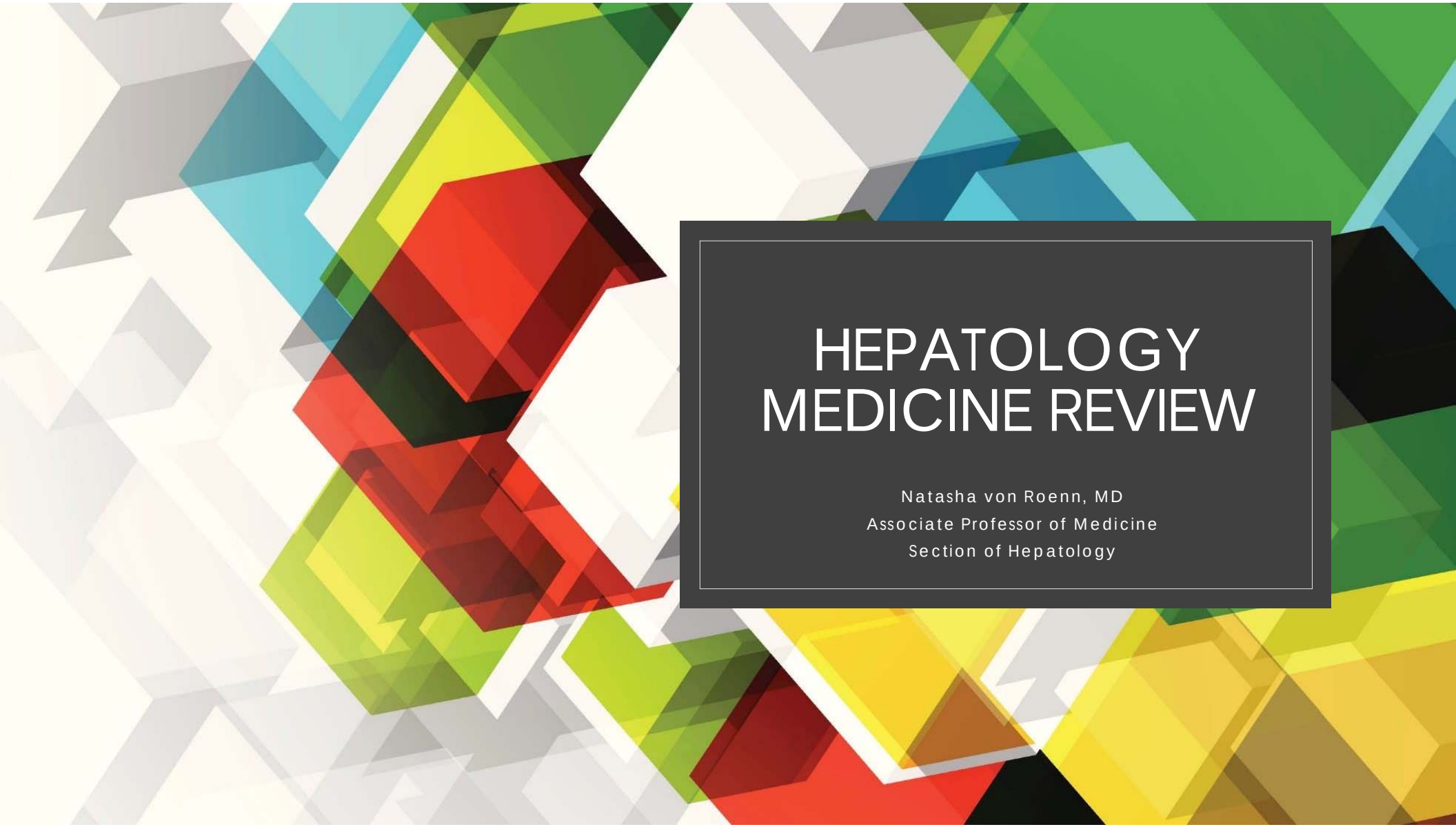


HEPATOLOGY MEDICINE REVIEW

Natasha von Roenn, MD
Associate Professor of Medicine
Section of Hepatology

Objectives

Identify a patient with chronic liver disease or cirrhosis

- Key Features on Presentation
- Review of Systems / Medical History

Risk Factors for chronic liver disease

- Social
- Medical
- Familial

Physical exam findings of chronic liver disease

Interpret and utilize testing appropriately in liver disease

- Laboratory tests of liver function vs inflammation
- Diagnostic laboratory tests of liver diseases
- Assessing severity of liver disease
  - MELD Score / Child's Pugh
  - Non-invasive measures of fibrosis
  - Liver Biopsy
- Upper Endoscopy
- Peritoneal Fluid Analysis

Management of Patients with Cirrhosis

- Hepatic Encephalopathy
- Ascites
- Spontaneous Bacterial Peritonitis
- Esophageal Varices

Utilize Scoring Systems for patients with cirrhosis

Discuss Complications of Cirrhosis

- Portal Hypertension
- Hepatocellular Carcinoma
- Decompensated Cirrhosis
- Acute on Chronic Liver Failure

Initial Evaluation of Patient with Suspected Liver Disease

- Does this patient have liver disease?
  - Laboratory Data
  - Imaging
  - Ascites
- Is it acute or chronic? (6 months)
  - Acute
    - Acute Hepatitis
    - Acute Liver Injury
    - Acute liver failure
  - Chronic
    - Chronic Hepatitis
    - Cirrhosis
- What is the cause?
- HPI
  - Symptoms
  - New Medications / Supplements
  - Risk factors or exposures for liver disease
- Past Medical History
  - Metabolic Syndrome
  - Autoimmune Disorders
- Family History
- Medications
- Physical Exam – Stigmata of Chronic Liver Disease
- Laboratory Testing
- Imaging

Patterns of Liver Injury

1. **Acute Hepatitis**
   - Temporary or new onset inflammation of the liver tissue
   - May or may not be symptomatic
   - Can resolve or become chronic

2. **Acute Liver Failure (Fulminant Liver Failure)**
   - Sudden loss of hepatic function in the **absence** of pre-existing liver disease
   - Can lead to multi-organ failure and death or recovery, depending on the cause
   - Results in severe liver dysfunction and may require liver transplantation

3. **Chronic Hepatitis → Cirrhosis**
   - Inflammation of the liver tissue that lasts at least 6 months
   - Often without symptoms
   - Can progress to cirrhosis

Laboratory Assessment of the Liver

Provide a noninvasive method to screen for liver disease

Markers of Hepatocellular Damage

- Serum Transaminases
  - ALT (Alanine aminotransferase)
  - AST (Asparate aminotransferase)

Markers of Cholestasis

- Alkaline Phosphatase
- Gamma Glutamyl Transpeptidase
- Bilirubin

Tests of Liver Function

- Prothrombin time
- Albumin
- Cholesterol
- Bilirubin

Aminotransferases

ALT

- Normal lab values range 29-33 IU/mL for males
- 19-25 IU/mL for females
- Primarily present in the liver
  - More specific marker of hepatocellular injury
  - Correlate with degree of abdominal adiposity

AST

- Present in other organs, including cardiac muscle, skeletal muscle, kidney, and brain
- 10-40 IU/mL for males
- 9-32 IU/mL for females

Most laboratories use > 2 SD to define abnormal

- The differences in clinical laboratories abnormal is based on the health of the reference population

A “normal” ALT does not exclude liver disease or histologic damage

Liver Injury Tests can be classified by:

1. Type
2. Duration
3. Magnitude

Type

- Hepatocellular Injury (ALT/AST elevation)
- Cholestatic Injury (Alk Phos / T.bili elevation)

Acute or chronic

- Acute
  - Abrupt onset
  - Less than 6 months but usually < 1 month
- Chronic
  - Greater than 6 months (arbitrary)

Magnitude

- Mild AST/ALT elevations <200 IU
- Moderate AST/ALT elevations 200-600 U
- Severe AST/ALT elevations > 600

Assessing the Severity of Liver Disease

Laboratory Testing	MELD Score / Child's Pugh	Non-invasive measures of fibrosis	Liver Biopsy
• Tests of Liver Function (PT/INR, T.bilirubin, Albumin) • Liver dysfunction present – either ALI/ALF or Cirrhosis	• Prognostic score in Cirrhosis to determine mortality	• Determines if advanced fibrosis / cirrhosis is present in the setting of chronic hepatitis	• Determine etiology of liver disease • Determine degree of fibrosis • Measure portal pressures

Acute Hepatitis : Etiology

Viral Hepatitis

- Hepatitis A, B, C, E
- CMV, EBV, Adenovirus, HSV

Excessive Alcohol Intake

- Alcoholic Hepatitis

Drug-Induced Liver Injury

Autoimmune Hepatitis

Circulatory Dysfunction

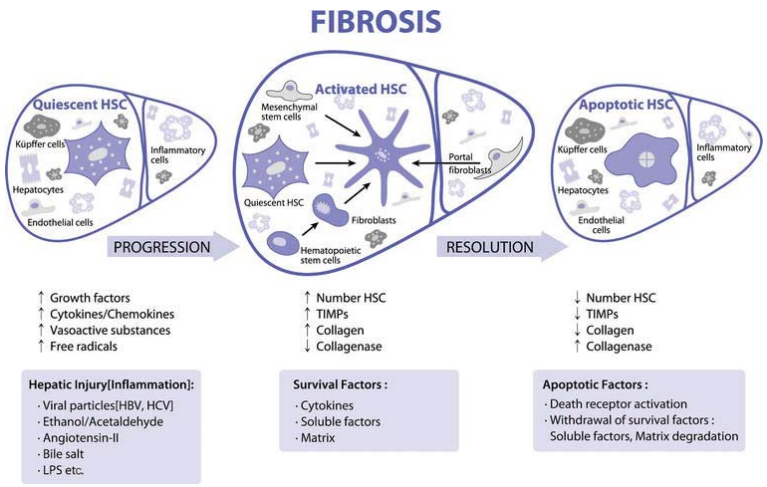
- Ischemia
- Budd Chiari
- Portal vein thrombosis

