BOOT CAMP: CIRRHOSIS

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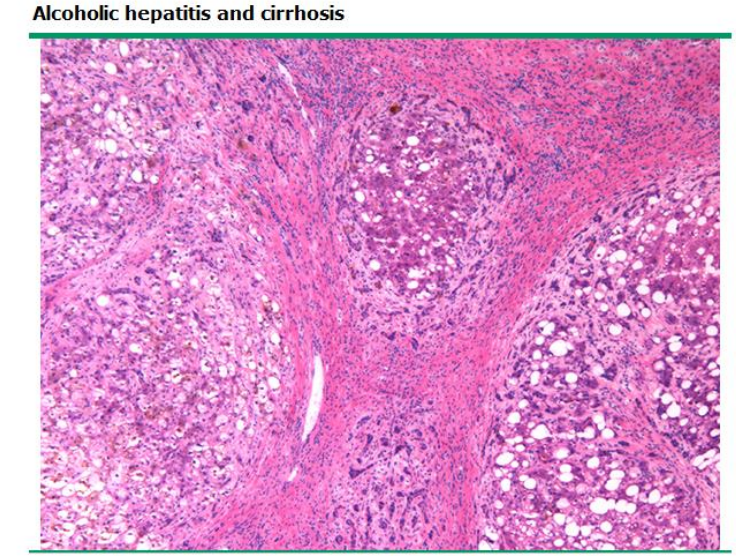
Objectives

- Brief review of pathophysiology of cirrhosis
- Overview of the evaluation of a cirrhotic patient
- Evaluation and management of common complaints and complications in cirrhotic patients
- Review key points regarding pre and post liver transplant

Cirrhosis

- Definition: end stage liver disease characterized by progressive liver fibrosis and regenerative nodules
- Causes:
  - Alcoholic liver disease
  - Non-alcoholic fatty liver disease
  - Chronic viral hepatitis (B, C)
  - Metabolic: Hemochromatosis, Wilsons, A1AT deficiency
  - Autoimmune hepatitis, PBC, PSC, vascular casuses (Budd Chiari, right sided heart failure)



Approach to Cirrhotic Patient

- Etiology of liver disease
- Complications (compensated vs decompensated)
  - Ascites (management strategy)
  - Varices (bleeding?)
  - Portosystemic encephalopathy
  - HCC screening
- Liver stamp = workup of chronic liver disease
- Know transplant status and candidacy
- Do they follow with a hepatologist?

The "Liver Stamp" – workup of chronic liver disease

- Viral hepatitis serologies: hepatitis A (total, IgM), hepatitis B (cAg, cAb), hep C (Ab, viral PCR if suspect early infection)
- ANA, AMA, ASMA, A1AT, ceruloplasmin, ferritin and transferrin saturation

- Liver US **with** doppler (write in special instructions)
- AFP
- Ammonia
- Fibrinogen

