# Inpatient management of liver disease and its complications

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# Disclosures

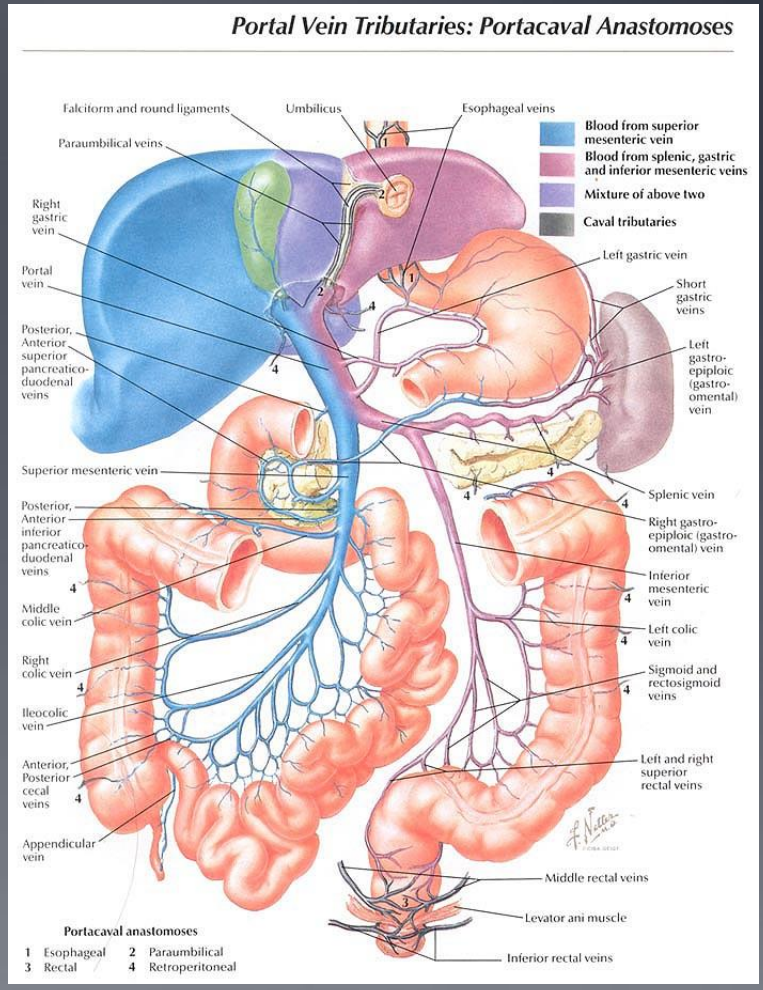
- None

# Objectives

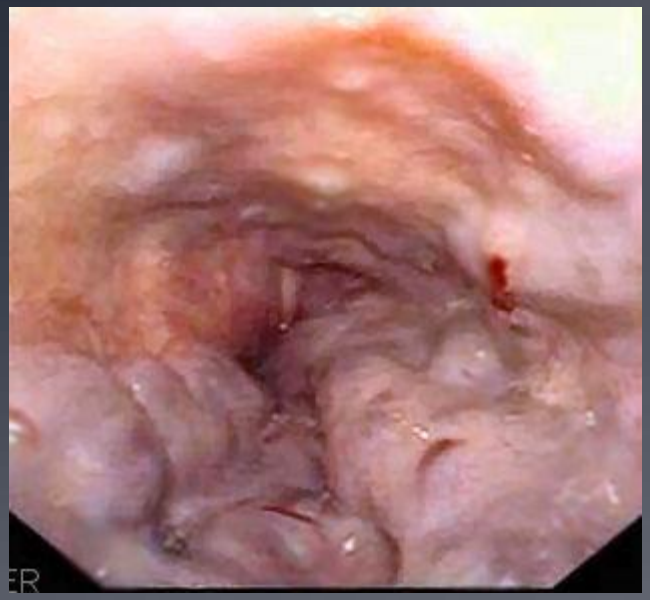
- Review the management of the following, according to the most recent available data/guidelines:
  - Variceal hemorrhage
  - Ascites/SBP
  - Hepatorenal syndrome
  - Hepatic encephalopathy