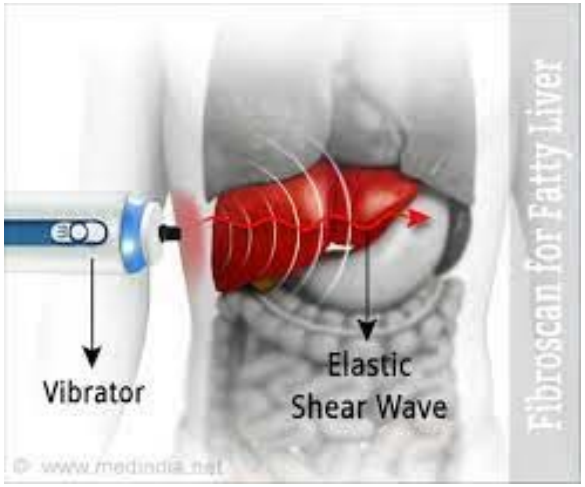
Chronic Hepatitis : Etiologies

- Hepatitis B, C, or D (Hep E, rarely)
- Autoimmune hepatitis
- Drugs
- Wilson's Disease
- Alpha-1 Antitrypsin Deficiency
- Hemochromatosis
- NASH
- Alcohol
- PBC
- PSC

Historical Clues

History Component	Disease Correlation
Remote history of jaundice	Viral hepatitis
Medical history of autoimmune diseases	AIH
Hypothyroidism	AIH, PBC
History of liver disease as a newborn	Alpha-1 antitrypsin deficiency
Family history of liver disease	HBV, hemochromatosis
History of alcohol abuse, DUI	Alcohol
History of IVDA, blood transfusion prior to 1990	HCV
Diabetes	Hemochromatosis, NAFLD
Components of Metabolic Syndrome	NAFLD
Medications, CAM therapy	Drug induced liver injury
Pruritis	PBC
Ulcerative Colitis	PSC
Arthritis	Hemochromatosis, HCV





NONVASIVE MARKERS OF FIBROSIS

- Serological Assays
  - Indirect Markers
    - APRI
    - Fib-4
    - NAFLD Fibrosis Score
    - ELF
  - Direct Markers (hepatic matric metabolism)
    - Hyaluronic Acid
    - Procollagen type III
    - Metalloproteinases, MMP-1, MMP-2
- Imaging Methods
  - Ultrasonography
  - Magnetic Resonance Imaging
  - Elastography

Indirect Measures of Fibrosis

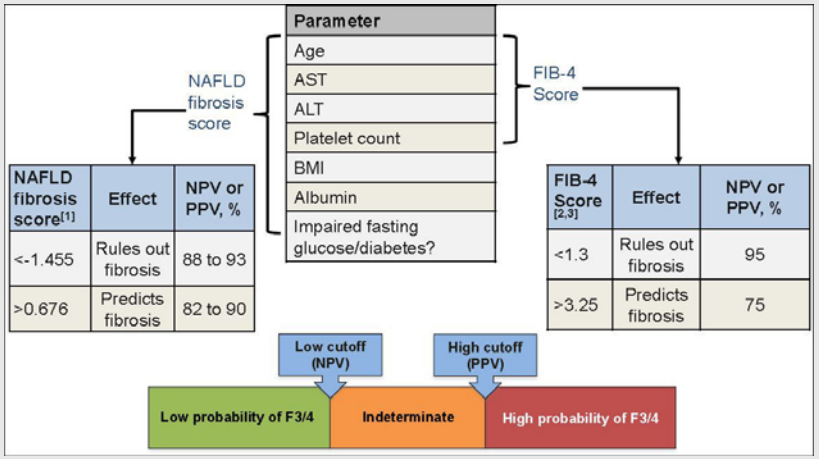
- APRI

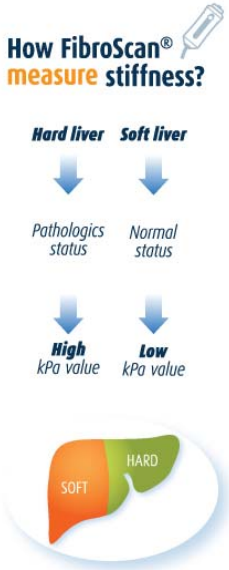
$$\text{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST (Upper Limit of Normal)}}}{\text{Platelet Count } (10^9/\text{L})} \times 100$$

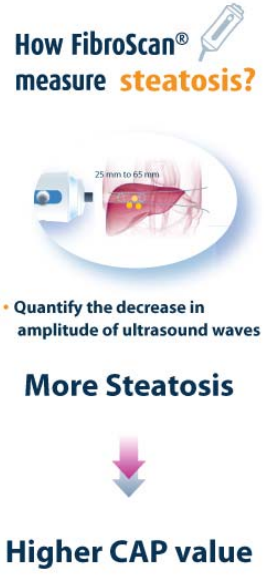
	Fibrosis		Total
	F0-F2	F3-F4	
APRI < 0.7515	24	2	26
APRI ≥ 0.7515	14	19	33
Total	**38**	**21**	**59**

- FIB-4

$$\text{FIB-4} = \frac{\text{Age (years)} \times \text{AST (U/L)}}{\text{Platelet Count } (10^9/\text{L}) \times \sqrt{\text{ALT (U/L)}}}$$



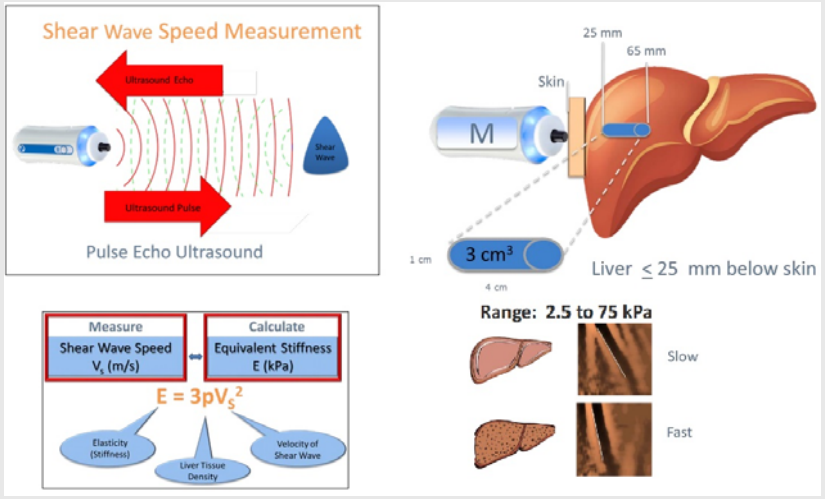


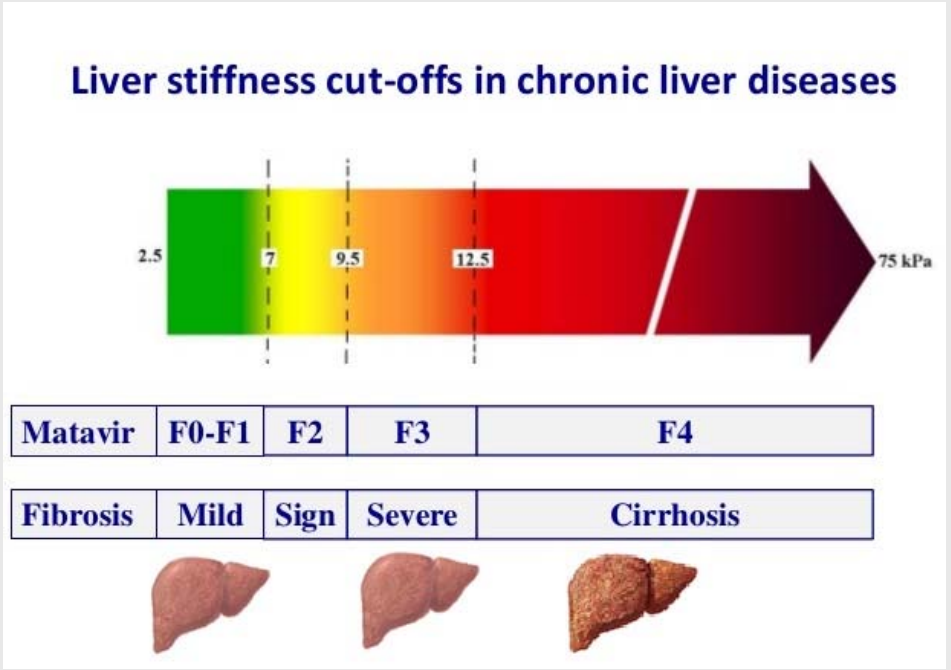


Fibroscan

- Transient Elastography
  - Non-invasive method for the assessment of hepatic fibrosis in patients with chronic liver disease
  - Measures liver stiffness
  - Can easily be performed at the bedside or in the outpatient clinic with immediate results and good reproducibility
  - Surface ultrasound probe that delivers a low frequency pulse or shear wave to a small volume of liver tissue under the rib cage

Fibroscan


Shear Wave Speed Measurement
Ultrasound Echo
Shear Wave
Ultrasound Pulse
Pulse Echo Ultrasound
Measure
Shear Wave Speed
V_s (m/s)
Calculate
Equivalent Stiffness
E (kPa)
$E = 3pV_s^2$
Elasticity (Stiffness)
Liver Tissue Density
Velocity of Shear Wave
25 mm
65 mm
Skin
M
1 cm
3 cm³
4 cm
Liver ≤ 25 mm below skin
Range: 2.5 to 75 kPa
Slow
Fast


Liver stiffness cut-offs in chronic liver diseases
2.5
7
9.5
12.5
75 kPa
Matavir
F0-F1
F2
F3
F4
Fibrosis
Mild
Sign
Severe
Cirrhosis

