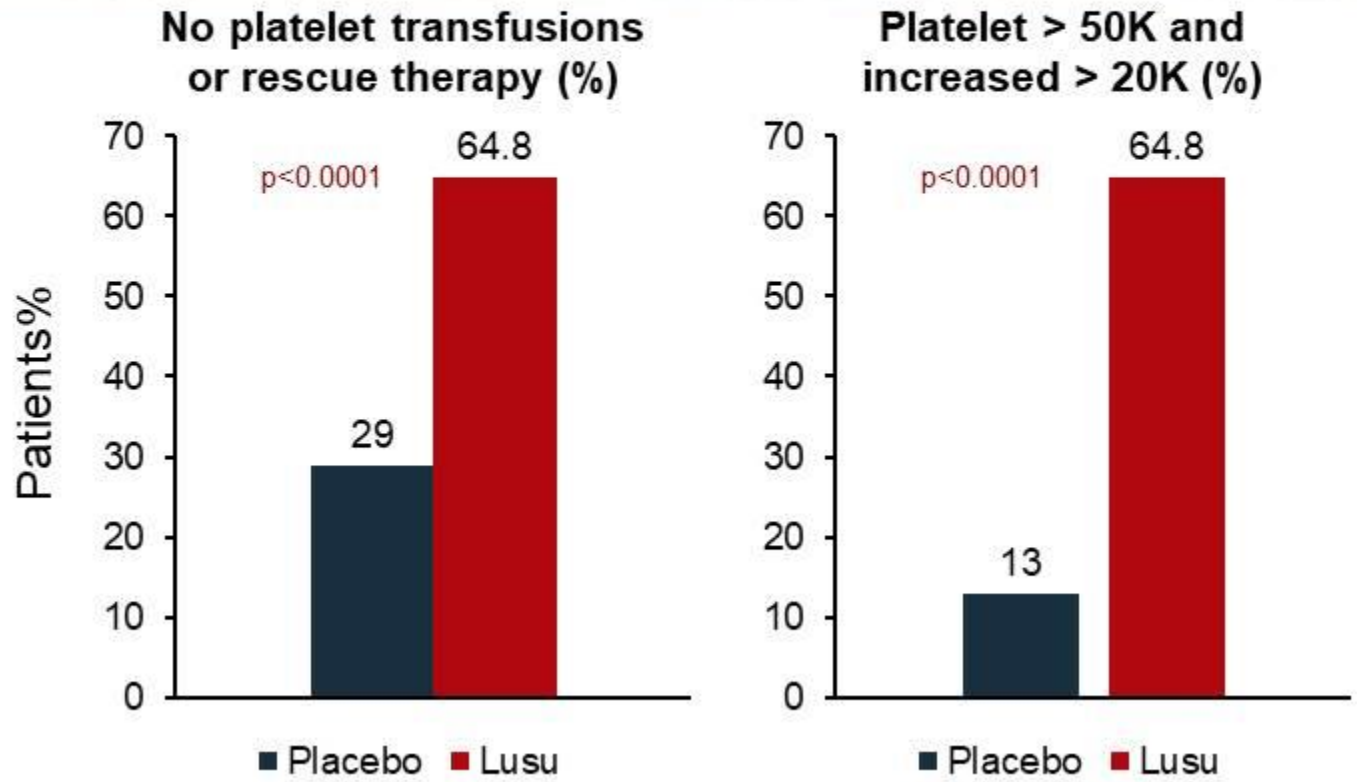
- Standard
  - Platelet transfusions
  - Splenic artery embolization
  - Splenectomy
  - Transjugular intrahepatic portosystemic shunts
- Thrombopoietin Receptor Agonists
  - FDA-approved in 2018: avatrombopag and lusutrombopag
  - Oral medications

Avatrombopag





Lusutrombopag



Conclusions

- Patients with cirrhosis often need multiple invasive procedures
- Thrombocytopenia is common in patients with cirrhosis
- Severe thrombocytopenia places patients at risk of bleeding with invasive procedures
- Use of platelet transfusion to mitigate the risk is cumbersome and can be associated with adverse events
- The use of TPO agonists significantly increases platelet counts and can avoid the need for platelet transfusion

Patient Case

67-yr-old man admitted for OHE for the first time

HISTORY & PE | MEDICATIONS | LABS | PROGRESS NOTES | OTHER

HPI

- History of NASH and noted cirrhosis based on abdominal US about 3 years ago
- Noted melena for 3 days
- His spouse noted that he has become confused in the last few days and became unresponsive on the day of admission

Social History

- Used to drink heavily as an auto plant worker when he was young
- Quit drinking and smoking for the last 12 years
- Lives with wife in an apartment
- Wife has chronic medical issues

Patient Case (cont.)

