COMPLICATIONS OF CIRRHOSIS:

CASES

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Defining Cirrhosis

- Histological diagnosis
- Nodules of regenerating hepatocytes surrounded by fibrous tissue
- Common final result of diverse, chronic inflammatory processes affecting the liver
- Fixed architectural distortion of the liver that results in organ dysfunction and portal hypertension

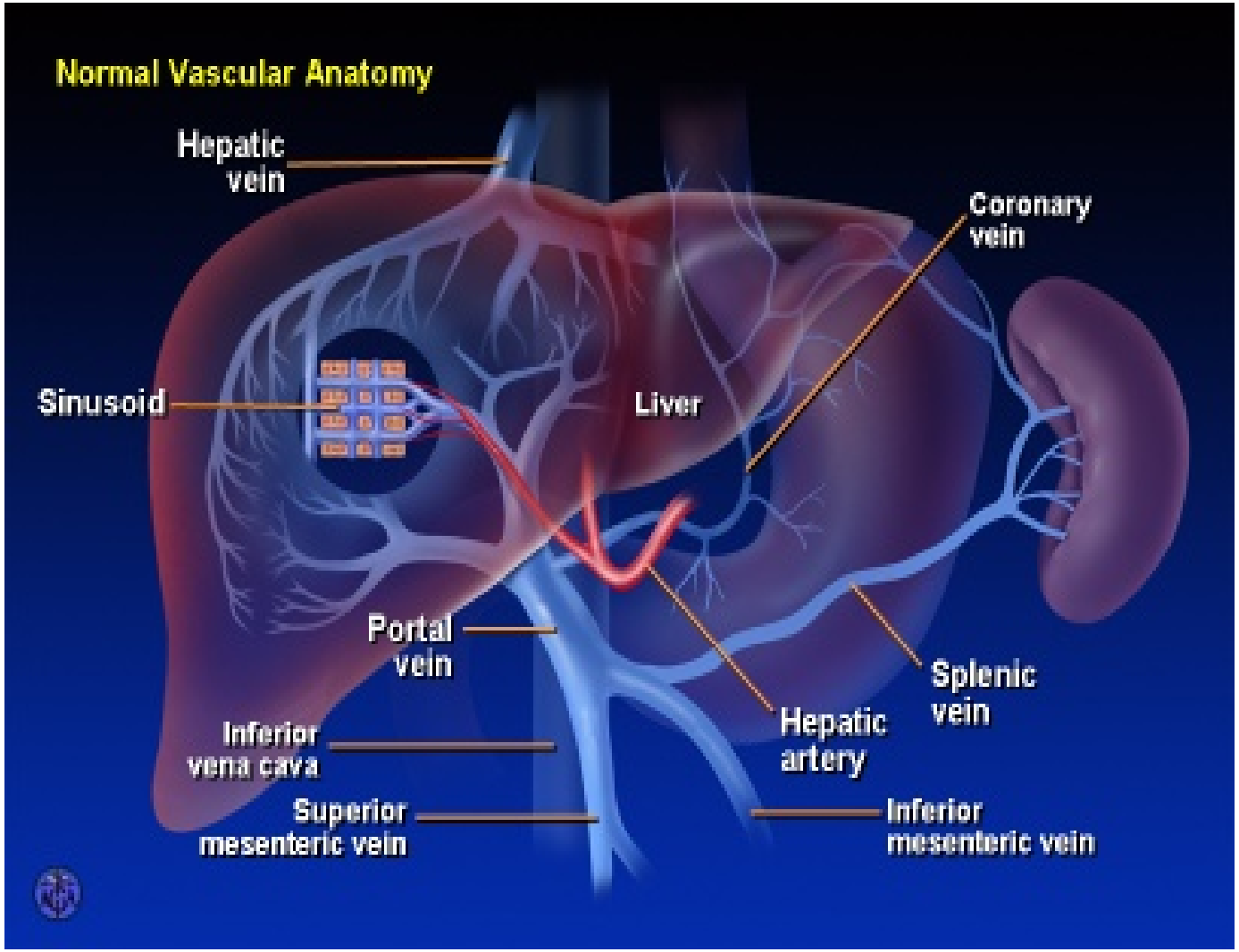
Normal Liver Blood Flow

- Dual blood supply: portal vein and hepatic artery

- Mixed blood joins in the hepatic sinusoid

- Drain from venules, into hepatic veins into IVC

- In a healthy liver, this is a low resistance circuit