Cirrhosis: Etiologies

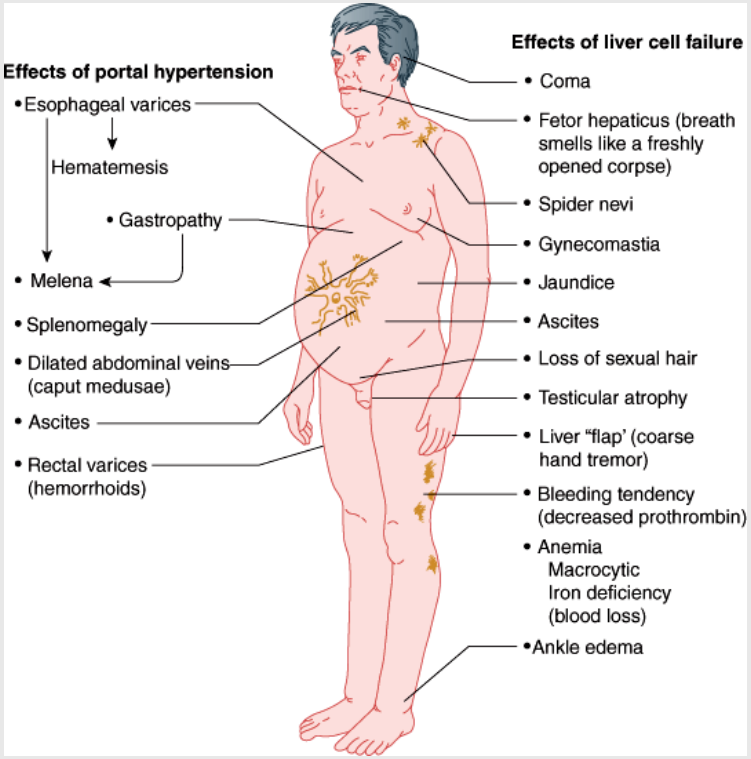
- **Alcoholic Liver disease**
- **Viral Hepatitis**
- **Non-Alcoholic Liver Disease (NASH)**
- **Chronic Biliary Obstruction**
- **Hemochromatosis**
- **Wilson's Disease**
- **Alpha-1 Antitrypsin Deficiency**
- **Metabolic Disorders**
- **Drug-Induced Liver Injury**
- **Autoimmune Liver Disease**
- **Primary Sclerosing Cholangitis**
- **Primary Biliary Cholangitis**
- **Cardiac Cirrhosis (Passive Congestion)**
- **Budd Chiari**

Physical Clues

Physical Exam Findings	Disease Correlates
Spider angiomas	Cirrhosis
Palmar erythema	Cirrhosis
Splenomegaly	Portal hypertension
Jaundice	Cirrhosis, Biliary obstruction, hemolysis, Gilbert's
Hyperpigmentation	Hemochromatosis
Kayser-Fleisher rings	Wilsons disease
Emphysema/Lung disease	Alpha-1 antitrypsin deficiency
Ascites	Portal hypertenson, cirrhosis
Asterixis	Portal hypertension
Xanthalasma	PBC

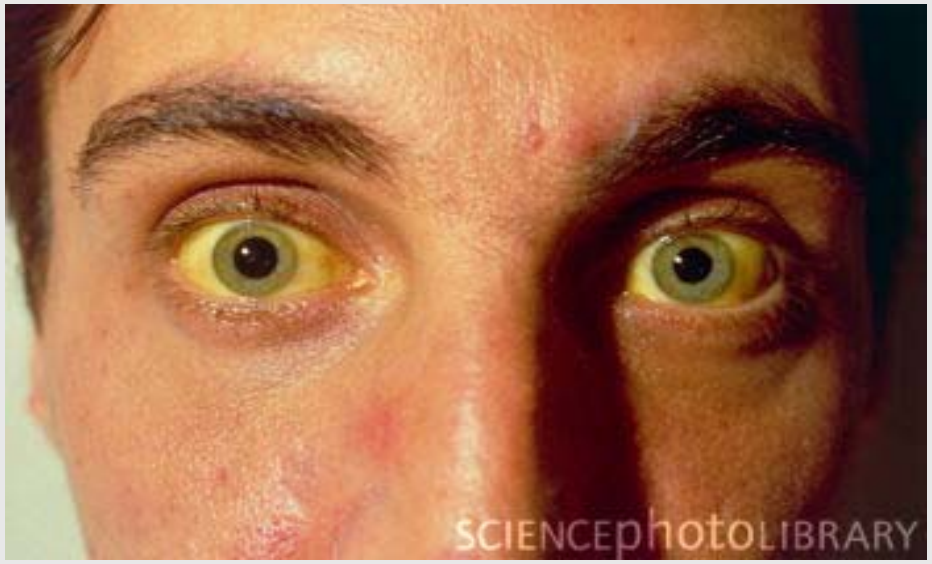
Cirrhosis: Clinical Symptoms

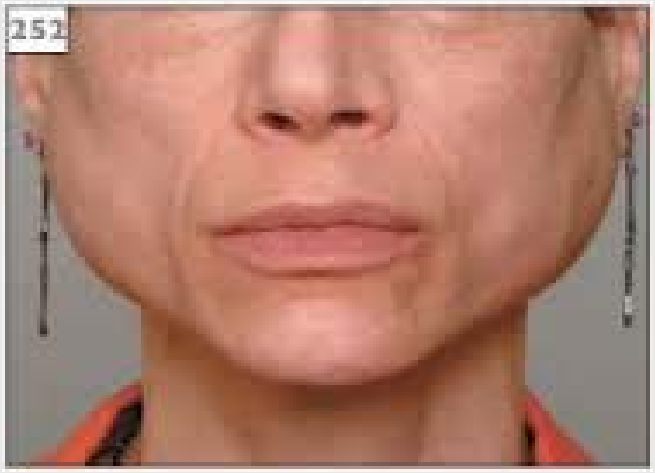
- **Lower Extremity Edema**
- **Abdominal Distension (Ascites)**
- **Gastrointestinal Bleeding (esophageal varices)**
- **Confusion (Hepatic Encephalopathy)**
- **Muscle Wasting and loss of muscle mass**
- **Muscle Cramping**
- **Gynecomastia**
- **Jaundice / Scleral Icterus**



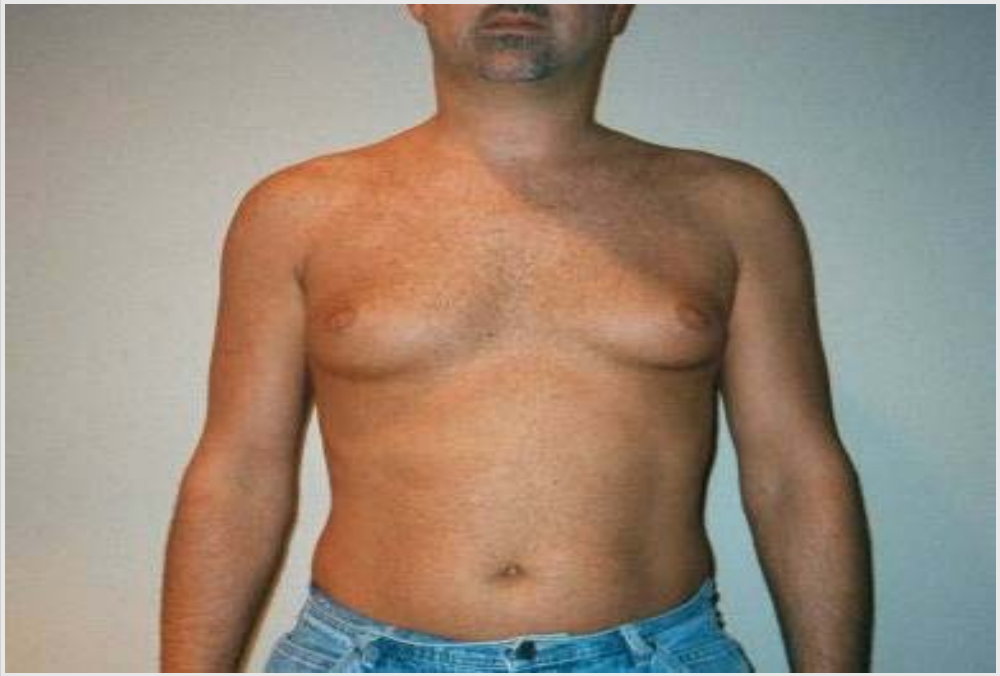
Jaundice

- Mental Status
- Alert, Drowsy, Obtunded
- Parotid Gland Enlargement
- Spider Angiomas
- Scleral Icterus

