Other
- Pts can not only decompensate but also develop acute on chronic liver failure
- Anytime a decompensated cirrhotic has an increased in TB, Cr, INR ALWAYS look for infection even if daily

Things to Assess
- Etiology, MELD/Child, LTx Assessment
- Decompensation Hx (HE, GIB, Ascites, SBP, HRS, HPS/PPH, HCC)
- HCC
- Impaired Liver Function
- Portal HTN Sequela

Mechanism
- **Bridging Fibrosis** AND **Nodular Regeneration** resulting in hepatocellular injury
    - Mechanism: Injury → Inflammation → Conversion of Quiescent Cells (Kupffer, Stellate, Endothelial) to Active Cells → Degradation of BM → Collagen Deposition in Space in Disse w/ Hepatocyte Regeneration
        - scarring is an active process that constantly turns over like bone hence cirrhosis is likely reversible
    - Nodular Regeneration
        - Epidemiology: seen in all cirrhotic livers (part of the definition) but only 25% are evident on CT
        - Pathogenesis: regeneration of islet of viable cells w/in an area of destroyed liver tissue from cirrhosis
        - Description: uniform micronodular <3mm (uniquely seen in cirrhosis 2/2 alcohol or hemochromatosis or biliary dz) vs variable macronodular >10mm (all other causes of cirrhosis)
        - Imaging: diffuse isodense nodules through-out liver but as they accumulate iron their density increases and are able to be visualized during non-contrast phase (do not enhance during arterial phase unlike HCC)
        - Bx: shows benign appearing liver tissue occasionally, however, cellular atypia can be present
        - Complications: unclear which regenerative nodules become dysplastic and, of these, which turn into HCC
- **CT** (nodular/shrunken, heterogenous changes, right lobe atrophy, left/caudate lobe hypertrophy, enlarged benign non-pathologic LNs in porta hepatis)

Etiology
- Infection (HepB/C, Schistosomiasis)
- Vascular (BCS/HVT, SOS/VOD, severe prolonged R-CHF)
- Drug (Idiosyncratic Drug Reaction)
- Steatosis (Alcohol, NAFLD)
- Metabolic (Pediatric, Hemochromatosis, Wilsons, AAT)
- Autoimmune
- Biliary Pathology
- Idiopathic (20%) aka Cryptogenic (may be 2/2 NAFLD or a new theory is telomerase mutations)

Prognosis
- MELD Score
    - 5yr Survival
        - <10 = 2-8%
        - 10-20 = 6-29%
        - 20-30 = 50-75%
        - 30-40 = 62-83%
        - >40 = <100%
    - 15 is a good cut-off
        - < = live longer w/ cirrhosis than with transplant
        - > = live longer w/ transplant than with cirrhosis
- Child-Turcotte-Pugh Classification System ("Child A/B/C Cirrhotic") originally used to assess overall mortality after portocaval shunt in cirrhotic pts w/ variceal bleed, Problem: subjective and ceiling effect (eg. TB 3.0 = 35.0)
    - Child A Cirrhotic 5-6, Mortality 5%
    - Child B Cirrhotic 6-9, Mortality 15%
    - Child C Cirrhotic 10-15, Mortality 35%
    - **"A-BEAN/P"**

	1 Point	2 Points	3 Points
Ascites	None	Controlled	Uncontrolled
Bilirubin	<2.0	2.0-3.0	>3.0
Encephalopathy	None	Minimal	Severe
Albumin	>3.5	3.0-3.5	<3.0
Nutrition Status or **P**T	Excellent or <4.0	Good or 4-6	Poor or >6.0

Complications

- Cancer Risk
  - **Hepatocellular Carcinoma (refer)**
- Impaired Liver Function
  - **Poor Elimination Function**
    - **Hyperbilirubinemia**
    - **Hepatic Encephalopathy (HE) aka Portal Systemic Encephalopathy (PSE)**
      - Mechanism
        - Brain Swelling: failure of liver to detoxify (b/c of decreased liver fxn and collateral formation) noxious agents primarily ammonia (produced from protein by colon bacteria and then converted to urea (via Urea Cycle) in the liver and then excreted by kidneys) as a result astrocytes tries to detoxify ammonia by joining it with glutamate to less toxic glutamine BUT the problem with this agent is that it is osmotically active causing brain swelling = therefore hyperammonemia is a surrogate marker
        - NT Alterations: inhibitory>excitatory NTs as glutamine is being used and as endogenous benzodiazepines escape liver metabolism
        - Altered Brain Glucose Metabolism
      - Precipitants
        - Increased Gut Ammonia Production
          - Increased Protein Digestion
          - Constipation
          - GIB
        - Decreased Renal Ammonia Excretion
          - Hypovolemia w/ AKI
          - Hyponatremia (promotes brain swelling)
          - Hypokalemia (increases renal ammonia production)
          - Metabolic Alkalosis due to diuretics hence use K sparing diuretics when treating ascites
        - Decreased Neurotoxin Clearance
          - Worsening Liver Function esp HCC
          - Decreased portal flow: portal vein thrombus, portosystemic shunting, TIPS
        - Increased Neurotoxin Production
          - Infection esp SBP
          - Sedatives or medicine noncompliance
      - West Haven Stage