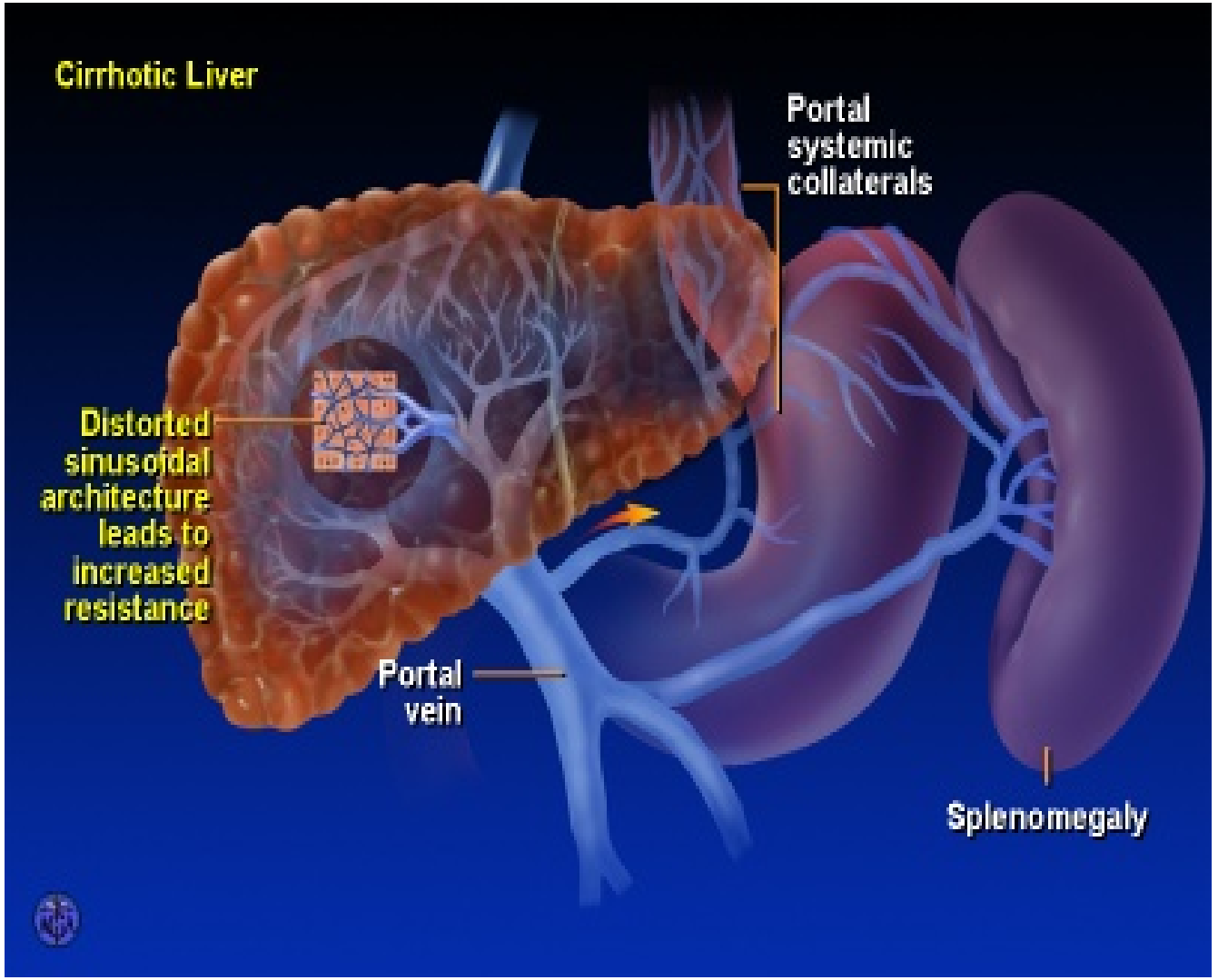
Blood Flow in Cirrhosis

- Distorted architectural leads to increased resistance

- As resistance increases, veins that drain into portal reverse flow

- Spleen enlarges and sequesters platelets

- A previously low resistance circuit becomes a high one



Portal Hypertension/Ohm's Law

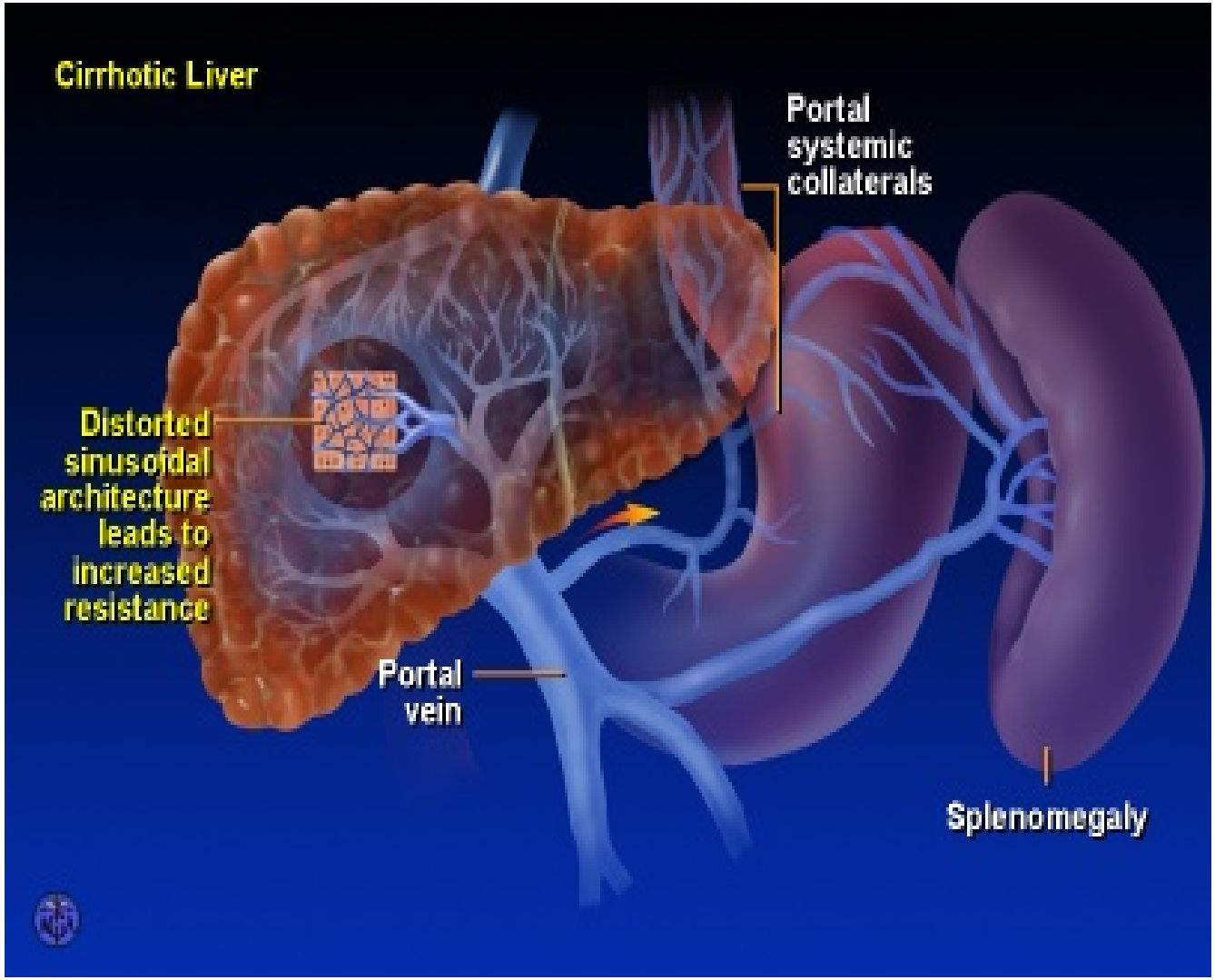
- Pressure =Flow x Resistance
- Increased Pressure in the liver (Portal Hypertension) can result from an increase in blood flow to the liver or an increase in resistance
- Cirrhosis creates a static, fixed resistance
- An increase in dynamic resistance and flow compound the problem