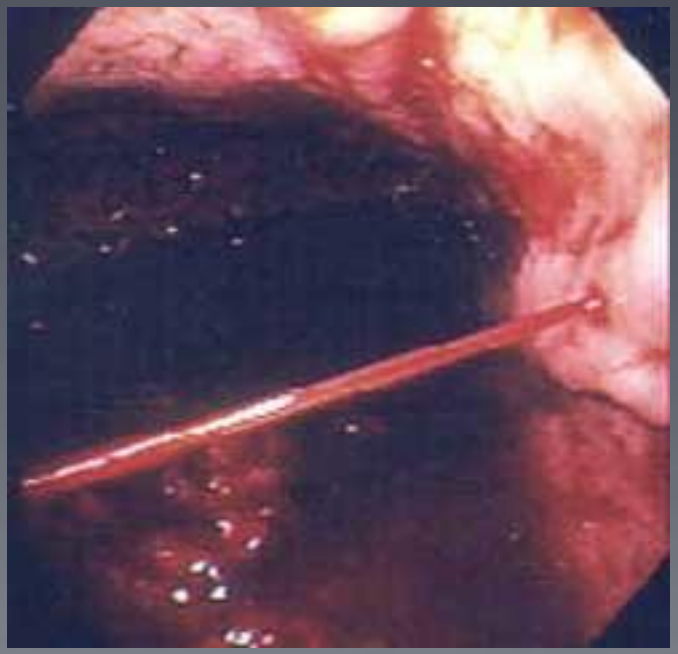
# Portal hypertension

- Elevated pressure in the venous bed which drains from the abdominal viscera and into the portal vein
- Results from
  - ↑resistance to venous flow through the liver + ↑arterial inflow through the mesenteric arteries



# Variceal hemorrhage





# Epidemiology

- Varices are present in about half of pts with cirrhosis at time of diagnosis
- Prevalence increases with severity of cirrhosis
  - Child's class A– 40%
  - Child's class C– 85%
  - May develop earlier in PBC patients
- Varices develop in about 7-8% of patients per year
- Progress from small to large at about 7-8% per year

Garcia-Tsao et al, Hepatology, 46(3), 2007:922-38.

# Epidemiology

- Rate of first variceal hemorrhage
  - 5% for small varices (at 1 year)
  - 15% for large varices (at 1 year)
- After an acute variceal bleeding episode
  - 1 year rebleeding rate: 60%
  - 6-week risk of mortality: 15-20%
    - 0% for Child's class A
    - 30% for Child's class C
- Cause of mortality with variceal bleeding has changed over past 30 yrs
  - Most deaths no longer due to uncontrolled bleeding
  - Infection, renal failure are more common causes now

# Management

- Volume resuscitation
  - Be cautious
  - Excessive resuscitation may ↑ portal pressure
    - ↑ risk of rebleeding
- Transfusion of RBC (if needed)
  - Target Hgb 8 g/dL
  - ↑ rebleeding risk with overtransfusion
- Correction of coagulopathy (if needed)
  - Little evidence for/against this
  - INR/PTT poor reflection of coagulation balance in cirrhosis
- Endoscopic evaluation

# Management

- Pharmacologic therapy
  - Vasopressin/octreotide
    - Both reduce splanchnic arterial flow, reducing inflow into the portal system
    - Both have been shown to reduce active bleeding at the time of endoscopy, no difference between them
    - If hypotensive, vasopressin
    - If not, octreotide
  - Proton pump inhibitors
    - Very little evidence of efficacy, but still commonly used
  - However, since source of bleeding is not known prior to endoscopy, both should be initiated until endoscopy has been performed

# Management

- Pharmacologic therapy (cont.)
  - All patients with cirrhosis and GI bleeding should receive IV antibiotics for prevention of infection (particularly SBP)
    - Bacterial infections occur in 40% of pts with variceal hemorrhage
      - SBP
      - UTI
      - Pneumonia
    - Antibiotic prophylaxis decreases risk of infection, rebleeding and mortality (Garcia-Pagan et al, Semin Resp Crit Care Med. 2012; 33:46-54)

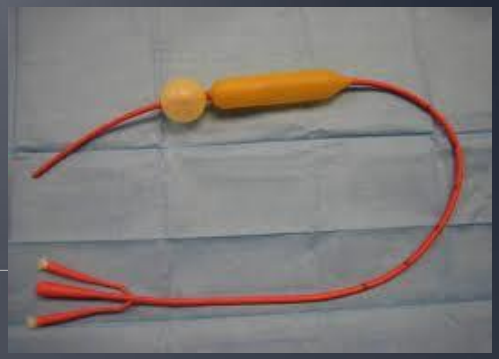
# Management

- Esophageal varices
  - EGD for diagnosis and initial management
  - Band ligation better than sclerotherapy for EV
  - TIPS if refractory
- Gastric varices
  - Obturation with cyanoacrylate glue injection is superior to banding (not widely available)
  - Other endoscopic therapies have much lower success rates and are not recommended
  - TIPS is standard of care for bleeding GV