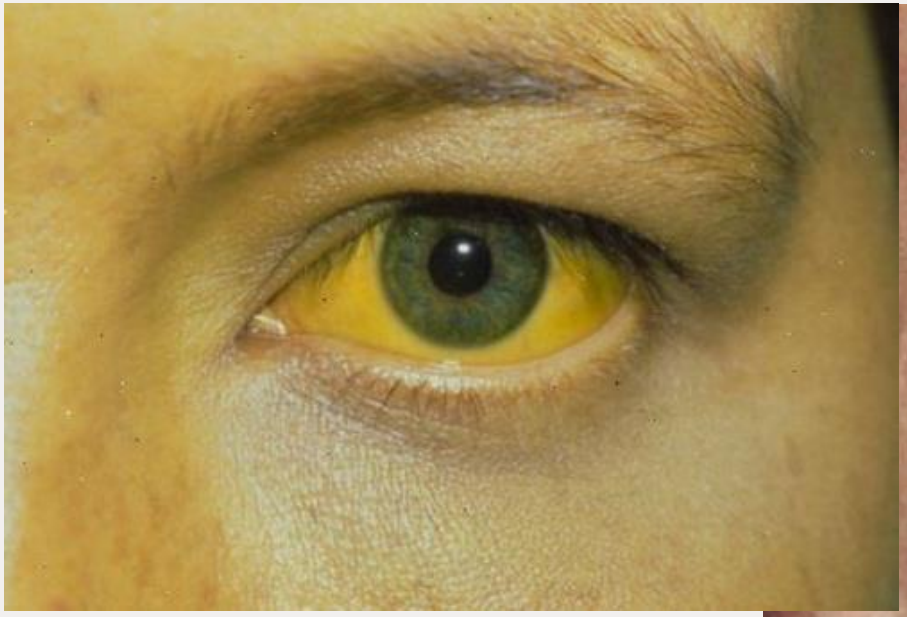
Disease Manifestations

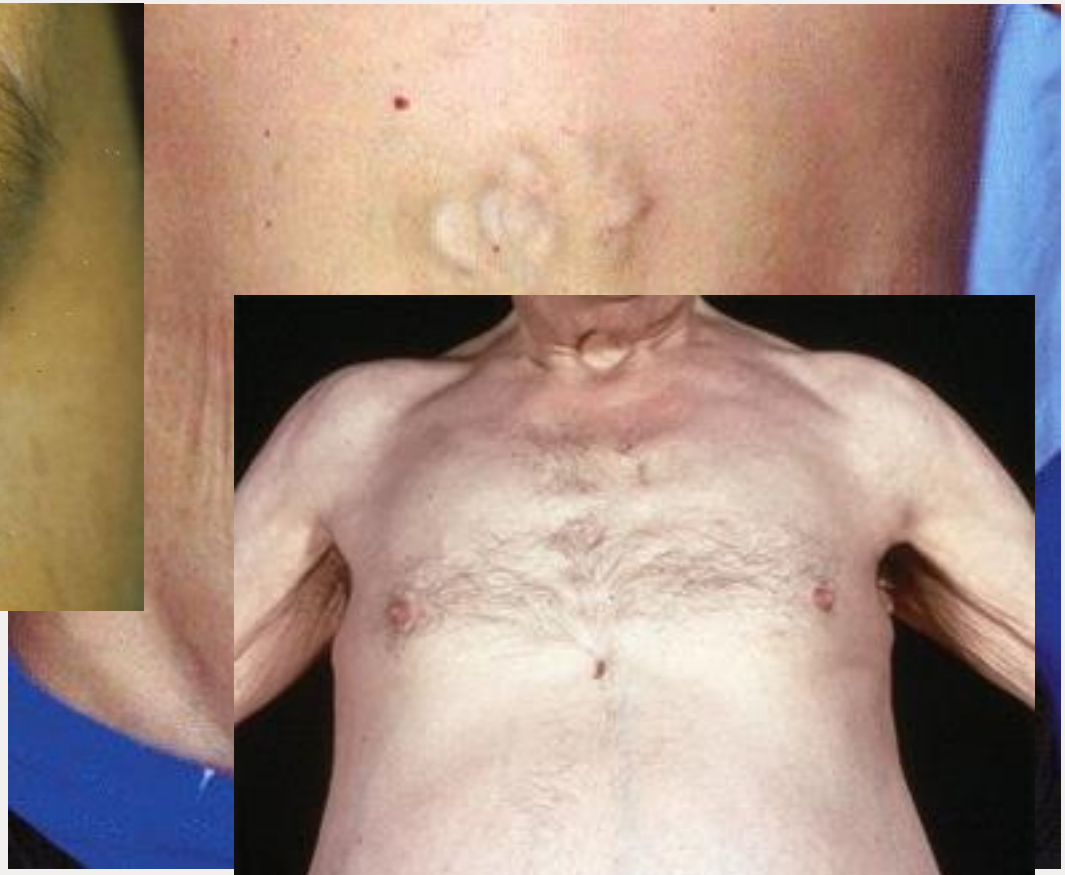
Physical Examination

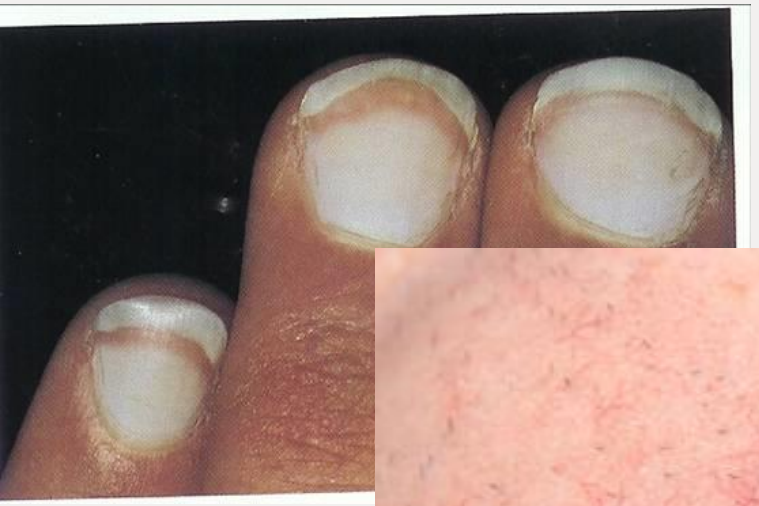
- Hypotension (splanchnic vasodilation – NO mediated)
- Jaundice
- Ascites
- Asterixis
- Nodular firm liver edge
- Caput medusa
- Gynecomastia
- Fetor hepaticus
- Terry nails (hypoalbuminemia)
- Clubbing, hypertrophic osteoarthropathy
- Palmar erythema
- Spider angiomata
- Cruveielhier-Baumgarten murmur (venous hum)