Nitric Oxide outside the Liver

• Elevated portal pressure leads to an increase in sheer stress in splenic vasculature

•There is an INCREASE in nitric oxide in the splanchnic vasculature promoting vasodiliation

•Vasodilation INCREASES blood flow to the liver



Portal Hypertension/Ohm's Law

- Resistance x Flow=Pressure

Resistance X Flow = Pressure

•Fixed: structural changes
•Dynamic: Decrease NO in the liver

•Increase NO in splanchnic vasculature

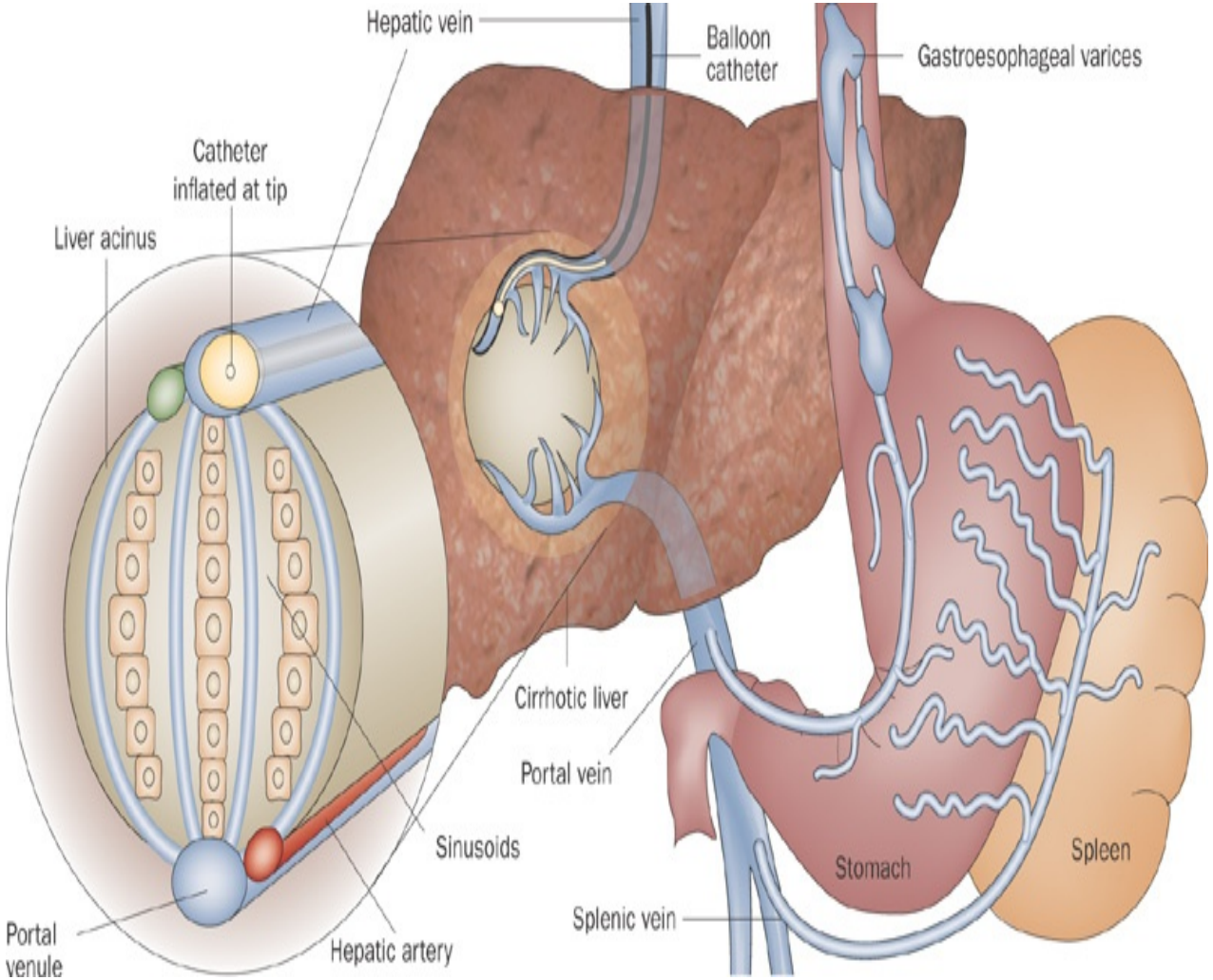
It gets worse….

- Portal hypertension leads to splanchnic and systemic arteriolar vasodilitation which leads to:
  - Decreased effective arterial blood volume
  - Upregulation of sodium-retaining hormones (renin-angiotensin-aldosterone axis)
  - Water retention

Pathogenesis

- Replacement of healthy liver tissue with fibrous, scar tissue
- Architectural distortion leads to loss of function and resistance of blood flow through the liver
- Responses are maladaptive as NO goes down in the liver but increases in the periphery
- As the disease and pressure progresses the effects are systemic: decreased effective circulating volume and activation of the RAAS