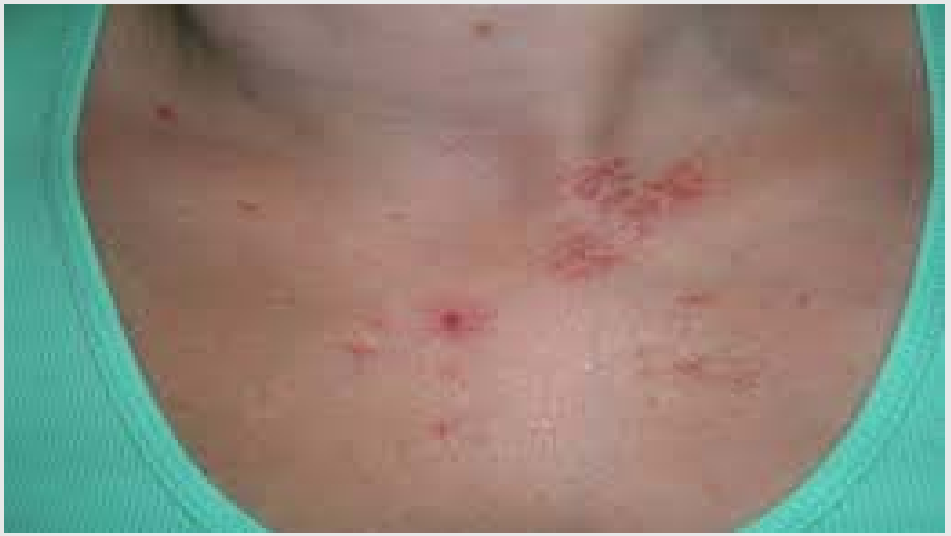




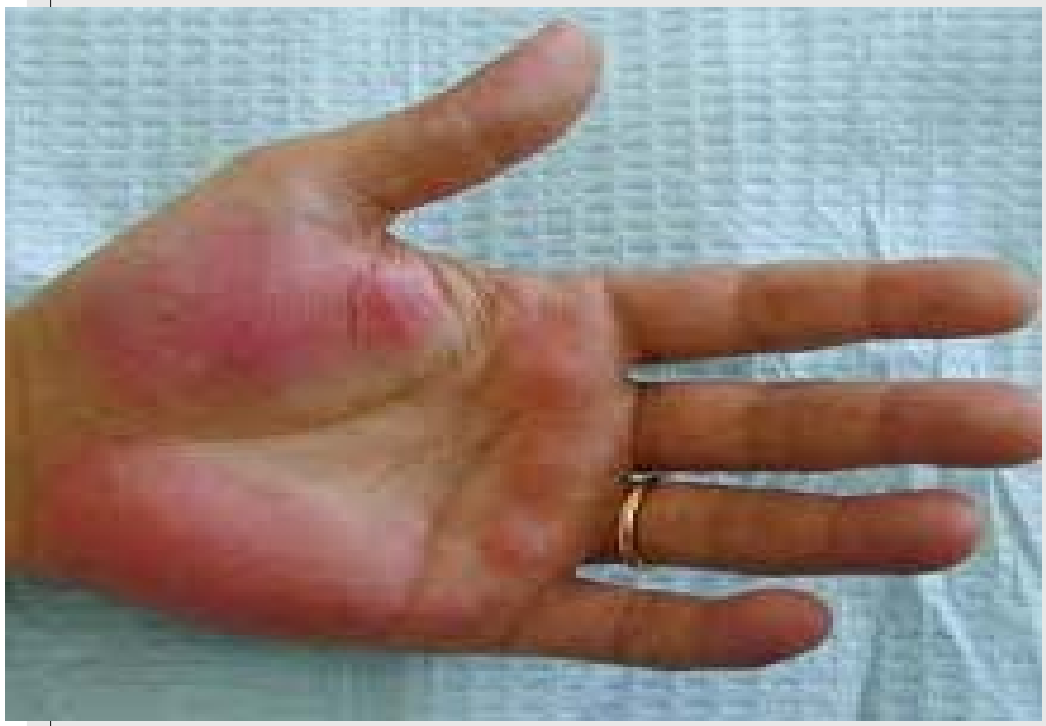
Gynecomastia



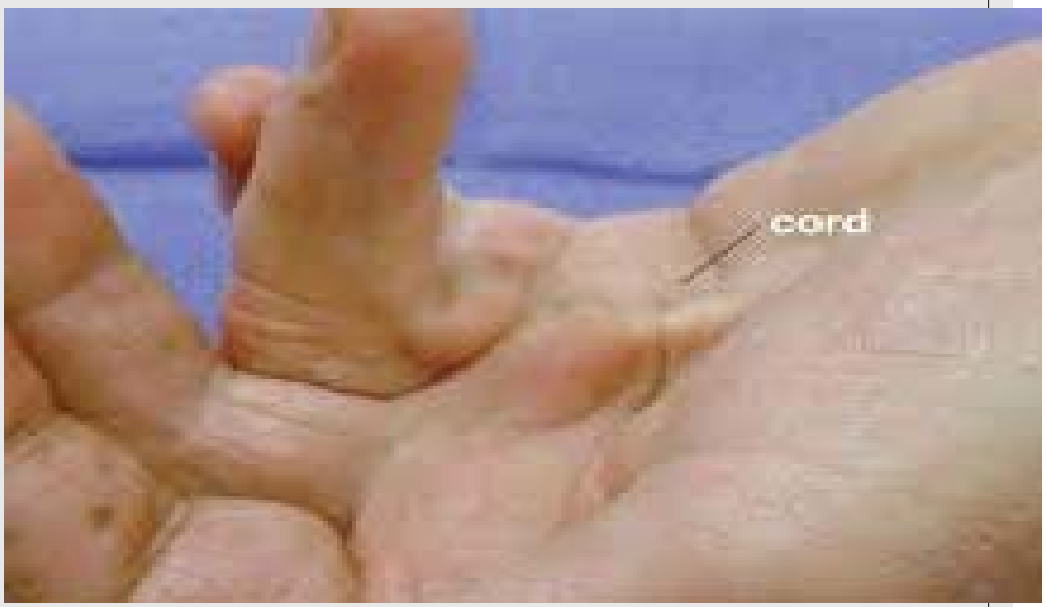
Spider Angiomata



Palmar Erythema



Duputyren's contracture



Prognosis of Compensated Cirrhosis

Median survival = 9-12 years

Majority of deaths: Non-liver related

- Cardiovascular, strokes, etc
- Liver-related deaths: HCC

Predictors of decompensation

- HVPG: HR 1.11
- MELD score: HR 1.15
- Serum albumin: HR .37

Prognosis of Decompensated Cirrhosis

- Median survival = 2 years
- Causes of deaths:
  - Portal HTN
  - Liver failure
  - Sepsis
  - HCC
- Predictors of death
  - Childs-Turcott-Pugh score
  - MELD score
  - Serum sodium

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
Clinical and Lab Criteria	**Points***		
	1	2	3
Encephalopathy	None	Grade 1 or 2	Grade 3 or 4
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
Prothrombin time			
Seconds prolonged *or*	<4	4-6	>6
International normalized ratio	<1.7	1.7-2.3	>2.3
***Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)**			
Class A = 5 to 6 points			
Class B = 7 to 9 points			
Class C = 10 to 15 points			

ASSESSING SEVERITY OF CIRRHOSIS: CHILD'S PUGH SCORE

MELD

Estimates the probability of dying over time in patients with chronic liver disease

Accessible

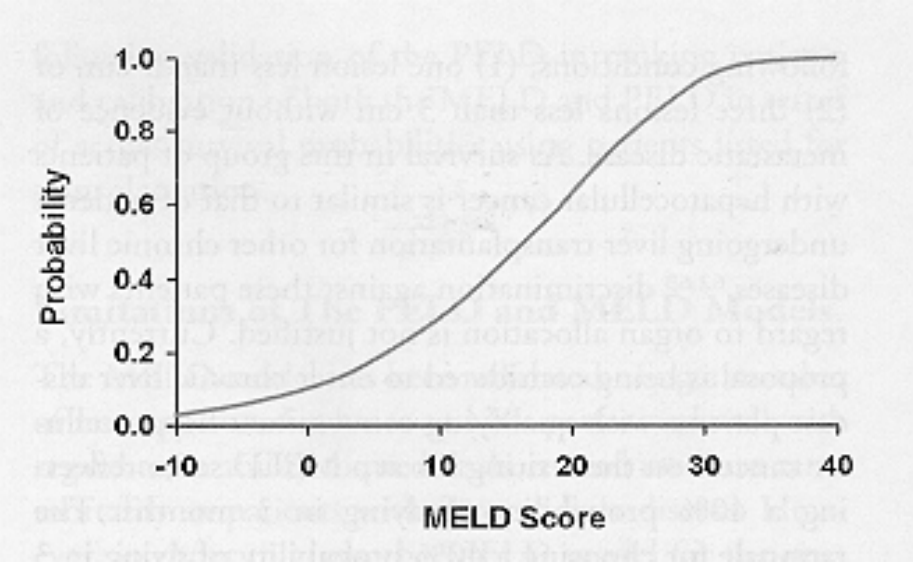
Validated measure of liver disease severity

Objective

Reproducible

$$MELD_{UNOS} = [(0.957*\ln Cr)+(0.378*\ln Bili) +(1.12*\ln INR)+(0.643)*10]$$

$$MELD\text{-}Na = MELD - Na+ - (0.025*MELD *(140 - Na+)) + 140$$



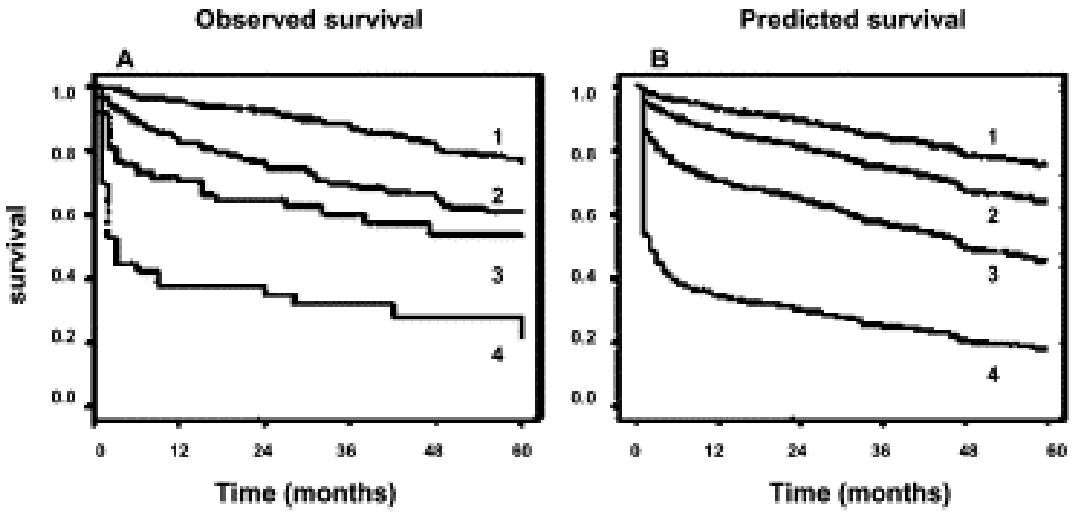
MELD SCORE

Malinchoc M, et al. Hepatology 2000;31:864-71

FACTORS THAT INFLUENCE MELD SCORE

Variable	Influencing factors
Bilirubin	Increased indirect bilirubin Hemolysis Blood transfusion Drug or sepsis-induced cholestasis[19, 20]
Creatinine	Acute renal failure[21, 22] Hepatorenal syndrome Other causes: shock, hypovolemia, drug-induced nephropathy, and medication-induced nephropathy
INR	Anticoagulant therapy: warfarin Hemodilution[23] Bleeding-induced coagulopathy[24] Disseminated intravascular coagulopathy[25] Malnutrition