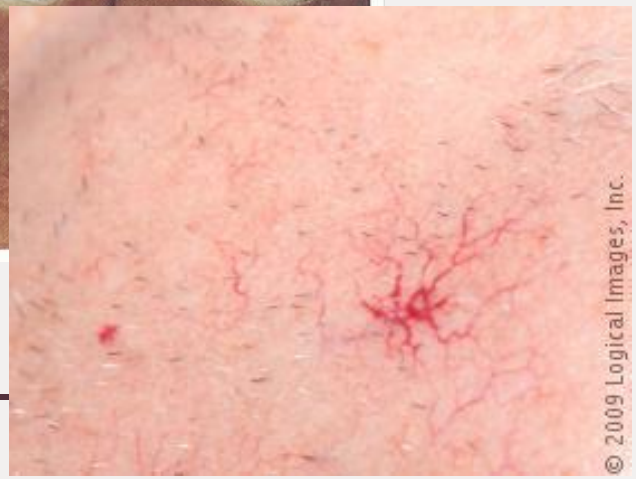
Labs

- Elevated PT/INR (coagulation factors)
- Decreased albumin
- Abnormal LFTs: AST >ALT, hyerbilirubinemia
- Thrombocytopenia (splenic sequestration)
- Hyperbilirubinemia
- Hyponatremia (↓EAV, ↑ADH)
- Pancytopenia (marrow suppression, hypersplenism)





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Coagulopathy of Liver Disease

- Generally believed that there is "re-balanced" hemostasis in end stage liver disease
  - Impaired hemostasis: coagulation factor defects (except VIII), thrombocytopenia, increased fibrinolysis
  - Prothrombotic: decreased production of protein C, protein S, and antithrombin, inflammatory endothelial changes, venous stasis
- PT and INR do not accurately predict bleeding/thrombosis risk – pts should not be assumed to be "auto-anticoagulated"
- DVT ppx indicated of pts at high risk of VTE and no contraindications
- Trial of vitamin K if nutritional deficiency considered (PO vitamin K 10 mg x3 days, use IV formulation if bleeding or significant cholestasis)

Prognostication

- MELD-Na (Cr, bili, INR, Na) – estimated 90 day mortality
- 0.957 X ln(Cr) + 0.378 x ln(bilirubin) + 1.120 x ln(INR) + 0.643 + 1.32 x (137-Na) – [0.033 x MELD] x (137-Na)] if >11 OR **MDCalc** ☺
- Childs Pugh Score:
  - A (5-6): well compensated, 85-100% 2 yr survivial
  - B (7-9): significant functional compromise, 60-80%
  - C (10-15): decompensated, 35-45%

Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/L)	2 to 3 mg/dL (34.2 to 51.3 micromol/L)	>3 mg/dL (>51.3 micromol/L)
Albumin	>3.5 g/dL (35 g/L)	2.8 to 3.5 g/dL (28 to 35 g/L)	<2.8 g/dL (<28 g/L)
Prothrombin time			
Seconds over control	<4	4 to 6	>6
INR	<1.7	1.7 to 2.3	>2.3
Encephalopathy	None	Grade 1 to 2	Grade 3 to 4

Common Clinical Presentations

CASE 1: Mrs. L is a 60 y/o with hx of AIH presenting with abdominal discomfort and distention.

Pt reports noticing gradual abdominal distention over the last month. Now having diffuse abdominal pain, slight chills, and nausea. No fever or emesis, no signs of bleeding.