Measuring Portal Hypertension



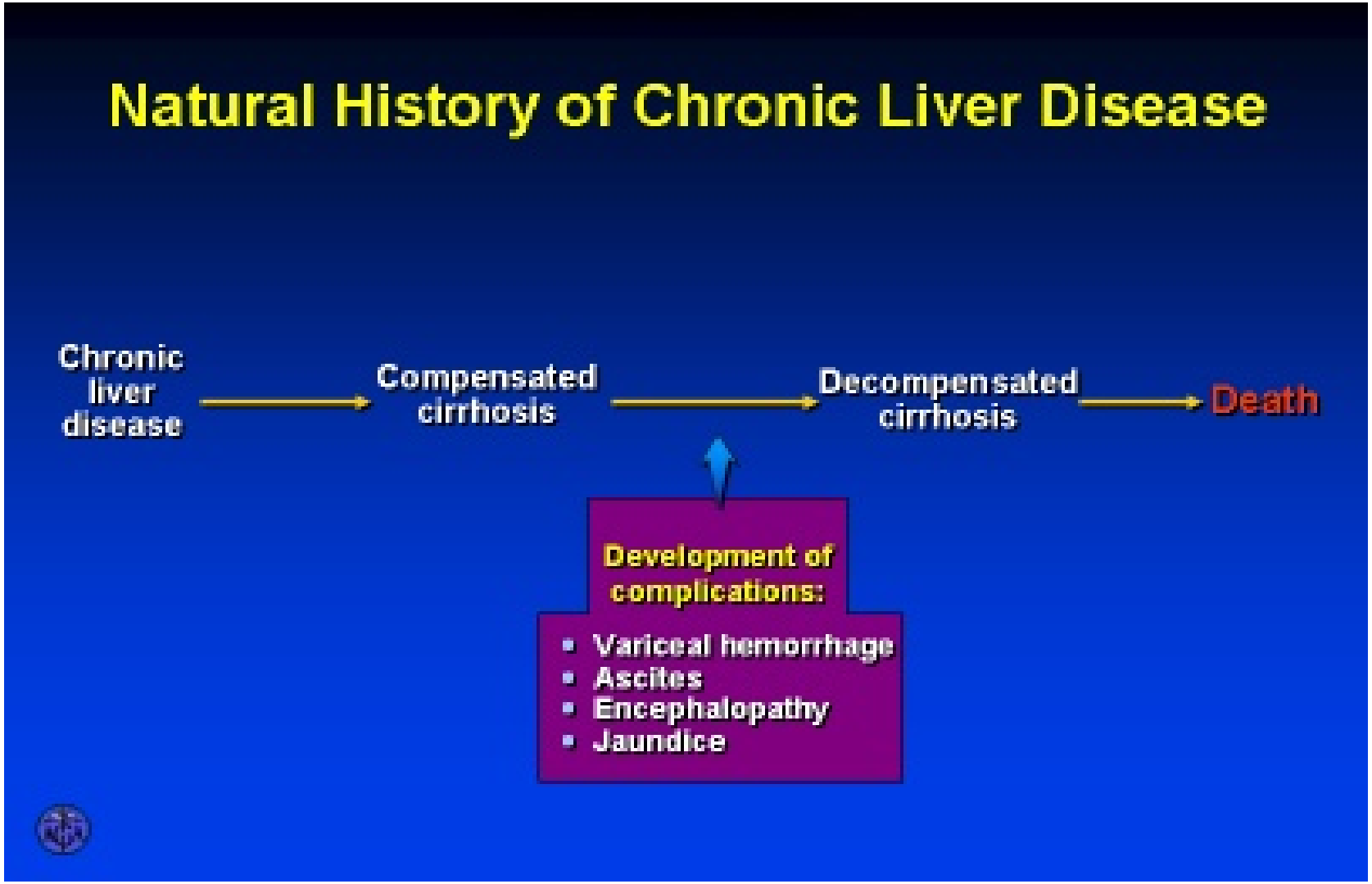
- Portal hypertension is equated to the hepatic venous pressure gradient (HVPG)

- HVPG=Wedged-Free

- HVPG=3-5 is normal

- With cirrhosis HVPG rises and so do complications

Cirrhosis: The Big Picture



Question 1:

- 60 year old male with history of HCV cirrhosis presents with hematemesis. No hx of NSAIDS. No previous bleeding history.

Vitals: Afebrile, HR: 90, BP: 90/60, 100% RA

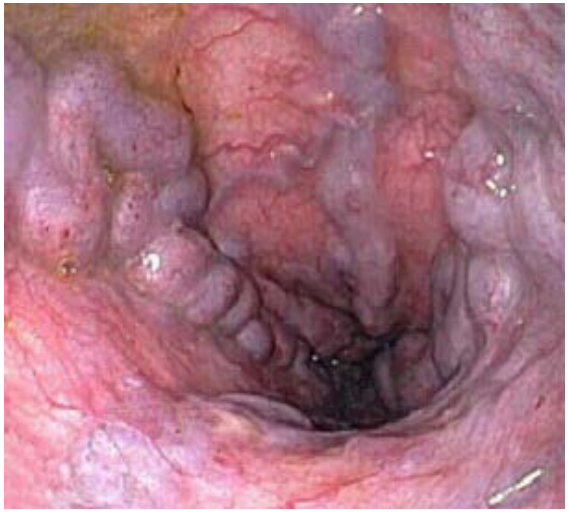
Exam: ATOx3, icterus, ascites, mild edema, melenic stool in rectal vault

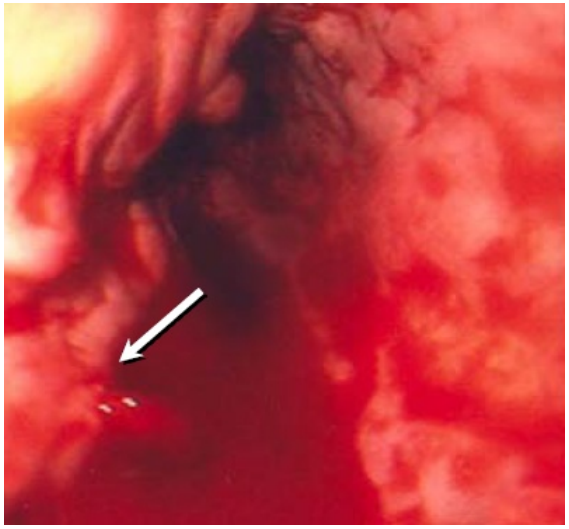
Labs: Hgb: 8 g/dL, plts: 25,000, INR: 1.6, Alb: 2.8