INR- International Normalized Ratio



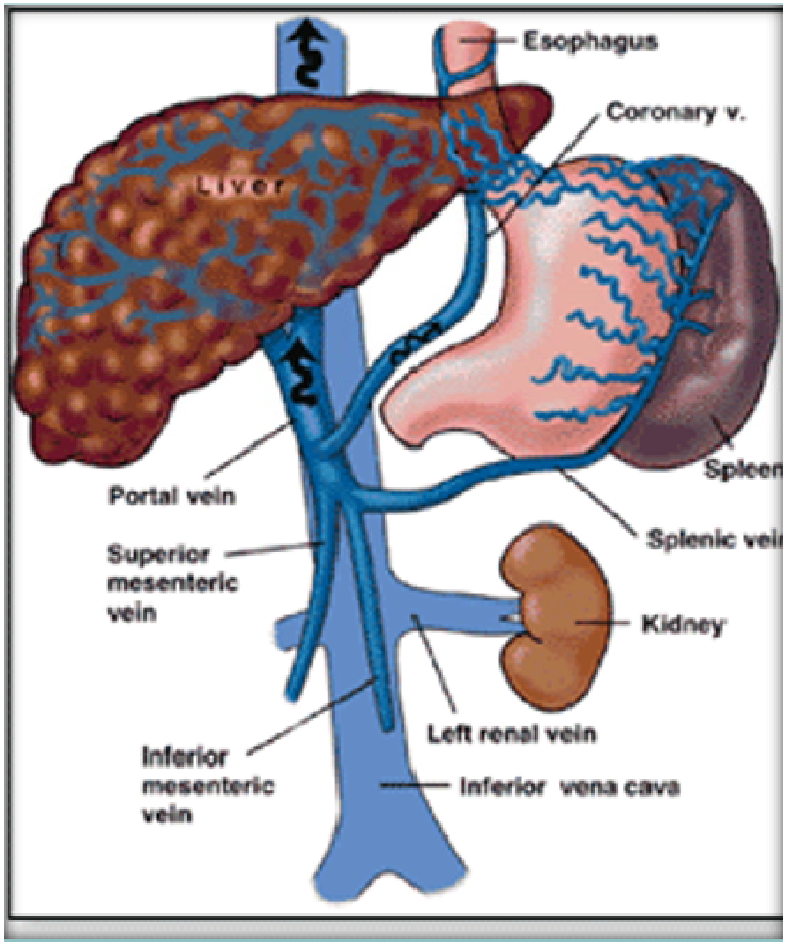
Categories: 1= MELD ≤9, 2=MELD 10 to 19, 3= MELD 20 to 29, 4=MELD ≥ 30

Pairwise comparisons	
1 vs 2	p<0.0001
1 vs 3	p<0.0001
1 vs 4	p<0.0001
2 vs 3	p=0.004
2 vs 4	p<0.0001
3 vs 4	p<0.0001

Comparison of observed (A) and Predicted (B) curves

Category 1 (≤ 9)	p=0.95
Category 2 (10-19)	p=0.05
Category 3 (20-29)	p=0.34
Category 4 (≥ 30)	p=0.51
Overall (non-categorized MELD)	p=0.18

MELD SCORE PREDICTS MORTALITY



Complications of Cirrhosis

Related to Portal Hypertension	Unrelated to Portal Hypertension
• Ascites • Hepatic encephalopathy • Spontaneous Bacterial Peritonitis • Esophageal Varices • Hepatorenal Syndrome	• Hepatocellular Carcinoma

Ascites

Bulging Flanks

Bulging Flanks

- Occurs when the weight of ascites is sufficient to push the flanks outwards
- Difficult to distinguish from obesity
- Sensitivity 72-93%
- Specificity 44-70%

What is a SAAG anyway???

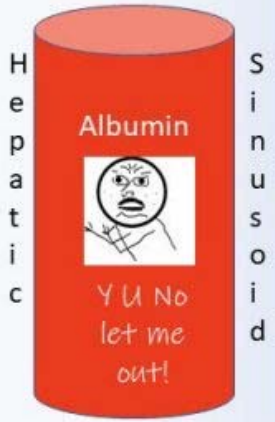
SAAG= **S**erum to **A**scites **A**lbumin **G**radient (Serum albumin- Ascites albumin)

Critical concepts:

- Ascites is either made in the liver sinusoid (hepatic lymph) or not by the liver
- **The hepatic sinusoid is designed to keep albumin in the blood**
- The diseased hepatic sinusoid becomes even less likely to allow albumin to escape blood into the hepatic lymph (due to capillarization and fibrosis)

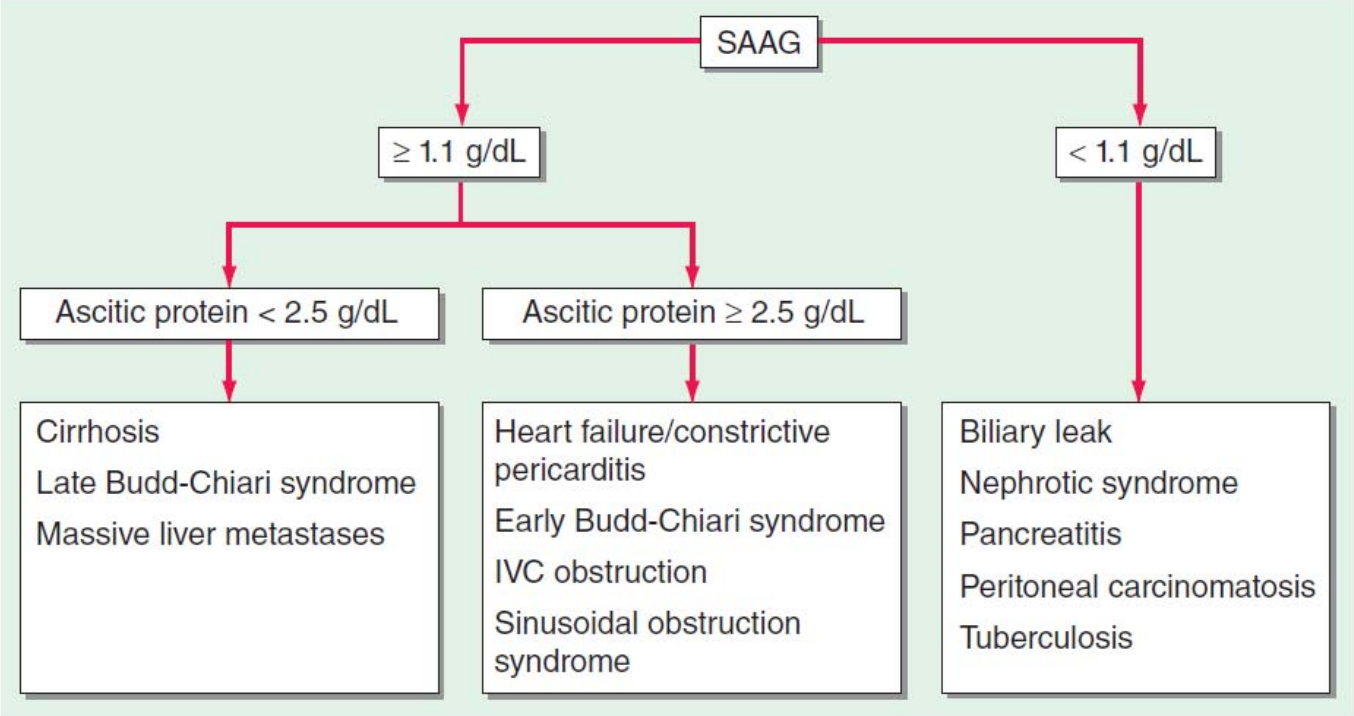
High SAAG= >1.1

- Aka not much albumin in the fluid
- Ascites is hepatic lymph!!!
- Produced by a sinusoid with:
  - ↑ hydrostatic pressure
  - ↓ oncotic pressure
  - AKA Portal Hypertension



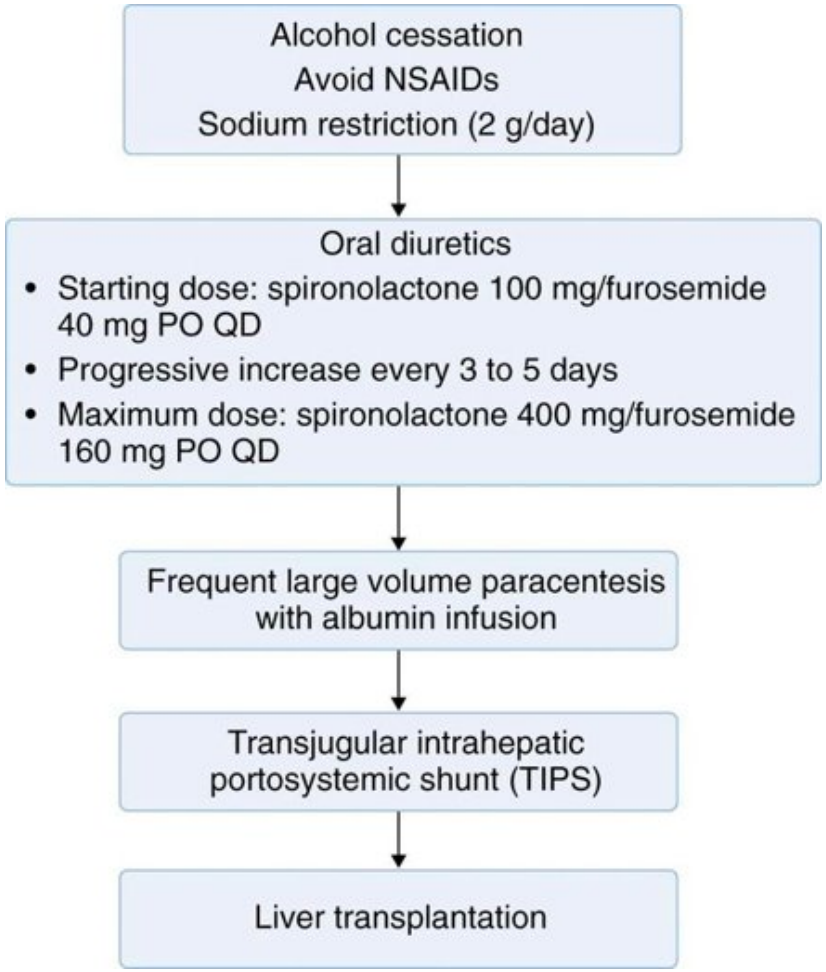
Low SAAG= <1.1

- Ascites albumin is close to plasma
- Because the ascites is plasma! "Not the Liver"
- Extrahepatic source:
  - Malignancy, Infection (TB), Trauma, Pancreatitis etc...