67-yr-old man admitted for OHE for the first time

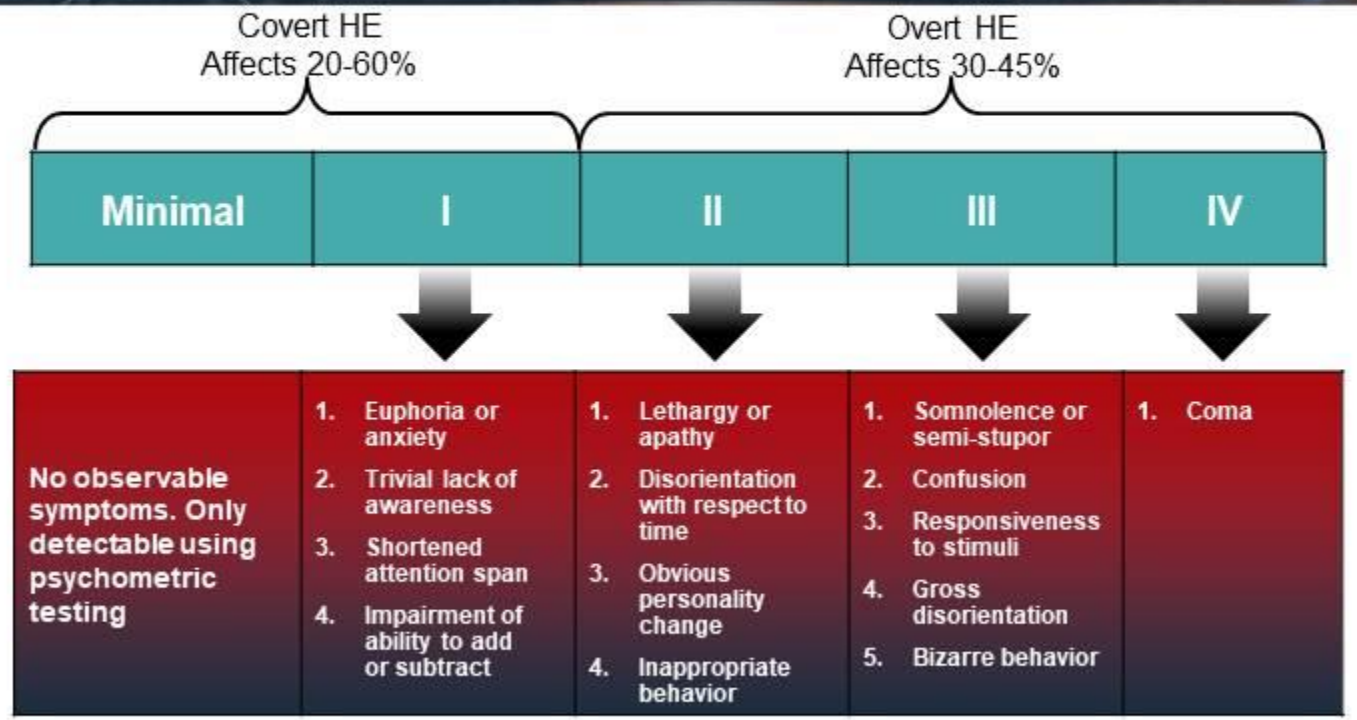
HISTORY & PE | MEDICATIONS | LABS | PROGRESS NOTES | OTHER

PE

- Confused, disoriented
- Anemic, but not icteric
- Positive flapping, tremor
- No ascites, not tender
- Trace edema
- Stool tarry and hemoccult (+)

BP	110/60 mm Hg
PR	110/min
RR	20/min
BMI	35 kg/m^2

HE Symptoms Can Be Subtle Should Be Considered in Any Patient with Cirrhosis



HE = hepatic encephalopathy

Vilstrup, H 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*. 60: 715–735.

No Role for 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)"[1]
- Except in acute liver failure, ammonia level>200 µmol/L is predictive of poor outcome[2]
- HE is a clinical diagnosis

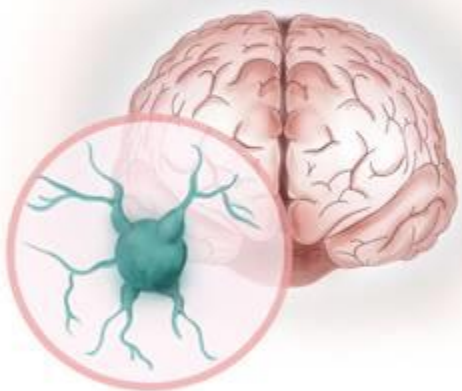
1. Vilstrup H et al. *Hepatology*. 2014;60(2):714-735; **2.** Bernal W et al. *Hepatology*. 2007;46(6):1844-1852.

Treatment Goals for OHE

- Provision for supportive care
- Identification and removal of precipitating factors
  - Infection, GI bleed, dehydration
- Reduction of nitrogenous load from the gut
- Correct electrolyte abnormalities
- Assessment of the need for long-term therapy
  - Control of potential precipitating factors
  - Higher likelihood of recurrent encephalopathy
  - Assessment of the need for liver transplantation

Blei AT et al. *Am J Gastroenterol.* 2001;96(7):1968-1976.