IV access established, Type and screened

- Which of the following is the next most appropriate course of management:
  - A) Platelet transfusion for goal >100,000
  - B) Vitamin K 10mg IV
  - C) Initiation of ceftriaxone IV
  - D) Consult for placement of transjugular intrahepatic portosystemic shunt
  - E) Initiation of propranolol BID titrated to a resting heart rate in the 50s

Variceal Bleeding





• Portal hypertension leads to reversal of blood flow away from the liver

•Gastroesophageal varices are present in approximately 50% of cirrhotic patients

•Prevalence increases with the severity of liver dysfunction/portal hypertension

•Vessels are under high pressure

•Rupture is a MEDICAL EMERGENCY

Acute Variceal Bleeding

- Initial steps are same for all upper GI bleeds
- Avoid over resuscitation
- Initiation of ceftriaxone IV 5-7 days
- Octreotide 50 microgram bolus and continued as 50 micrograms/hr (probably 72 hrs)
- Urgent endoscopy with intent of variceal band ligation
- If rebleeding, consider repeat endoscopy or TIPS

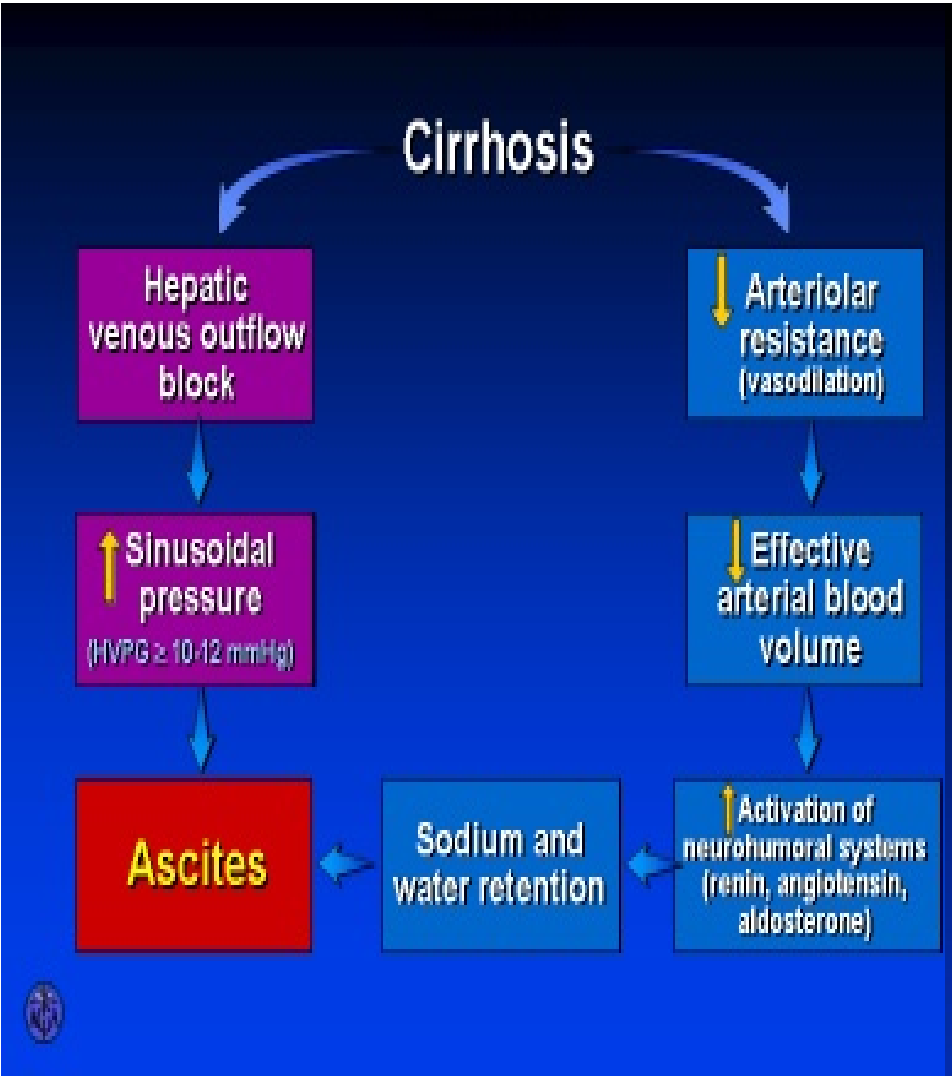
Preventing Variceal Bleeding

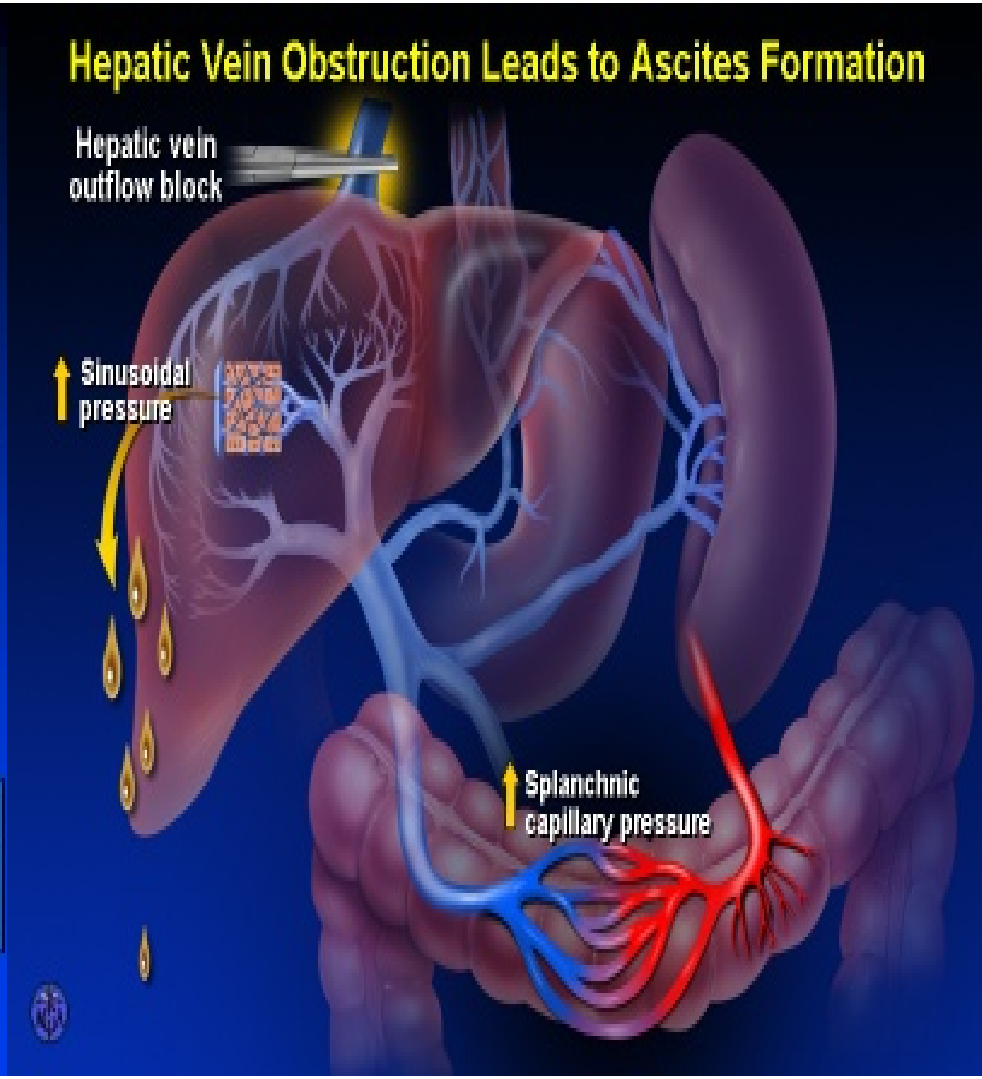
- Screening: EGD with new diagnosis of cirrhosis
  - EGD at cirrhosis diagnosis
  - If 2 negative exams 1-2 years apart can d/c
  - Reconsider if clinical status changes