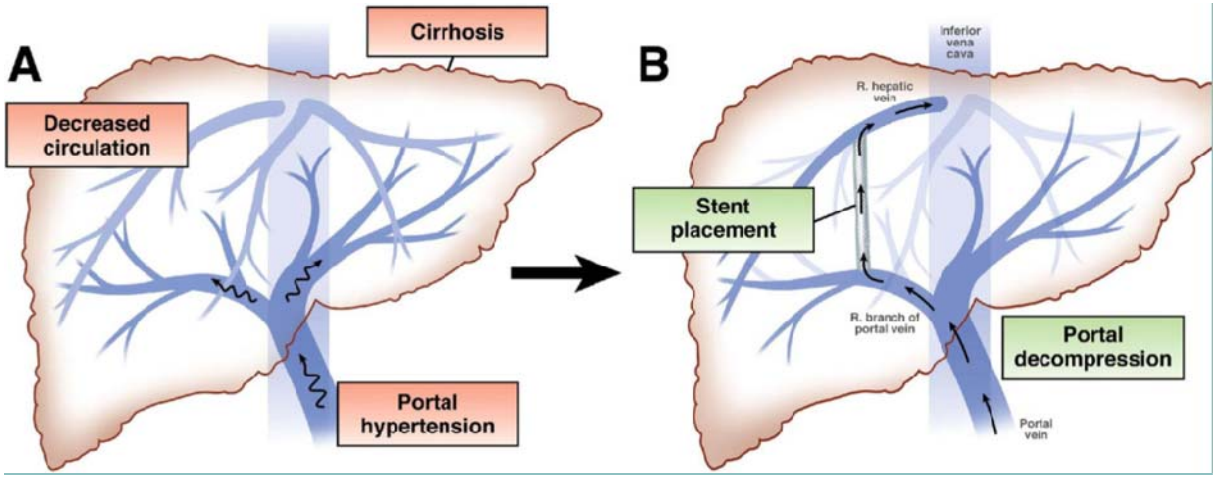
Algorithm for the diagnosis of ascites according to the serum-ascites albumin gradient (SAAG). IVC, inferior vena cava.

Source : Harrison's Principles of Internal Medicine (19th Ed)



MANAGEMENT OF ASCITES IN CIRRHOSIS

Management of Ascites Due to Cirrhosis
1. Treatment of underlying disorder (e.g. alcoholic liver disease, hepatitis B, autoimmune hepatitis)
2. Dietary sodium restriction (less than 2000 mg per day)
3. Diuretic therapy (maintain ratio spironolactone 100 mg: furosemide 40 mg)
4. Therapeutic paracentesis
5. Fluid restriction only if serum sodium <120 mEq/L or symptomatic hyponatremia



TIPS (TRANS-JUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT)

Table 5. Definition and Diagnosis of Bacterial Peritonitis in Cirrhotics

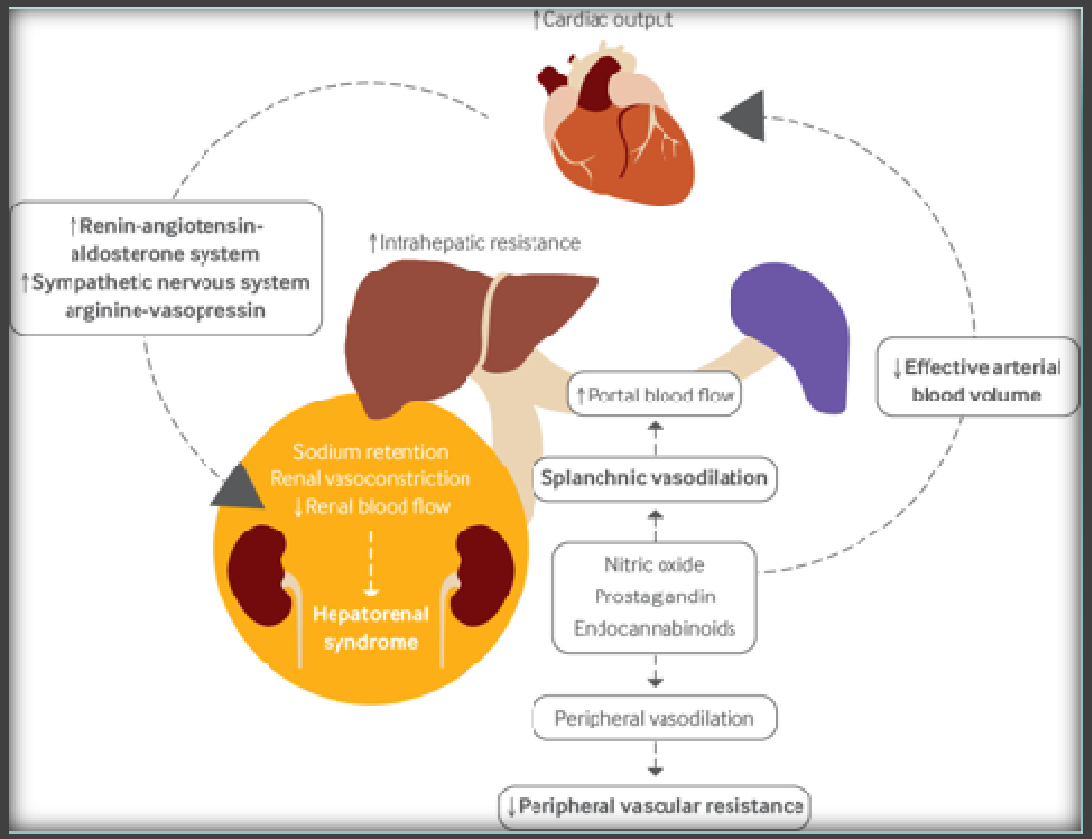
TYPE	ASCITIC CELL COUNT	ASCITES CULTURE	TREATMENT
Sterile	< 250 PMNs	Negative	None
Spontaneous bacterial peritonitis	≥ 250 PMNs	Monobacterial infection	3rd generation Cephalosporin
Culture negative neutrocytic ascites	≥ 250 PMNs	Negative	3rd generation Cephalosporin
Non neutrocytic bacterascites	< 250 PMNs	Monobacterial infection	Only if symptomatic or persistently positive culture
Secondary	≥ 250 PMNs	Polymicrobial infection	(1) Base on culture and sensitivities (2) Identify the source of infection

Rimola A, Gracia-Tsao G, Navasa M, et al. J Hepatol 2000;32:142–153

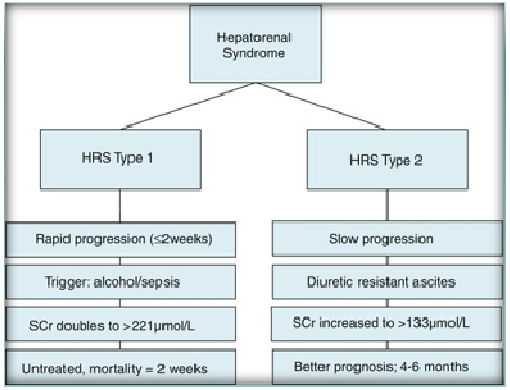
Peritonitis

- **Spontaneous bacterial peritonitis:**
- **Bacterial translocation across bowel**
- **Low opsinization ability of ascites**
- **Absolute WBC > 500 cells/mm3 or PMN count >250 cells/mm3**
- **Cultures + only 50-75%, usually single organism**
-
- **Secondary peritonitis:**
- **Free perforation, abscess, or ischemic bowel**
- **Typically very high PMN count and multiple organisms on gram stain/culture**