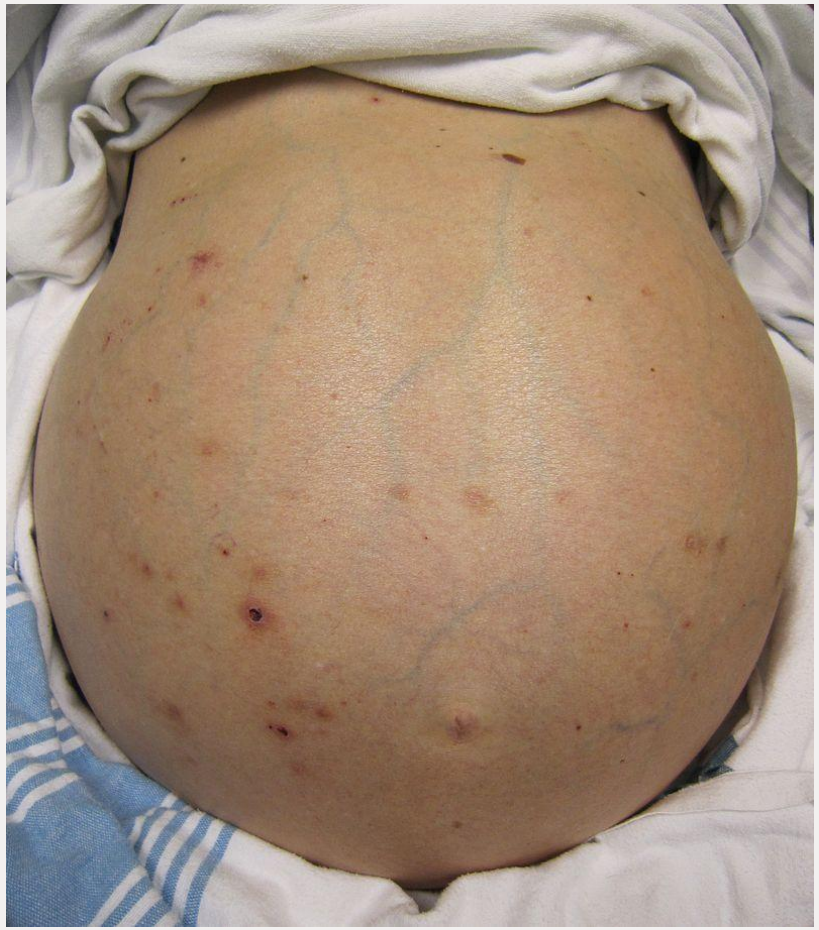
Vitals: 36.8, HR 94, RR 14, BP 102/65, SpO2 95% on RA

Exam: Diffuse abd tenderness w/o peritoneal signs. ->

Pertinent Labs: WBC 12K, hgb 10, plt 40, INR 3, bili 1.2, Na 132, Cr 0.9

Next Steps?

DDx?



New onset ascites

Diagnosis:

•Diagnostic paracentesis should be performed for all new onset ascites (AASLD class I)

•SAAG >= 1.1 (serum albumin – ascitic fluid albumin), total protein low characteristic of portal HTN related ascites

Long Term Management: (related to portal HTN)

•Salt restriction (2 g / day), avoid NSAIDs

•Diuretics: 5:2 ratio of spironolactone and furosemide

•Serial large volume paracentesis if not able to be controlled by diuretic regimen

Paracentesis

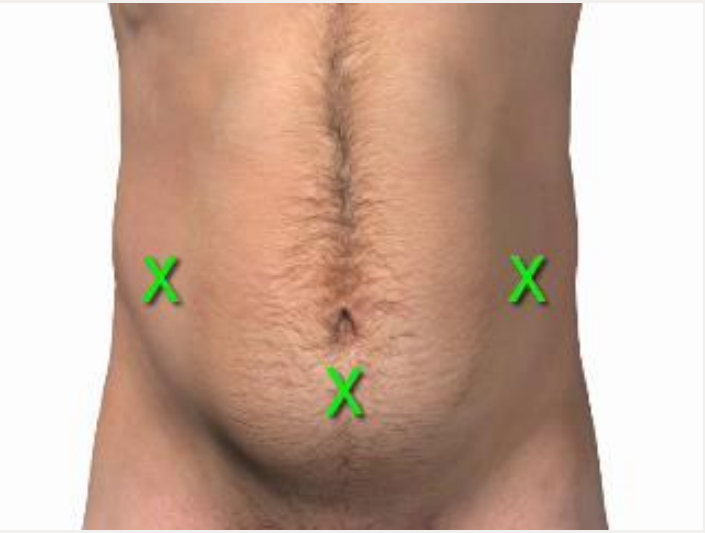
- Consent, ultrasound, gloves, gown, bandage, marker, paracentesis kit, blood culture bottles

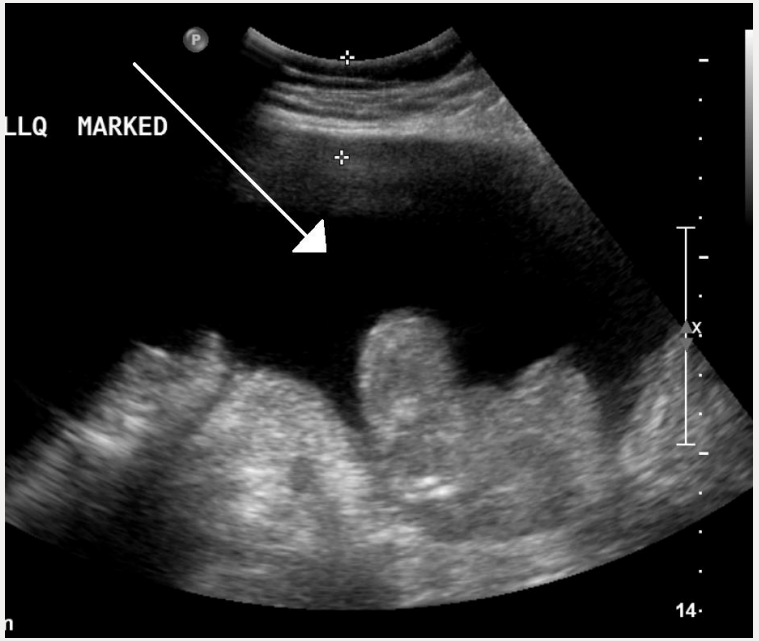
- What about the INR of 3 and platelet count of 40K???