  - No role for non selective beta blockers
- Primary Bleed Prophylaxis (Present, no bleed hx):
  - Size matters; generally EGD annually
- Secondary Bleed Prophylaxis (Varices have bled):
  - Variceal Banding + NSB
  - TIPS

Question 2:

- A 59 year old man with hx of alcohol dependence presents with new onset abdominal distension. AVSS. Exam notable for: temporal wasting, palmar erythema, shifting dullness, fluid wave, non tender to palpation, LE edema. Labs notable for: Alb: 2.3, INR: 1.6, AST: 100, ALT: 40, Tbil: 3.8, Platelets: 50,000
- You elect to perform a diagnostic paracentesis with the following results: ANC: 150 cells, Alb: 1.0, Tprot: 1.8. No orgs on G/S
- Which of the following is correct:
  - A) SAAG of 1.3 implicates nephrotic syndrome and 24 hr urine protein should be collected
  - B) ANC of 150 confirms the diagnosis of SBP and admission is warranted
  - C) SBP is unlikely as there is no abdominal pain
  - D) Restriction of dietary salt intake is expected to be beneficial

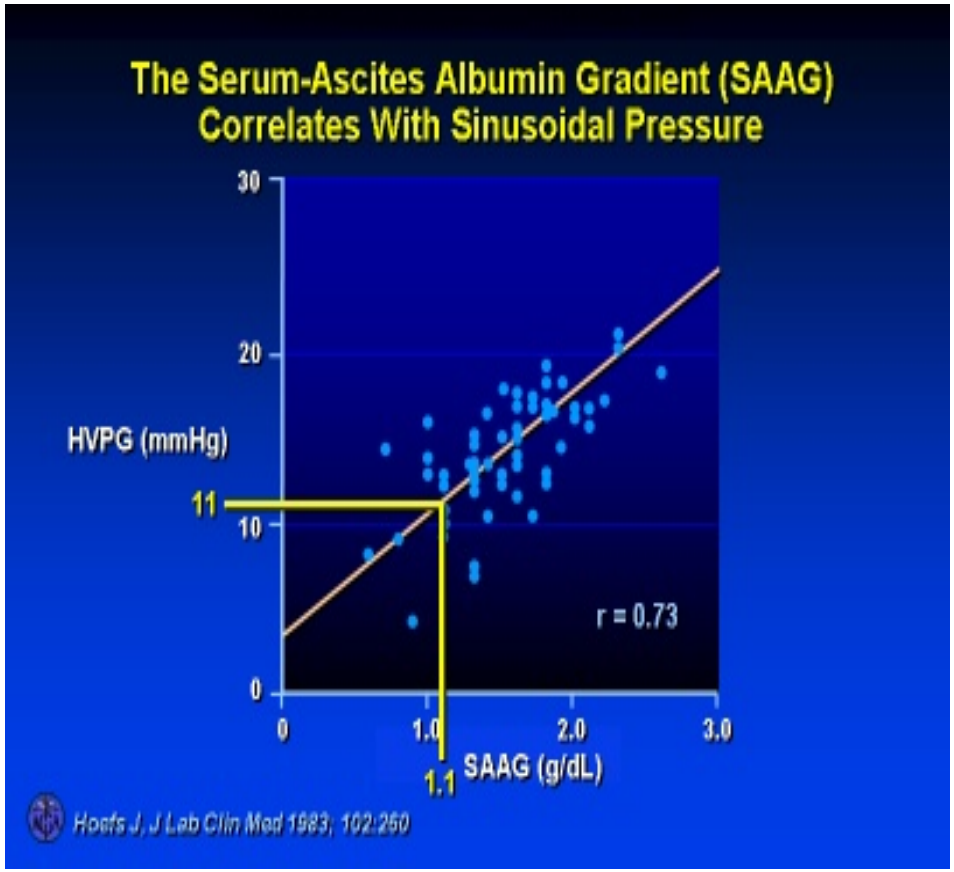
Ascites


Cirrhosis
Hepatic venous outflow block
Arteriolar resistance (vasodilation)
Sinusoidal pressure
(HVPG ≥ 10-12 mmHg)
Effective arterial blood volume
Ascites
Sodium and water retention
Activation of neurohumoral systems (renin, angiotensin, aldosterone)