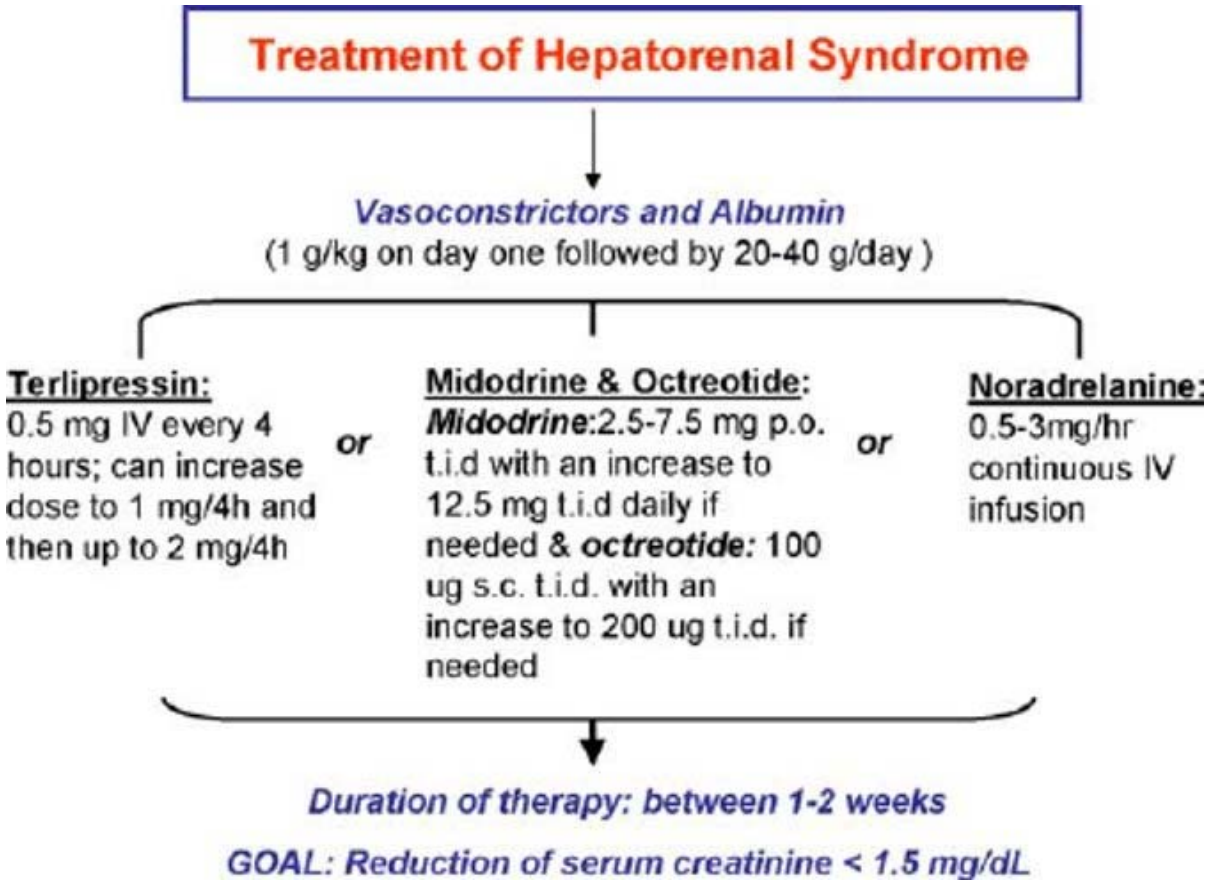
HEPATORENAL SYNDROME



1. Cirrhosis with ascites;
2. Serum creatinine > 133 μmol/L (1.5 mg/dl);
3. No sustained improvement of serum creatinine (decrease to a level of 133 μmol/L or less) after at least 2 days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of bodyweight per day to a maximum of 100 g/day;
4. Absence of shock;
5. No current or recent treatment with nephrotoxic drugs;
6. Absence of parenchymal disease as indicated by proteinuria >500 mg/day, microhematuria (>50 red blood cells per high power field) and/or abnormal renal ultrasononography.



HEPATORENAL SYNDROME



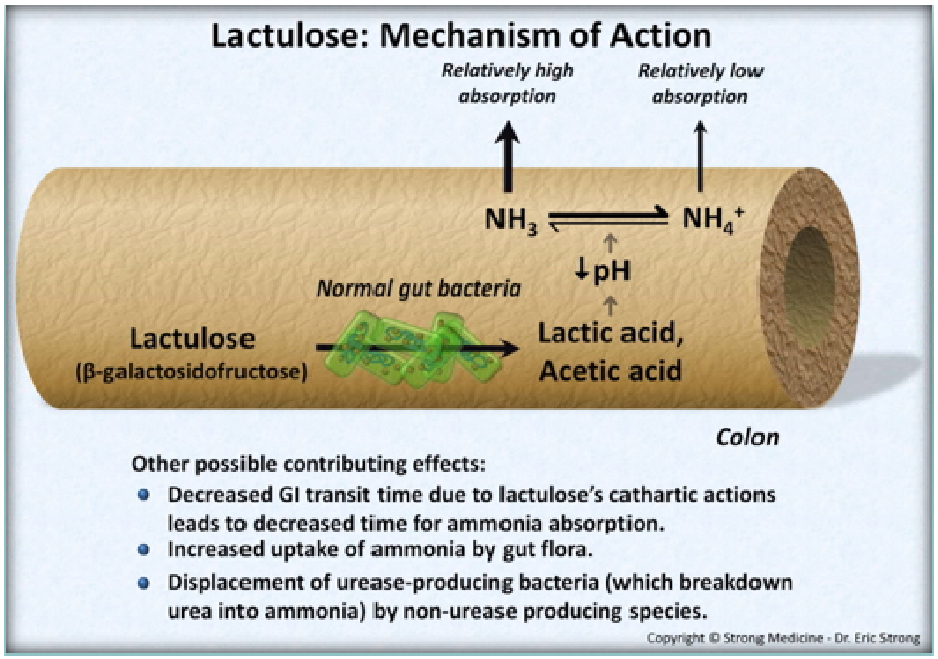
TREATMENT ALGORITHM FOR HRS

STAGING OF HEPATIC ENCEPHALOPATHY

West Haven Criteria for Semi-Quantitative Grading of Mental State	
Grade	**Criteria**
1	Trivial lack of awareness
	Euphoria or anxiety
	Shortened attention span
	Impaired performance of addition
2	Lethargy or apathy
	Minimal disorientation of time or place
	Subtle personality changes
	Inappropriate behavior
	Lethargy or apathy
3	Somnolence to semi-stupor but responsive to verbal stimuli
	Confusion
	Gross disorientation
4	Coma (unresponsive to verbal or noxious stimuli)

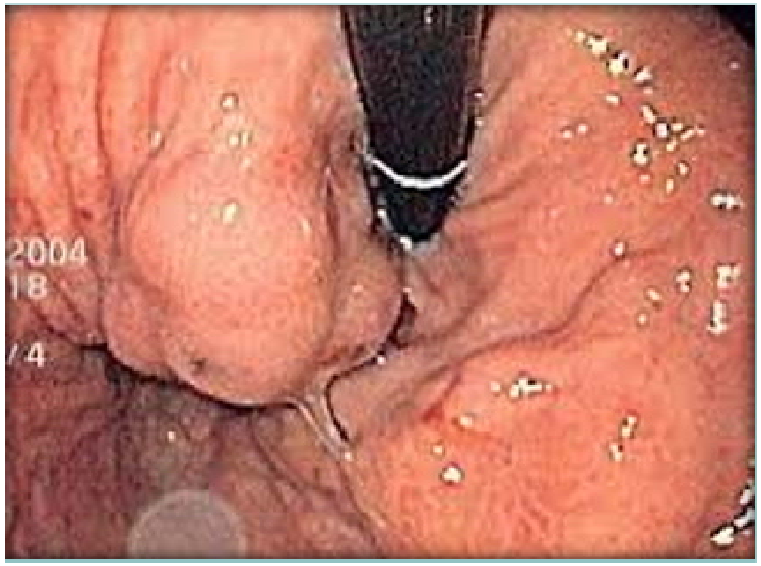
Asterixis

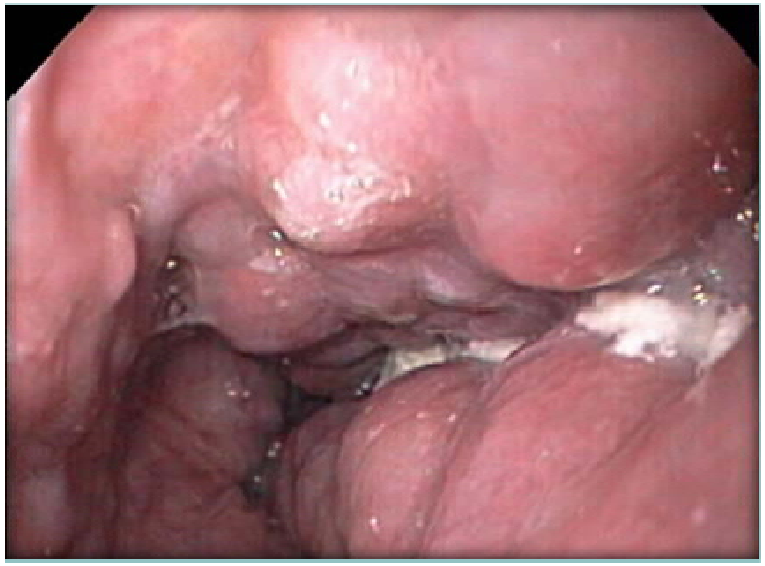
- Non-rhythmic Asymmetric lapse in voluntary sustained posture of extremities
- Arms Outstretched and Fingers separated by hyperextending the wrists
- Absent at Rest
- Rapid Flex-extension movements at the wrist joint
- Usually Bilateral
- Impaired inflow of afferent information to the brainstem resulting in lapses in posture



Treatment of Hepatic Encephalopathy

- Lactulose
  - Nonabsorbable Disaccharides
  - Acts like a probiotic by enhancing growth of certain bacterial strains
  - Low cost making it the preferred agent
  - Reduces pH of the colon, thereby prevents absorption of NH3
  - Converts NH3-->NH4 so that it can be excreted
- Rifaximin
  - Nonabsorbable antibiotic
  - Equivalent or slightly superior to Lactulose or Neomycine





GASTROESOPHAGEAL VARICES

Treatment of Esophageal Varices

Primary Prophylaxis

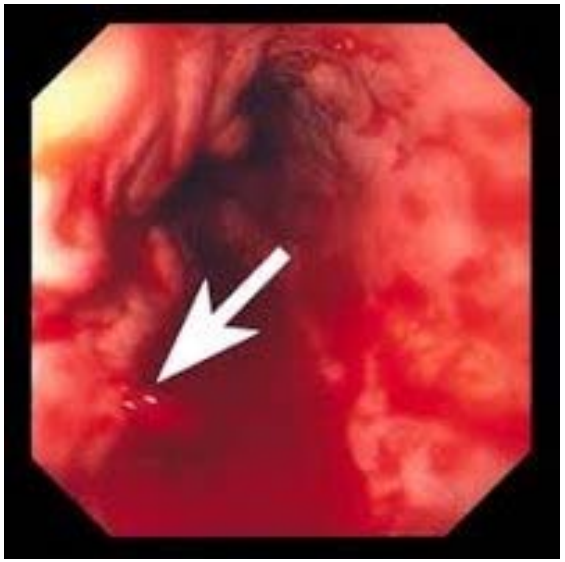
- **Nonselective beta blocker (nadolol, propranolol)**
  - Splanchnic Vasoconstriction
  - Reduce portal inflow
- **Endoscopic band ligation**