- Fluid studies: always send **cell count + diff, total protein, albumin**
  - Concern for infection or secondary peritonitis: gram stain and culture (inoculate at bedside), LDH, glucose, amylase
  - Bile leak: bilirubin
  - Chylous: triglycerides
  - TB: AFB smear and culture, ADA
  - Cancer: cytology

- If >5L removed, administer 6-8 grams of albumin for every 1L removed (25 gram/3L removed)

Paracentesis





Case 1, continued

- Diagnostic paracentesis performed: 250 cc slightly turbid yellow fluid
  - **TNC 3000**, 60% PMNs, 20% lymph, albumin 0.8, TP <1.0
  - Gram stain: PMNs, no organisms, culture pending
  - Serum albumin 2.8
- Next steps??

SBP

- Diagnosis and treatment
  - **PMN > 250,** single organism commonly enterics
    - *Pts with PMN <250 but high clinical suspicion for SBP should be treated empirically while waiting for culture results*
  - **Ceftriaxone 1-2 gram q24H** (cefotaxime referenced in guidelines but not always available here),alt: Unsayn, Zosyn, narrow to FQ pending sensitivities)
  - IV albumin 1.5 gram/kg with 6 hours and 1 g/kg on day 3 (prevent HRS in pts with Cr >1, BUN >30, or bili >4)

- SBP prophylaxis:
  - continued following 1st episode of SBP
  - also consider as primary prevention when TP <1.5 and altered renal function (Cr > 1.2, BUN >25, Na <130) or liver failure (Child score 9+ and bili 3+)
  - In setting of UGIB

CASE 2: Ms. S is a 54 y/o female w/ hx of EtOH cirrhosis presenting with confusion.

HPI: Close friend brought her to the ED because pt was "acting strangely." She seemed very sleepy and could not answer simple questions.

Vitals: Afebrile, HR 60, BP 110/60, RR 14, SpO2 94% on RA

Pertinent exam: Lethargic, arousable, oriented to person and city but cannot recall todays date, flapping tremor present when pt asked to outstretch her hand, skin deeply jaundiced, abdomen soft and nondistended, no focal neurologic deficits appreciated.

Workup?

DDx?

Hepatic or Portosystemic Encephalopathy

Definition: brain dysfunction caused by liver insufficiency

Pathophys: increase ammonia, increased tone of GABA neurotransmission

Grading System:

- Minimal/Covert – neuropsychiatric alterations
- Grade I – impaired attention, anxiety, alteration in sleep-wake
- Grade II – lethargy, apathy, personality change, inappropriate behavior, disorientation to time, asterixis
- Grade III – Somnolent, gross disorientation, bizarre behavior
- Grade IV – Comatose, does not respond to even painful stimuli

Hepatic Encephalopathy

- **Precipitants**: infection, GIB, electrolyte disturbance, constipation, medication noncompliance, TIPS, meds (sedatives)
- Diagnosis of exclusion: **r/o other neurologic, infectious, or metabolic processes** (chem panel, VBG, CTH, EEG, tox screen, EtOH level, culture, CXR etc)
  - Cirrhotic pts are particularly prone to **renal failure, uremia, hyponatremia, uncontrolled DM, sepsis, thiamine deficiency, and intracranial hemorrhage.**
  - Check **ammonia** but no need to trend (high level dose not add staging or prognostication, low level should make you challenge the diagnosis)
- Treatment:
  - Address underlying/ precipitating factors
  - **Lactulose,** titrate to 2-3 BMs/day can be given q2H initially if needed (continue as secondary prevention) – decreases GI absorption of ammonia

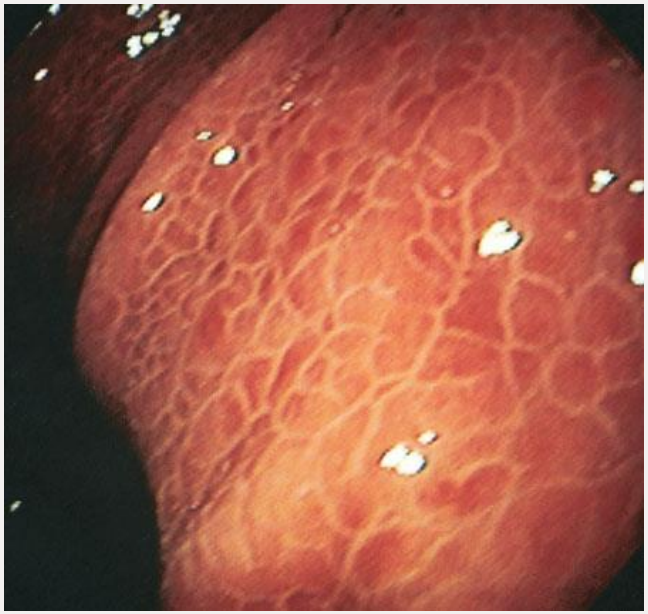
  ** may need to placed Dobhoff for administration if pt high aspiration risk
  - Rifaxamin (add on for secondary prevention following second episode of HE) – decreases bacterial production of ammonia