Hepatic Vein Obstruction Leads to Ascites Formation
Hepatic vein outflow block
Sinusoidal pressure
Splanchnic capillary pressure

Ascites

- Ascites may be due to several causes but cirrhosis is the most common



• The clinical workup of ascites starts with calculation of the Serum-Ascites Gradient or SAAG

•The SAAG correlates directly with sinusoidal pressure

•A SAAG>1.1 implicates portal hypertension or cirrhosis as the cause

Ascites Complications

- Spontaneous Bacterial Peritonitis
  - Translocation of gut flora from the intestine into ascitic fluid
  - Diagnosed by cell count/differential in ascitic fluid
    - >250pmns
    - Initiation of cefatoxime or ceftriaxone
  - Albumin given as adjunct
    - 1.5grams/kg BW day 1; 1 grams/kg BW day 3

Prophylaxis to prevent second episode

Ascites Management

- Dietary salt restriction (around 2 grams daily)
- Initiation of diuretics
  - Furesomide and aldactone
- Paracentesis
  - Albumin replacement >5 L
  - Between 5 and 10 g of albumin per liter of fluid removed……No study has compared doses
- TIPS

Question 3:

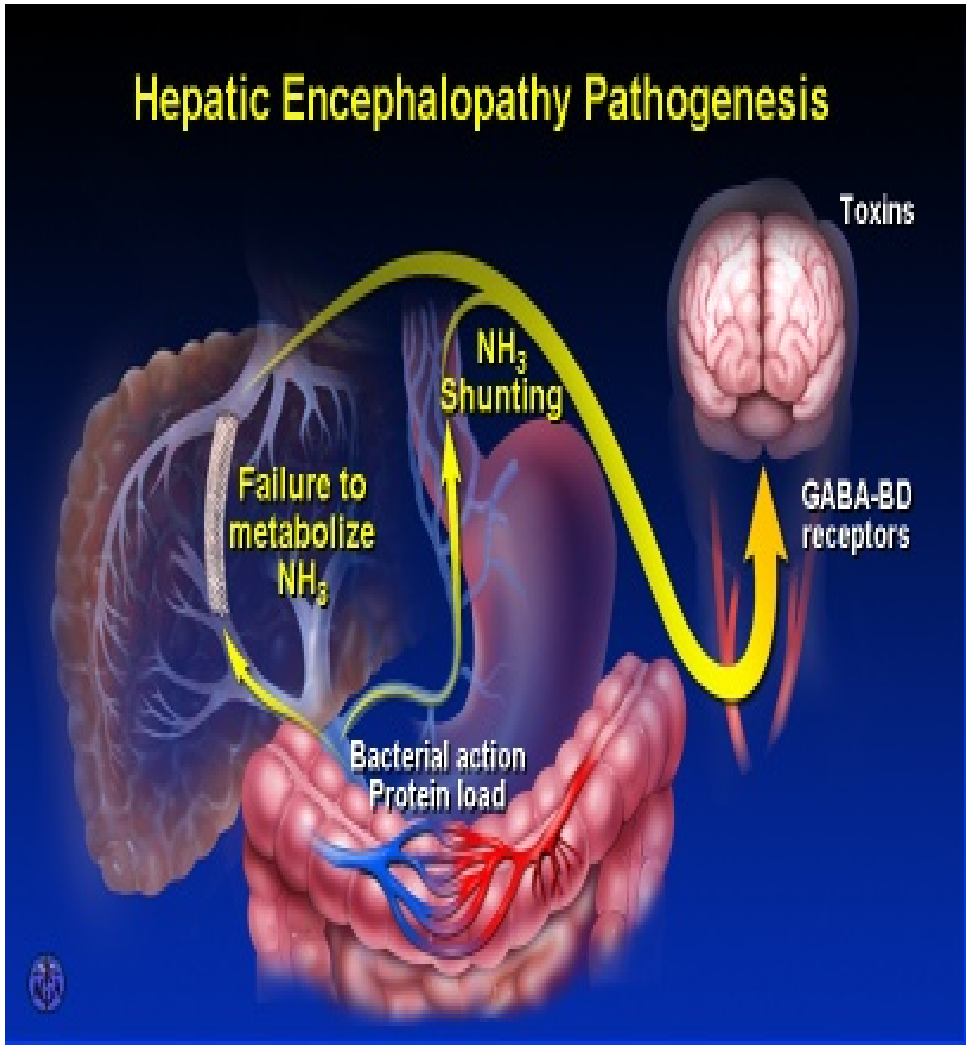
- 58 y/o WM hx of HCV Cirrhosis, listed for liver transplantation presents with altered level of consciousness. He is arousable to noxious stimuli. AVSS. Ascites on exam, abd non tender.

  Labs: INR: 1.8, Na: 130 Cr: 1.6 (at baseline), Tbil: 2.8, Dx tap: ANC=78 cells

  Head CT: unremarkable

- Which of the following is true regarding hepatic encephalopathy?
  - A) Degree of hepatic encephalopathy correlates directly with serum ammonia level
  - B) Degree of hepatic encephalopathy correlates directly with MELD score
  - C) Documentation of hepatic encephalopathy (requiring hospital admission and daily medical therapy) disqualifies active drivers license in some states
  - D) Restriction of dietary protein is recommended as first line therapy

Hepatic Encephalopathy



- Ammonia is a product of bacterial action and digestion

- Faulty metabolism or shunting through collaterals allows ammonia to reach the brain