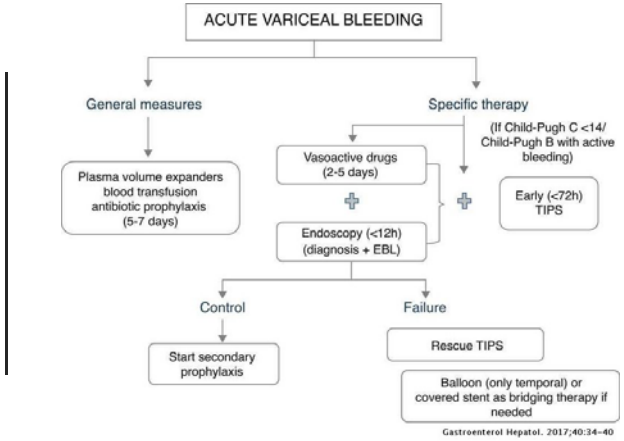
Treatment of variceal bleeding

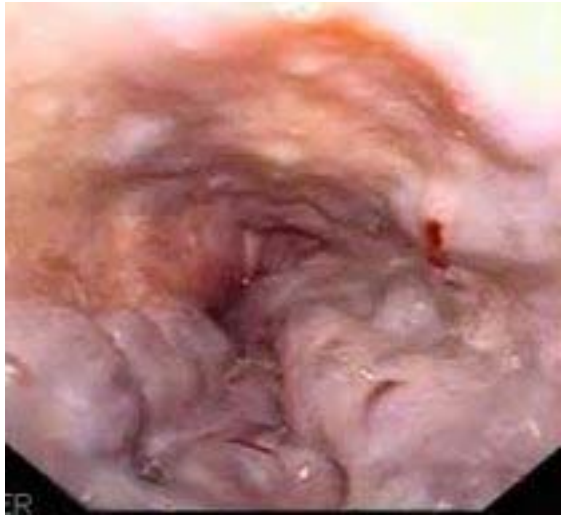
- **Octreotide**
- **Endoscopic band ligation/Sclerotherapy**
- **TIPS**

Secondary prophylaxis

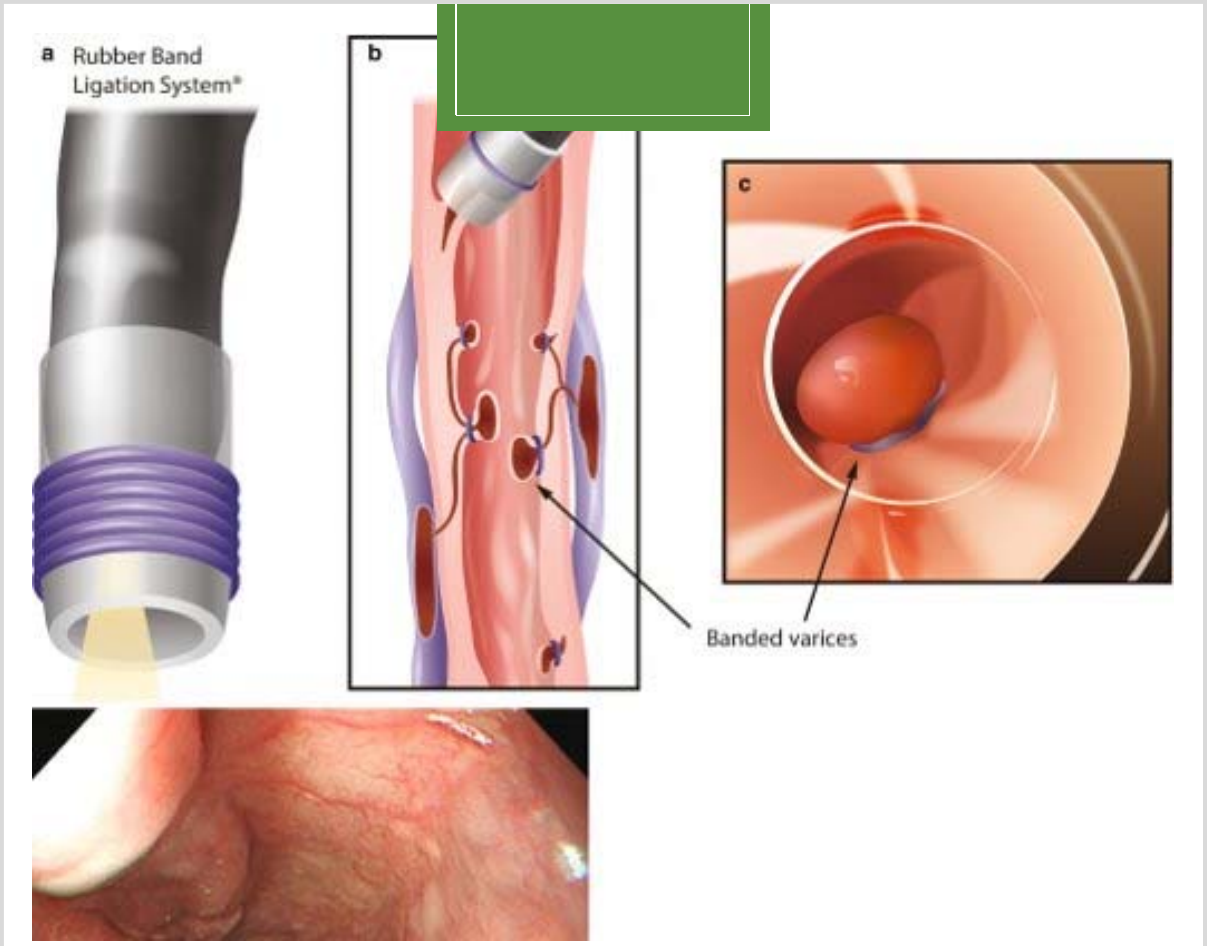
- **Endoscopic band ligation**
- **TIPS**





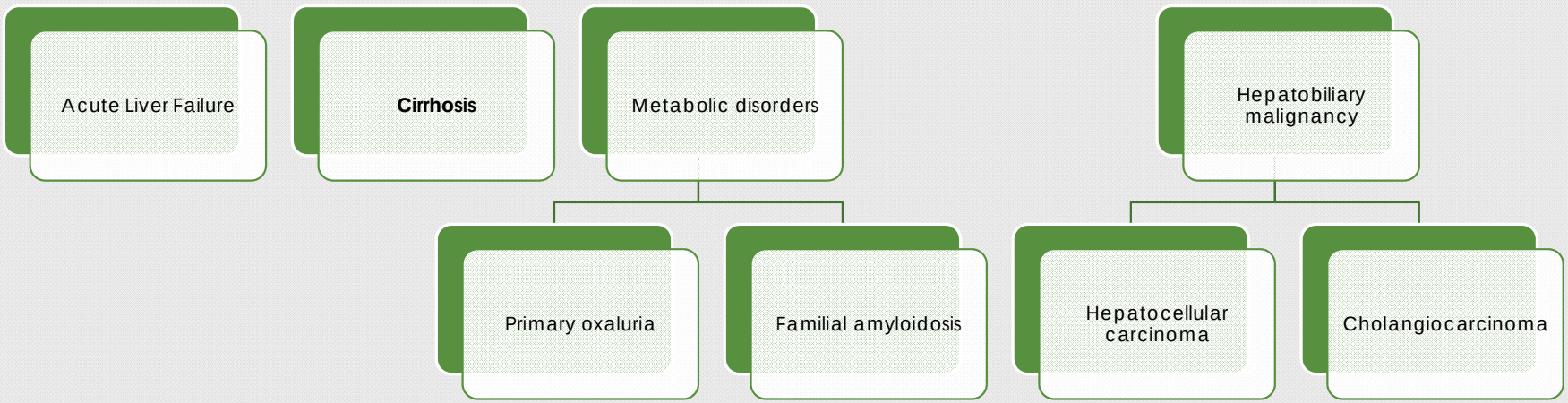


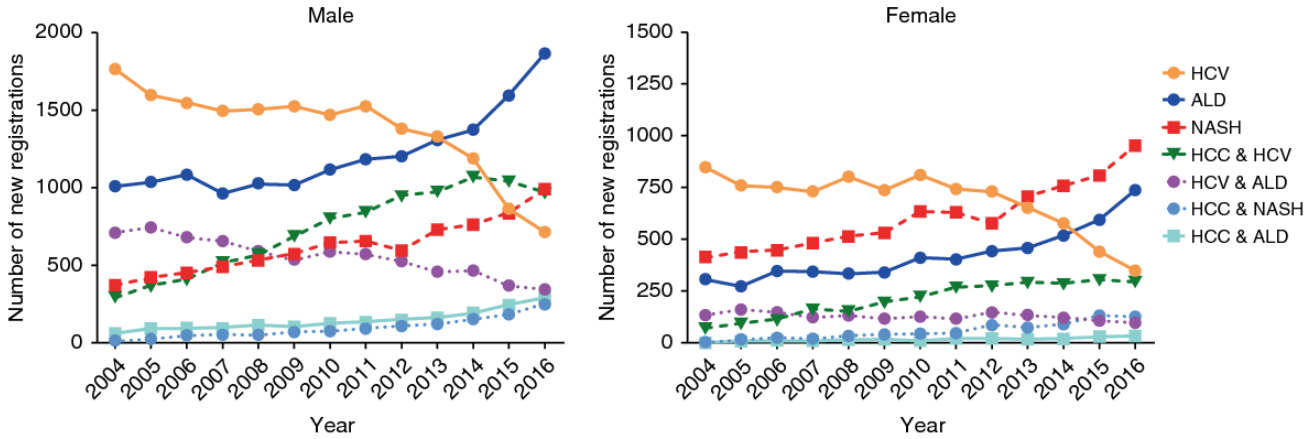
MANAGEMENT OF ESOPHAGEAL VARICEAL BLEEDING



ESOPHAGEAL VARICEAL BAND LIGATION

Liver Transplant: Indications





Mazzen, et al. *American Journal of Gastroenterology,* 2018.

- **Adult patients registered for Liver Transplant in the UNOS Database between 1/2004 and 12/2016**
- **NASH is the 2nd leading cause for LT overall and the 1st leading cause in women**

LIVER TRANSPLANTATION

DONATE LIFE

Coalition on Donation