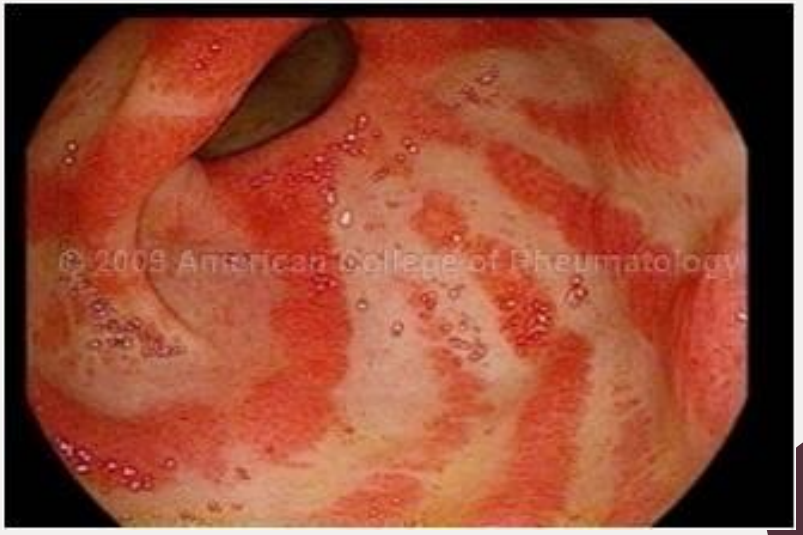
CASE 3: Mr. Z is a 70 y/o male with hx of HCV cirrhosis presenting with dizziness and hematemesis.

- Pt reports acute onset of bloody emesis with clots a few hours prior to arrival. He feels dizzy and weak.
- Vitals: temp 37, HR 115, RR 12, BP 88/60, RR 12, SpO2 90% on RA
- Exam: A&Ox3, pale, diaphoretic, tongue coated with blood, abd soft and nontender
- Next steps?

DDx

- Esophageal varices
- Gastric varices
- Non – variceal
  - PUD
  - PHG
  - GAVE
  - Esophagitis
  - Dielafoys
  - Cancer
  - And more