# Management

- Early TIPS
  - Several studies showing very good outcomes with TIPS as initial therapy once source of bleeding confirmed with endoscopy
    - For CTP class B/C cirrhosis
  - Studies have been small in size, but consistent
  - Not yet standard of care in US
    - But may get there…

# Bridge therapy



- Balloon tamponade
  - Several devices available (Sengstaken-Blakemore tube, Minnesota tube, etc)
  - All involve large nasogastric tube with 1 or more balloons that can be inflated to provide compression of varices
  - Can be effective as a bridge to more definitive therapy if endoscopy or TIPS are not immediately available
  - None should be used >24 hours
    - Risk of aspiration and perforation

# Variceal hemorrhage

- Other aspects
  - If banding is performed, patients should have **either**
    - Repeat endoscopy in 2-4 weeks for reevaluation and possible repeat banding
    - Initiation of nonselective beta-blocker therapy

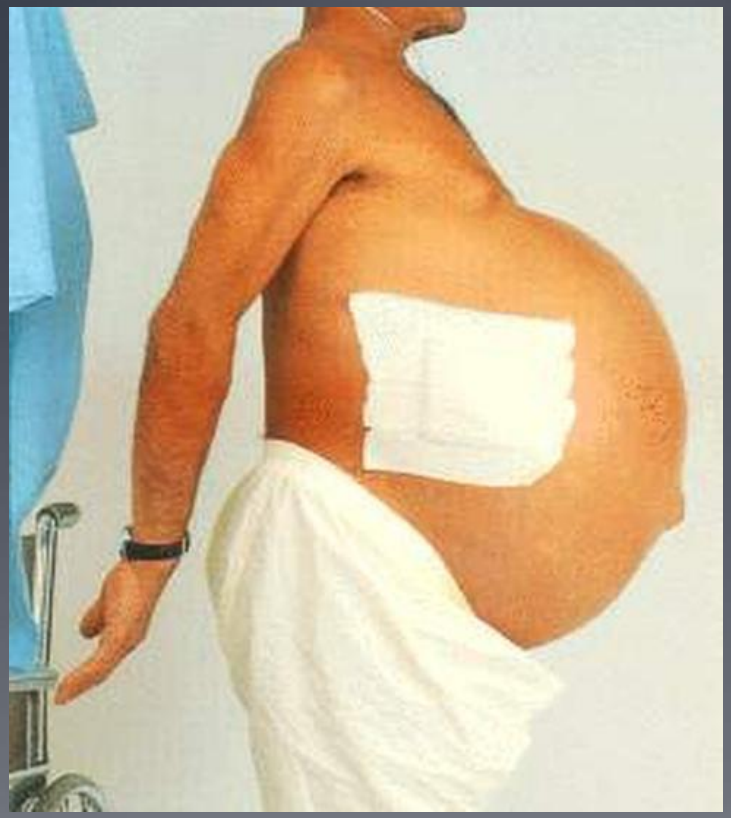
# About beta-blockers

- Nonselective beta-blockers
  - Shown to reduce portal pressure in patients with clinically significant portal hypertension
  - Recommended to reduce risk of bleeding in patients with medium-to-large varices
  - DO NOT prevent varices from forming in patients without varices
  - ARE NOT useful in preventing/treating ascites
  - More on this later…