- Ammonia crosses blood-brain barrier which modulates GABA receptors

- GABA modulation leads to clinical syndrome of confusion and lethargy

- Ammonia levels DO NOT correlate to degree of encephalopathy

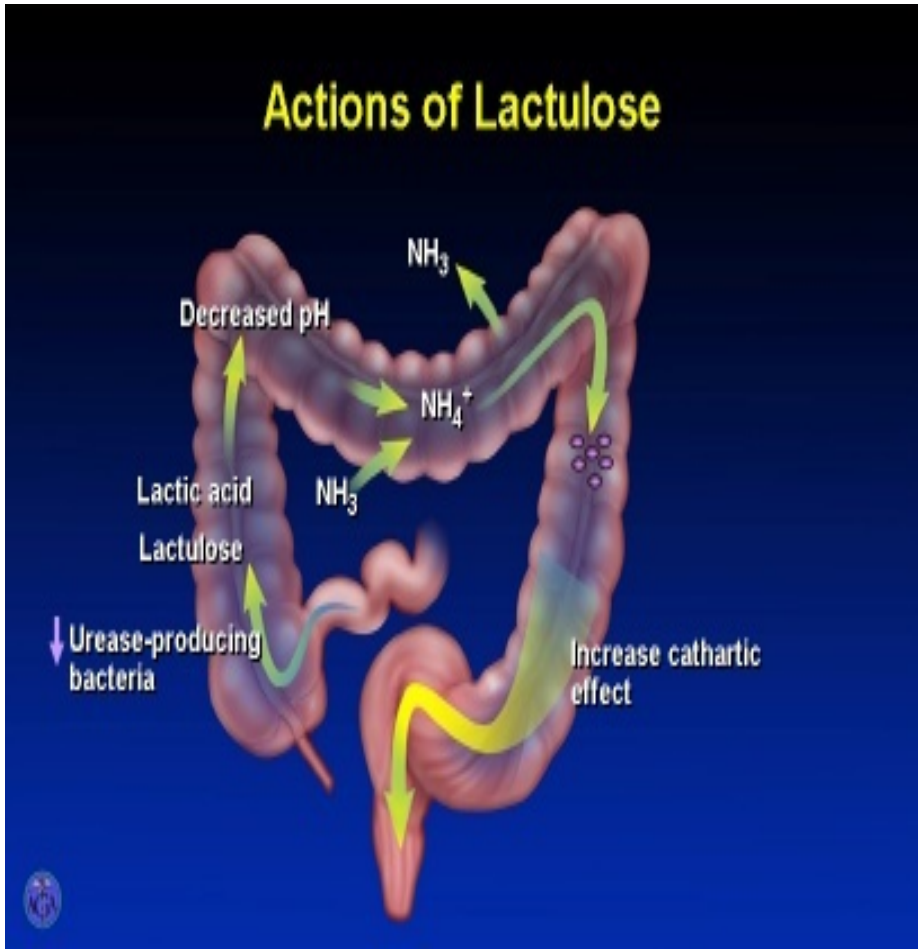
- Other decompensating events often precipitate encephalopathy

Reasons for Encephalopathy

- Lactulose deficiency is a diagnosis of exclusion

- Search for other causes:
  - Infection
  - GI Bleeding
  - Overdiuresis, azotemia
  - Hepatocellular Cancer
  - Portal vein thrombus (new)

Encephalopathy Treatment



- Treatment: identify and correct precipitant
- Lactulose: reduces ammonia causing bacteria, NH3 excretion, promotes catharsis
- Rifaxamin/Xifaxin 550mg BID: non absorbable antibiotic

Question 4:

- 62 y/o WM with HCV Cirrhosis presents with hepatic encephalopathy. Dx tap reveals SBP. Admission creatinine was 1.0. Received antibiotic therapy per protocol and albumin at day 1 and 3. On day 4 of hospitalization Cr rises to 3.5. Over the following day, diuretics held, re-tap shows treated SBP, given volume expander and kidney ultrasound is unremarkable. Day 5: Cr: 4.2, and spot urine Na<15. Which of the following is false regarding hepatorenal syndrome (HRS):

  - A) HRS is characterized by extreme sodium retention
  - B) Explanted kidneys are structurally normal
  - C) It is often precipitated by SBP
  - D) Recognition should lead to consideration of liver transplantation
  - E) A trial of IV lasix should be given to assess urine output

Hepatorenal Syndrome

- Renal failure in advanced chronic liver disease characterized by marked renal vasoconstriction and decreased GFR (Cr>1.5, Cr<40)
- Diagnosis of exclusion
- High sodium avidity, low urine sodium
- Fluid challenge helps distinguish from pre-renal
- Type 1: rapidly progressive, Type 2: slower
- Albumin, midodrine and octreotide
- Dialysis
  - Is the patient a transplant candidate?

Question 5:

- 55 y/o with HCV related cirrhosis comes to see you for progressive dyspnea on exertion. He complains of diffuse chest pain related to activity and progressive fatigue. Physical exam is notable for: clubbing, a loud P2, right ventricular heave and TR murmur. At rest Pox: 92%
- You get a cardiac echo with bubble study that is negative for shunt, estimated PASP on the echo is 45. CXR: borderline cardiomegaly; lungs clear
- The patient is excited because Dr. Wong said he was nearing the top of the transplant list. You call Dr. Wong but he's out of town.
- The appropriate next step is:
  - Consider right heart catheterization to evaluate for portopulmonary hypertension
  - Observation, this is hepatopulmonary syndrome that will be helped with transplant

2 Very Different Liver-Lung Syndromes

- Hepatopulmonary Syndrome
  - Advanced liver disease, increased A-a gradient, intrapulmonary vascular dilations
  - Often asymptomatic, but can have orthodeoxia (desats sitting up) or platypnea (increase in SOB sitting up)
  - Diagnosis made with Echo: delayed bubble entry into the left atrium (3-6 cardiac cycles)
  - Often improved by liver transplantation

Portopulmonary Hypertension

- Advanced liver disease and pulmonary hypertension
  - PASP>35, normal wedge pressure
- Vasconstriction
- Signs of right heart failure
- Look for other causes
- Right heart catheterization
- Generally a contraindication to transplant if mean PA pressure >35

Summary

- Cirrhosis represents the common final result of prolonged liver injury from diverse causes
- Architectural distortion causes loss of function and triggers mechanisms that lead to portal hypertension
- Portal hypertension is the driving force for complications with cirrhosis
- Decompensation of cirrhosis is diverse and lethal