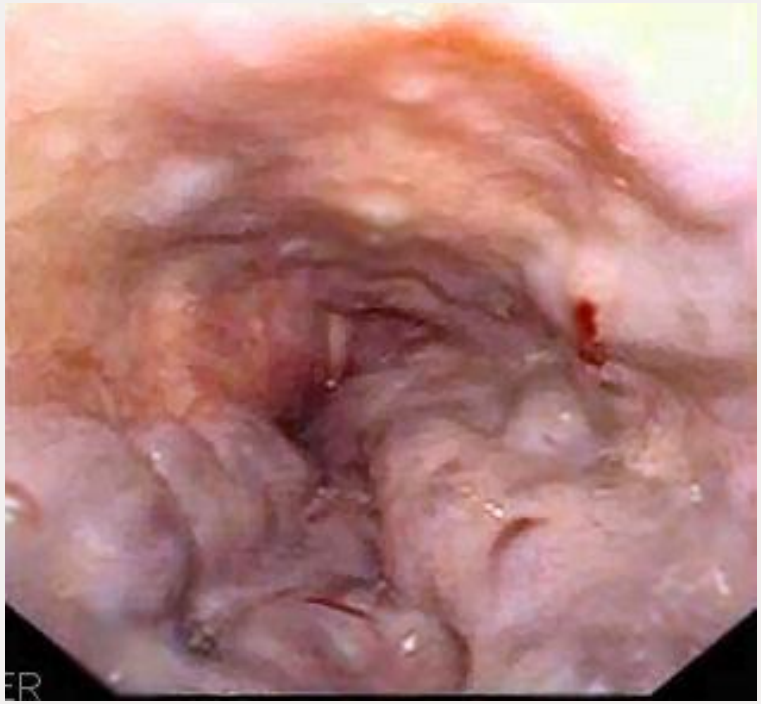
Medical Management

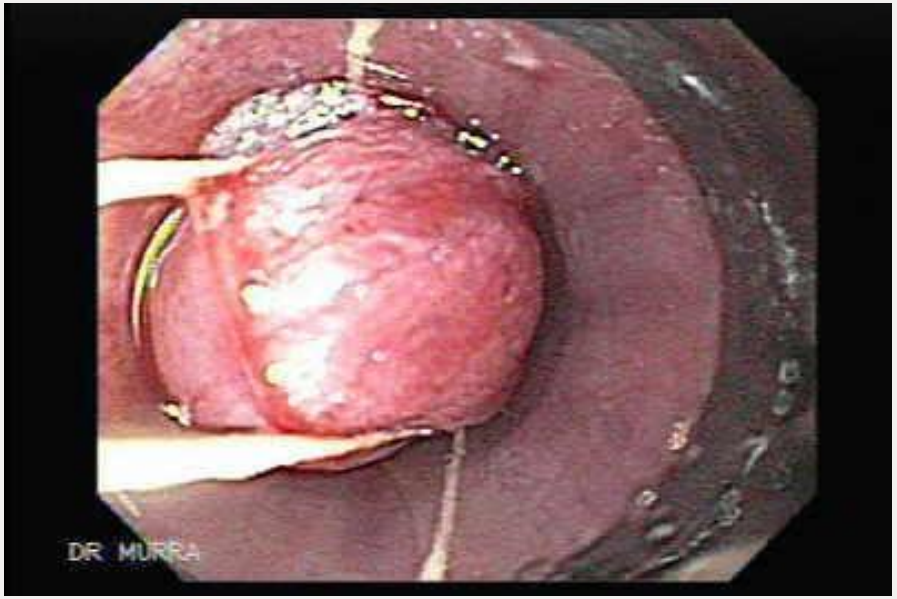
- Initial Management: **STABILIZE**! Remember ABCs.
  - Stabilize and resuscitate, 2 large pIVs (20 guage min), maintain T&S, reverse coagulopathy, check fibrinogen
  - Conservative transfusion threshold (hgb <7) to avoid worsening portal HTN
- **IV PPI 80 mg bolus then 8 mg/hr**
- **IV octreotide 50 mcg x1 then 50 mcg/hr** *(splanchnic vasoconstriction)*
- IV ceftriaxone x 7 days *(SBP ppx)*

– PAGE GI FELOW! If variceal bleeding considered pt should be monitored in ICU setting.

– Early endoscopy needed. If unable to control endoscopically then Minnesota/Blakemore tamponade may be needed and possible TIPS.

EGD performed following resuscitation revealing 3 columns of grade 3 varices with stigmata of recent bleeding. Banding performed.





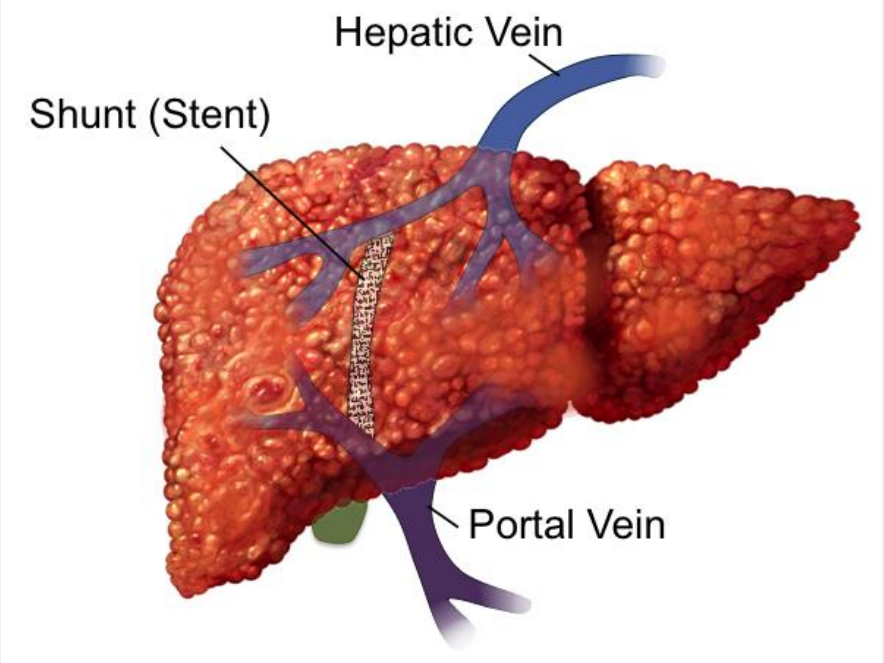
- Octreotide should be continued for min 72 hours
- Repeat EGD in 2-3 weeks for serial banding until eradicated
- Nonselective beta-blocker should be started when pt clinically stable

TIPS

- Shunt placed by interventional radiology to reduce portal hypertension by redirecting blood from the portal vein to the hepatic vein (and thus the IVC).

- Goal is to reduce the portal pressure gradient between portal and hepatic veins to < 12 mmg Hg.