# Looking into the future

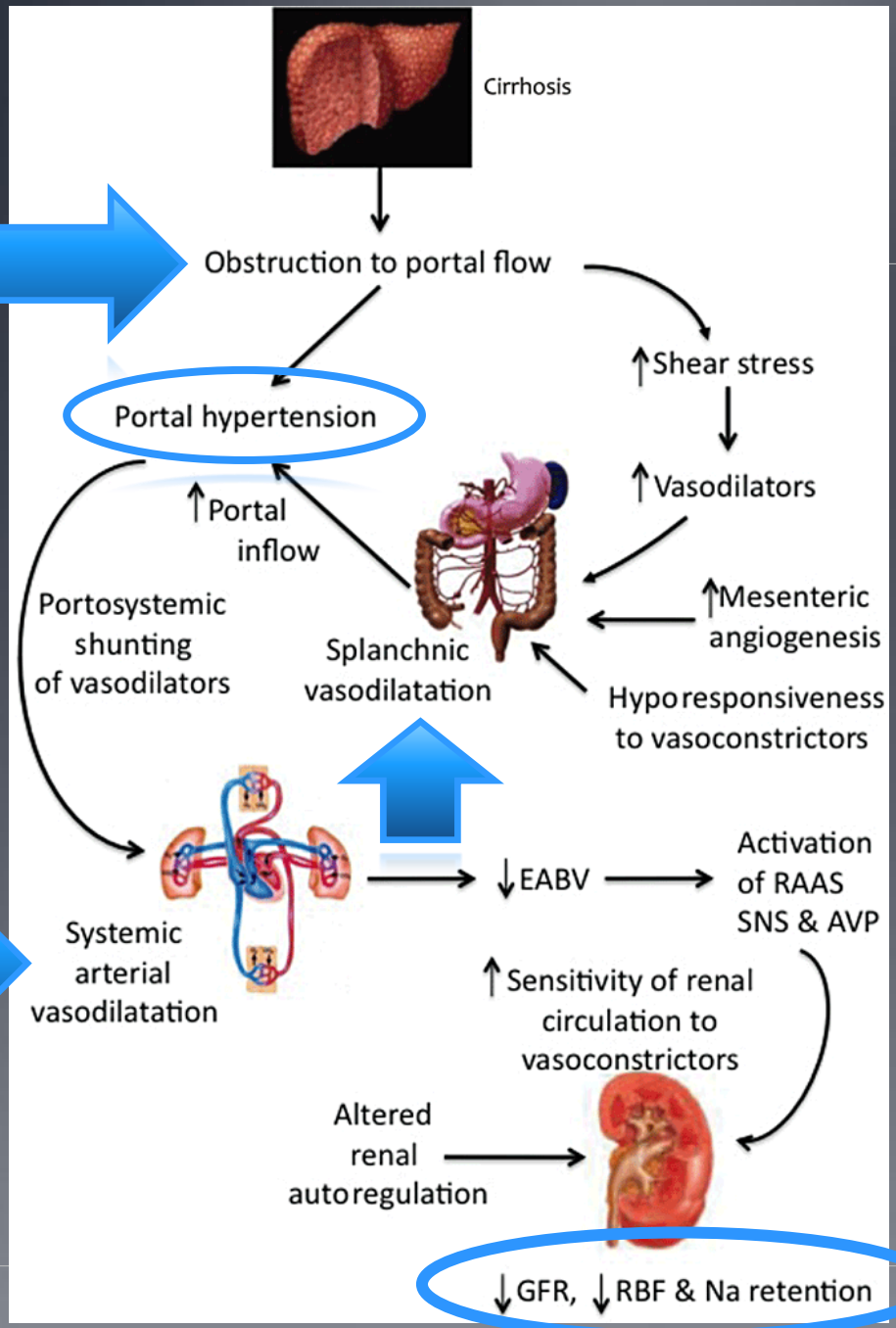
- Esophageal stenting
- Hemostatic sprays/powders
- Expanded roles for cyanoacrylate injection

# Ascites



# Ascites

- Cirrhosis/disruption of hepatic architecture
- ↑pressure within portal venous system
- Extravasation of fluid from sinusoids
- Weeps across the capsule of the liver
- Outpaces capacity of abdominal lymphatics to reabsorb
- Exacerbated by renal sodium retention from ↑ aldosterone activity




Wong F, Journal of Gastroenterology and Hepatology **27 (2012) 11–20**

# Management

- Dietary sodium restriction
  - 2g Na/day (evidence is mixed, but Na-restriction is universally recommended in specialty guidelines)
- Diuretics
  - Spironolactone is more effective
  - Furosemide is added to help offset K retention
  - Must watch electrolytes and kidney function
  - If hyponatremia becomes a problem, then free water restriction may be necessary
- Therapeutic paracentesis
  - Can be done repeatedly as often as needed (with caution)
- TIPS may be considered in patients with refractory ascites without encephalopathy

# Complications of ascites

- Hepatic hydrothorax
  - Due to translocation of ascites across the diaphragm
  - May develop in absence of visible ascites
    - Negative intrathoracic pressure
  - Treat with thoracentesis, NO CHEST TUBES
- Hernias
  - Umbilical, inguinal, femoral, incisional
  - May develop incarceration/strangulation
  - High surgical risk with repair
    - May not have a choice
- Spontaneous rupture/leak
  - High risk of mortality, generally requires surgical repair

# Spontaneous bacterial peritonitis

- Infection of ascites
  - Can also occur in hepatic hydrothorax (spontaneous bacterial pleuritis)
- Should be suspected in any patient with cirrhosis with new abdominal pain, sudden worsening of ascites, fever, or worsened hepatic encephalopathy
- Can develop while in the hospital
  - About 50% of cases of SBP in hospitalized patients are not present at the time of admission