Precipitating Factors for HE



<u>Increased ammonia production</u>

UGI hemorrhage

Excessive dietary protein

Blood transfusion

Dehydration/electrolyte imbalance

Constipation

<u>Portosystemic shunts</u>

Spontaneous

Iatrogenic (eg, TIPS)

<u>Other</u>

Drugs (eg, opioids, benzodiazepines)

Infections (eg, SBP)

Malignancy (eg, hepatoma)

Vilstrup H et al. *Hepatology*. 2014;60(2):714-735.

AASLD Recommends 4-Pronged Approach to Treating OHE*

*Grade II-2, A, 1 recommendation.
Vilstrup H et al. *Hepatology*. 2014;60(2):714-735.

Current Therapy Options for HE

Agent	Drug Class	Indication
Lactulose[1]	Poorly absorbed disaccharide	• Decrease blood ammonia concentration • Prevention and treatment of portal-systemic encephalopathy
Rifaximin[2]	Non-aminoglycoside semi-synthetic, nonsystemic antibiotic	Reduction in risk of OHE recurrence in patients ≥18 years of age
Neomycin[3]	Aminoglycoside antibiotic	Not to be used, renal and ototoxic risk
Metronidazole[1]	Synthetic antiprotozoal and antibacterial agent	Not approved for HE
Vancomycin[1]	Aminoglycoside antibiotic	Not approved for HE

1. USNLM. DailyMed. Available at https://dailymed.nlm.nih.gov/dailymed. Accessed March 22, 2018; **2.** Xifaxan (rifaximin) [prescribing information]. Valeant Pharmaceuticals North America LLC; Bridgewater, NJ; 2018; **3.** Mullen KD et al. *Semin Liver Dis*. 2007;27(Suppl 2):32-47.

Prevention of Overt HE (OHE)

- Lactulose is recommended for prevention of recurrent episodes of HE after the initial episode (GRADE II-1, A, 1)
- Rifaximin as an add-on to lactulose is recommended for prevention of recurrent episodes of HE after the second episode (GRADE I, A, 1)
- Routine prophylactic therapy (lactulose or rifaximin) is not recommended for the prevention of post-TIPS HE (GRADE III, B, 1)
- Under circumstances where the precipitating factors have been well controlled (i.e., infections and VB) or liver function or nutritional status improved, prophylactic therapy may be discontinued (GRADE III, C, 2)

AASLD Practice Guideline, 2014.

Conclusions

- Hepatic encephalopathy is an economic and social burden
  - Increased burden is realized not only by patients but also experienced by caregivers
- Hepatic encephalopathy is an important cause of hospital readmission
  - To avoid the “revolving door”, treat after discharge
- Lactulose and rifaximin are important for secondary prophylaxis

HEPATOLOGY NEWS
TONIGHT
MANAGING COMPLICATIONS OF CIRRHOSIS

HCC Screening: Patients with Cirrhosis

Major Guidelines Recognize the Importance of Routine Surveillance in High-Risk Populations

Society/Institution	Guidelines
AASLD[1] American Association for the Study of Liver Diseases	US +/- every 6 months
EASL[2] European Association for the Study of the Liver	US every 6 months
APASL[3] Asian-Pacific Association for the Study of the Liver	AFP + US every 6 months
NCCN[4] National Comprehensive Cancer Network	AFP + US every 6-12 months
JSH-HCC[6] Japan Society of Hepatology	*High-risk:* US every 6 months + AFP/DCP/AFP-L3 every 6 months *Very High-risk:* US every 6 months + AFP/DCP/AFP-L3 every 6 months + CT/MRI (optional) every 6-12 months

AFP=alpha-fetoprotein; AFP-L3=*Lens culinaris* agglutinin-reactive fraction of AFP; CT=computerized tomography; DCP=des-γ-carboxyprothrombin; MRI=magnetic resonance imaging; US=ultrasound.

1.Marrero JA et al., *Hepatology,* 2018; 68(2): 723-750; 2. EASL, EORTC. *J Hepatol.* 2012;56(4):908-943; 3. Omata M et al. *Hepatol Int.* 2010;4(2):439-474;
 5. Kokudo N et al. *Hepatol Res.* 2015;45.

Take Home Points

- Further work up for advanced liver disease if platelets <100,000 x 10^9/L
- Don't rule out advanced liver disease if LFTs WNL
- Order INR in all patients with jaundice
- Order upper endoscopy if upper GI bleed
- Blood ammonia levels not important if HE is suspected
- Order abdominal US if no evidence of one within the past 6 months in all patients with advanced liver disease

Hot Topics in Liver Disease 2019

Thanks!!

QUESTIONS??