- Indications: esophageal varices bleeding, persistent ascites
- CI: grade II HE, CHF, pulmHTN, biliary obstruction/infection



CASE 4: Mr. W is a 50 y/o male hx of NASH cirrhosis presenting with decreased UOP.

- Pt has noted poor urine output for the last day. No recent changes in his health except for slight worsening abdominal distention. No new meds or NSAID use. Home meds include: spironolactone 100 mg and lasix 40 mg daily.
- Vitals WNL
- Pertinent exam findings: abdominal distention with fluid wave, jaundice
- RFP 135/3.5/100/26/40/2.5 (b/l Cr 0.6)
- DDx:
  - usual culprits + hepatorenal syndrome

Hepatorenal Syndrome

- Diagnostic Criteria (ICA)
  - Presence of cirrhosis and ascites
  - Serum Cr > 1.5 mg/dL
  - No improvement in Cr after diuretic withdrawal and volume expansion (1 g/kg/day, max 100 gram albumin /day)
  - Absence of shock
  - No current or recent treatment with nephrotoxic drugs
  - Absence of parenchymal kidney disease (proteinuria >500 mg/d, hematuria, abnormal renal US)
- Type 1: rapidly progressive renal failure, 2x Cr or > 2.5 mg/dL in <2 weeks, often precipitating event present (SBP), very poor prognosis
- Type 2: moderate renal failure, Cr >1.5, frequently associated with refractory ascites

Management of HRS

- Hold diuretics and other potential nephrotoxins
- Volume expansion: albumin 1 g/kg/day, max 100 gram
- R/o other process: UA w/ microscopy (bland in HRS), urine lytes (UNa <10 in HRS), renal US to exclude post renal process
- If no improvement despite these measures, start "HRS cocktail"
  - **Midodrine** 7.5 - 10 mg TID (alpha-1 agonist causing renal vasoconstriction - can increase to 15 mg TID based on MAPs)
  - **Octreotide** 100 mcg SQ TID (alt 50 mcg/hr infusion)
  - **Albumin** (50-100 g/day in divided doses)
  - NE and albumin if pt in the MICU
- Dialysis sometimes initiated as bridge to transplant

Transplant – Key Points

- Evaluation undertake when MELD 15+
- Indications: recurrent/severe HE, refractory ascites, variceal bleeding, HRS, HCC (if limited), ALF
- Contraindications: poor social support, active EtOH use (must attend IOP in OH to be considered), sepsis, extrahepatic CA, noncompliance, significant comorbidities
- If decision made to pursue transplant, complete workup as quickly as possible (see next slide)
- Calculate MELD score daily if pt listed for transplant
- Notify transplant hepatologist and surgeons when listed pt is admitted! Also make sure to touch base with them when any code status changes being considered

Liver Transplant Workup:

- - ABO blood type and Screen x2
- - ABG
- - Complete Metabolic Panel, Magnesium, Phosphorus
- - GGT
- - Ammonia
- - Alpha Fetoprotein
- - Lipid Panel
- - TSH, T_4
- - CBC
- - PT/INR
- - TPA EIA (RPR)
- - EBV IgG
- - CMV IgG
- - HIV

- Iron Studies (Iron level, TIBC, Transferrin, % sat, ferritin)
- Ceruloplasmin
- Hep A Ab,
- HBsAg (if HBsAg +, then check Hep B DNA quant and HBeAg)
- HBsAb
- HBcAb
- Hep C Ab (HCV genotype and viral load if HCV +)
- Quantiferon Gold
- UA and culture
- PSA (if male >50)
- HCG (if female >12)

- CXR
- EKG
- ECHO
- Dobutamine Stress Test
- Ultrasound of the Abdomen with Doppler flow
- Obtain records of last colonoscopy
- PFTs
- Mammogram and pap smear for females

Post transplant

- Post transplant:
  - When? Where? Why?
  - Check MELD labs to assess graft function
  - Notify transplant surgery and hepatology
  - Immunosuppression regimen
    - Prednisone
    - Tacrolimus (Prograf) – check a level on admission (30 min before dose)
    - Mycophenolate Mofetil (Cellcept)
    - Cyclosporine (Neoral or Sandimmune) – check a level on admission
    - Sirolimus (Rapamycin)
  - PPx: TMP/SMX, valacyclovir, fluconazole for prophylaxis
  - Complications

ANY QUESTIONS?

References

- AASLD Clinical Guidelines
- EASL Clinical Guidelines
- International Ascites Club, HRS Guidelines

Other Presentations to be Aware Of:

- Hepatohydrothorax – pleural effusion caused by diaphragmatic defect, often right sided, management same as ascites, DO NOT place chest tube ** can develop spontaneous empyema
- Hepatopulmonary syndrome
- DIC vs decompensated liver disease: factor VIII level can help differentiate