# SBP

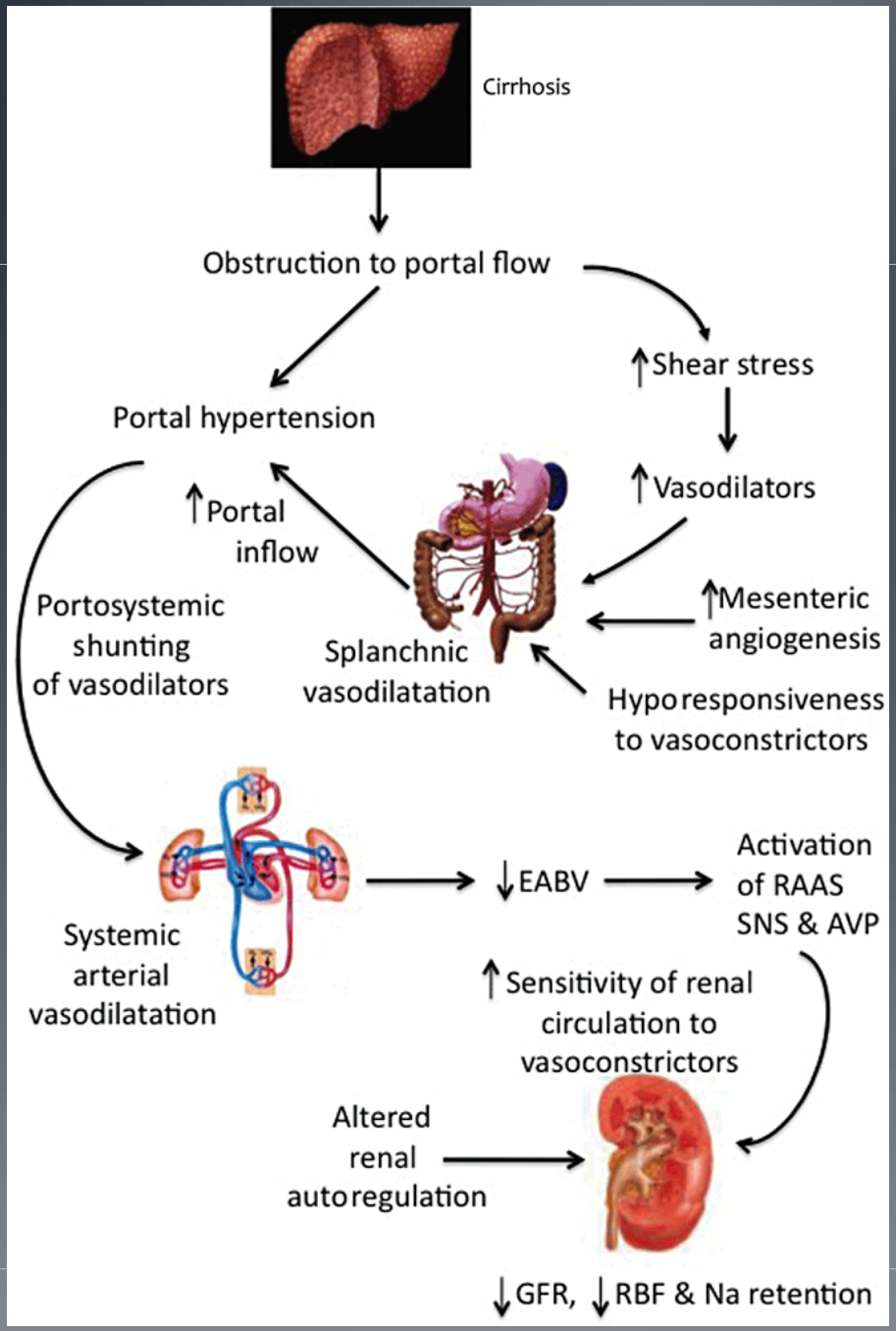
- Diagnosis
  - Requires diagnostic paracentesis
  - Diagnosis requires fluid PMN count > 250
  - Fluid should be sent for culture as well
    - Fluid should be put in culture at bedside as soon as collected
      - Increases diagnostic yield by about 25%

# SBP

- As with any infection, cirrhotic patients with SBP are at increased risk of developing hepatorenal syndrome
- Risk can be reduced by administration of IV albumin

# Hepatorenal Syndrome

- Renal failure arising in the setting of decompensated cirrhosis
  - Typically in patients with
    - Ascites
    - Hypotension
- Related to severely decreased renal blood flow
  - Renal vasoconstriction in the setting of peripheral vasodilation
- Not associated with parenchymal kidney injury

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# Significance

- Common
  - Occurs in 18% of cirrhotics within 1 yr of diagnosis
  - 40% within 5 years
- High mortality
  - Median survival for HRS patients without treatment is weeks to months
  - Patients often do not do well with dialysis
    - Hypotension
    - Hypoalbuminemia
    - Increased risk for infections with cirrhosis

# Definition

- Cirrhosis with ascites
- Serum creatinine > 1.5 mg/dL, (or 50%) above baseline
- No improvement of serum creatinine (decrease to a level ≤ 1.5 mg/dL) after at least two days of diuretic withdrawal and volume expansion with albumin. The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/day, microhematuria (> 50 red blood cells per high power field), and/or abnormal renal ultrasonography

# Other findings

- Poor urine output
- Very low urine sodium
  - Similar to hypovolemia, but does not improve with volume challenge
- Type 1 vs Type 2 HRS
  - Type 1 is more rapid, progresses over days
    - Median survival 2 weeks
    - More often encountered with inpatients
  - Type 2 is more gradual, progresses over weeks to months
    - Median survival 4-6 months

# Triggers

- Sudden acute stressors
  - Infection (esp. SBP)
  - Hypovolemia
    - Hemorrhage (varices)
    - Other volume depletion (diuretics)
    - Other sudden fluid shifts (post-paracentesis)
  - Surgery
- Medications
  - NSAIDs

# Management

- Focuses on improving renal perfusion
  - Increased intravascular volume
    - IV albumin 1 g/kg per day, up to 100g per day
    - Continue x 2 days, then give 20-40 g/day
    - Avoid crystalloid
      - Most goes into extravascular space (ascites)
  - Vasoconstrictor therapy
    - Vasopressin or norepinephrine if in ICU
    - Octreotide/midodrine if not
      - Consider moving to ICU even if not meeting traditional criteria

# Renal Replacement Therapy

- Patients often do not tolerate conventional hemodialysis due to hypotension
- Continuous renal replacement therapy is often better tolerated
- Initiation of RRT is not recommended unless
  - Patient is suitable candidate for liver transplantation, or
  - Patient has transient cause of decompensation that is expected to resolve quickly

# HRS-- Prevention

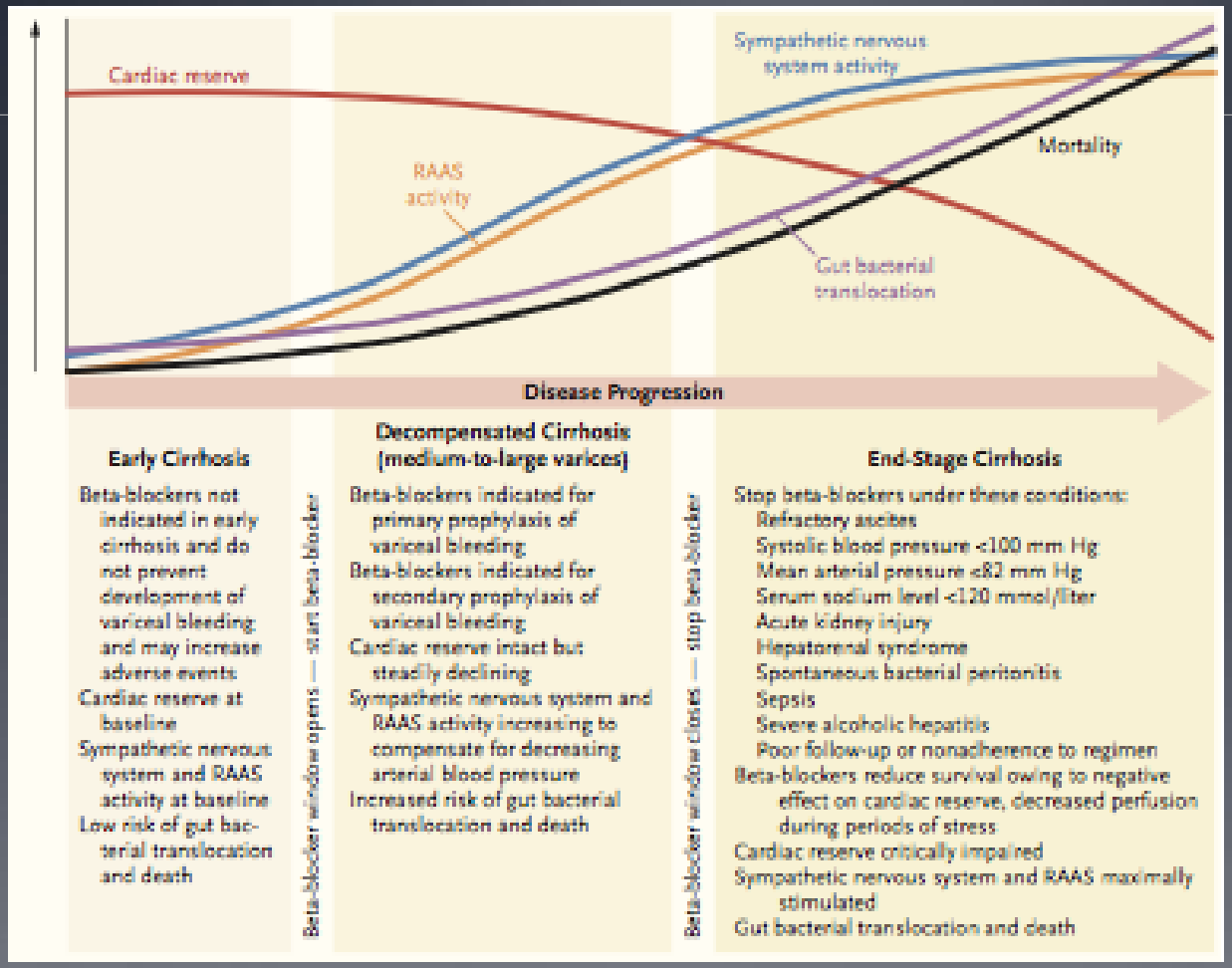
- Prevention is the best treatment for HRS
  - Avoiding triggering events as much as possible
    - Avoid aggressive diuresis
    - Avoid NSAIDs
    - Screen for esophageal varices and initiate prophylaxis if needed
    - Avoid dehydration
    - Immunizations as appropriate

# HRS-- Prevention

- Prevention is the best treatment for HRS
  - Give IV volume with albumin when appropriate
    - With any therapeutic paracentesis >5L
      - 8g albumin per liter of fluid removed
    - With any episode of SBP
      - IV albumin on days 1 and 3
    - Monitor creatinine in patients at risk for HRS and initiate treatment early for any significant changes

# Beta-blockers

- Recent concern about increased risk with use of nonselective beta-blockers in advanced-stage patients
  - Refractory ascites
  - Hypotension (systolic BP < 90)
  - SBP
  - Severe alcoholic hepatitis
- Many groups have advocated stopping/avoiding NSBB in patients with any of these


Cardiac reserve
Sympathetic nervous system activity
RAAS activity
Mortality
Gut bacterial translocation
Disease Progression
Early Cirrhosis
Beta-blockers not indicated in early cirrhosis and do not prevent development of variceal bleeding and may increase adverse events
Cardiac reserve at baseline
Sympathetic nervous system and RAAS activity at baseline
Low risk of gut bacterial translocation and death
Beta-blocker window opens — start beta-blocker
Decompensated Cirrhosis (medium-to-large varices)
Beta-blockers indicated for primary prophylaxis of variceal bleeding
Beta-blockers indicated for secondary prophylaxis of variceal bleeding
Cardiac reserve intact but steadily declining
Sympathetic nervous system and RAAS activity increasing to compensate for decreasing arterial blood pressure
Increased risk of gut bacterial translocation and death
Beta-blocker window closes — stop beta-blocker
End-Stage Cirrhosis
Stop beta-blockers under these conditions:
Refractory ascites
Systolic blood pressure <100 mm Hg
Mean arterial pressure ≤82 mm Hg
Serum sodium level <120 mmol/liter
Acute kidney injury
Hepatorenal syndrome
Spontaneous bacterial peritonitis
Sepsis
Severe alcoholic hepatitis
Poor follow-up or nonadherence to regimen
Beta-blockers reduce survival owing to negative effect on cardiac reserve, decreased perfusion during periods of stress
Cardiac reserve critically impaired
Sympathetic nervous system and RAAS maximally stimulated
Gut bacterial translocation and death

# Hepatic Encephalopathy

- Alteration in mental status due to accumulation of ammonia and other toxins in the bloodstream
- Symptoms range from mild sleep disturbances to easy distraction/poor concentration, personality changes, overt confusion, stupor, and eventually coma
- Related to combination of decreased hepatocyte functional mass AND shunting of blood away from hepatocytes through collaterals

# Diagnosis

- There are no set criteria for diagnosis of HE
- Requires some degree of mental status change that is attributable to chronic liver disease
- Other causes of altered mental status must be ruled out
- An elevated ammonia level does NOT make a diagnosis of hepatic encephalopathy
  - Ammonia levels do not necessarily correlate with altered mental status and the level at which patients develop symptoms varies from one patient to another

# Staging of HE (West Haven Criteria)

| Stage | Consciousness | Intellect/behavior | Neurologic findings |
|---|---|---|---|
| 0 | Normal | Normal | Normal |
| MHE | Normal | Normal | Impaired specific psychomotor testing |
| 1 | Mild lack of awareness | Shortened attention span | Impaired addition or subtraction; mild asterixis or tremor |
| 2 | Lethargic | Disoriented, inappropriate behavior | Obvious asterixis; Slurred speech |
| 3 | Somnolent but arousable | Gross disorientation, bizarre behavior | Muscular rigidity and clonus; Hyperreflexia |
| 4 | Coma | Coma | Decerebrate posturing |

COVERT

OVERT

# Triggers

- Any patient presenting with acute HE should be evaluated for
  - Infections (especially SBP)
  - GI bleeding
  - Hypovolemia (esp. excessive diuretics)
  - Electrolyte disturbances
  - Constipation (medication noncompliance?)
  - New medications

# Treatment

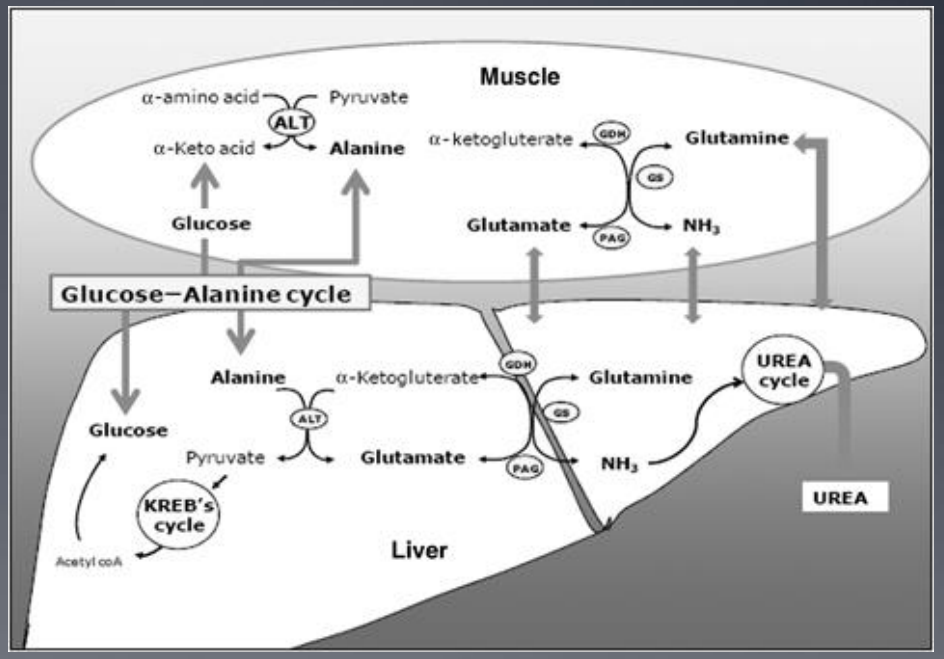
- Two mechanisms of treatment
  - Stool acidification (lactulose)
    - Converts ammonia to charged $NH_4+$ ion, trapping it in the gut lumen and allowing excretion in stool
  - Reduction in gut flora (rifaximin and other antibiotics)
    - Reduce the number of ammonia-generating bacteria in the gut lumen, reducing ammonia production

# Management

- For acute HE
  - Identify and address triggers
  - Lactulose
    - Oral if mental status allows
    - Rectal as a retention enema if not
      - Seems to work faster
  - Assess response clinically, not by serum ammonia levels
- For outpatient maintenance
  - Lactulose
    - Titrated to 2-4 stools per day (educate patient/family)
  - Rifaximin
    - Should always be used along with lactulose unless patient cannot take lactulose
  - No role for serial ammonia monitoring
    - Progress is monitored based on clinical picture

# Other issues

- Muscle wasting (sarcopenia) is a major issue in cirrhosis
  - Negative prognostic factor
- Muscle tissue helps absorb excessive ammonia in the blood
  - Conversion of glutamate to glutamine



# Other issues

- Sarcopenia is associated with increased risk of HE
- Dietary protein restriction is no longer recommended in HE management
  - Accelerates sarcopenia
- Physical activity that maintains or increases muscle mass may be of benefit in HE

# Other issues

- Because of the impairment of concentration in HE, patients are at an increased risk of accidents with driving
  - Even with minimal HE
- Patients with HE usually have very poor insight into the degree of their impairment
- There are no strict guidelines for restricting driving in patients with HE
  - Significant variability between physicians
  - Family usually have to be involved

# Liver Transplant

- Should be considered in any patient with decompensated cirrhosis with MELD score > 14
- Transplants often happen in the setting of an acute decompensation
- If patients are improving and likely to be discharged soon, then reasonable to refer for outpatient transplant evaluation
- If patients are sick and failing to improve, then better to pursue transplant evaluation as an inpatient

# If you need help…

- Call (501) 686-8000, ask to speak to one of the hepatologists
- One of us is always on call and available to answer questions or help facilitate transfer

# Questions?