Stage	History	PEx
0	Normal	Normal
Minimal	"Minimal Hepatic Encephalopathy" usually dx w/ neuropsych tests, characterized by disorders of executive function, disturbed sleep patterns, memory problems, problems w/ hand-writing, difficulty driving, cannot concentrate	Normal
I	Behavior Changes (irritable, depressive, etc)	Tremor, Poor Coordination
2	Disoriented, Slow Mentation, Drowsy	Asterixis aka Liver Flap (failure to maintain extensor tone w/ hands stretched upward, DDx: hypercarbia, uremia, etc), Ataxia, Fetor Hepaticus ("Corpse"), Slurred Speech
3	Sleep Most of the Time, Arousable to Vocal Stimuli, Marked Confusion, Incoherent Speech	Rigidity, Hypor/hypereflexia, Nystagmus
4	Coma	Decorticate/Decerebrate Posturing

      - Dx
        - Clinical
        - Labs: hyperammonemia
          - It was once believed that arterial draws on ice were better b/c delayed tourniquet venous draws resulted in falsely higher levels but this is not really true
          - good to monitor in Stage IV and ALF when you can't assess anything else otherwise do not measure as studies show little correlation
          - can be elevated in other states: Urea Cycle Defects
        - EEG: slow, high-amplitude, triphasic waves
        - MRI: increased T1 signal in globus pallidus

- Tx (Tx of minimal HE is a new concept)
    - 1st: rule out other causes of encephalopathy in cirrhotic pts
        - DDx: intoxication from alcohol or other drugs, subdural hematomas, hypoglycemia, hyponatramia
        - Some inhibit Benzo/Serotonin/Opioid CNS Effects (flumazenil/methysergide/naltrexone) to ensure that AMS is not from these causes
    - 2nd: correct precipitants
    - 3rd: nonabsorbable disaccharide = (1) gut acidification as gut bacteria convert into a SCFA which lowers colon pH <5 which converts NH_3 to NH_4^+ and thus no longer can be absorbed, (2) decreases urease-producing bacterial flora decreasing ammonia production, (3) b/c not absorbed the diarrhea that results overwhelms bacteria and any ammonia that is being made or its substrates (amino acids) are flushed out
        - Lactulose (Kristalose)
            - 10g/15mL-solution, start w/ 10g aka 15mL PO QD w/ max of 60g/d titatrating to 2-3 BM/d
            - You can also give 300mL of 10g/5mL solution mixed w/ 700mL of NS and give as a retention enema Q4-6hrs
            - pts w/ lactase deficiency essentially have the same effect when taking normal lactose
            - SEs: diarrhea, dehydration, hypernatremia
        - Lactitol (as effective, more palatable, fewer SEs, not available in US)
    - 4th gut decontamination of ammonia producing bacteria w/ non-absorbale antibiotics
        - 1° Rifaximin
        - 2° Neomycin
        - 3° Flagyl
    - 5th: Other treatments but poor date
        - no data to suggest that protein restriction is helpful but you can tell pts to switch from animal proteins to vegetable proteins which are less ammoniagenic
        - increase fiber intake
        - search for spontaneous porto-systemic shunts
        - Zinc Acetate/Sulfate 220mg PO QD (zinc is found in presynaptic vesicles of stimulatory glutaminergic neurons, cirrhotics are often deficient in Zn, Zn increases ornithine transcarbamylase enzyme in the urea cycle)
        - Melatonin (help with sleep-wake cycle)
        - Probiotics (*Enterococcus faecium*)
        - Stimulate Ammonia Metabolism (L-carnitine 2g PO BID, L-ornithine L-aspartate 18g PO QD, sodium benzoate 5g PO BID) NB only use briefly
        - Occlude porto-systemic shunts
    - 6th: Transplant or MARS
        - Recent evidence suggests that HE does not completely resolve after transplant

- **Poor Synthetic Function**
    - **Hypoalbuminemia**
    - **Coagulation Defects**
        - decreased synthesis of all coagulation factors except 8 w/ VitK dependent factors 2/7/9/10/S/C affected early on 2/2 decreased production, Tx: replete VitK but usually this does not help that much as such FFP is necessary but it also causes volume overload
            - NB even though cirrhotics have abnormal coagulation studies and are assumed to be "anticoagulated" they are actually at INCREASED r/o VTE dz b/c there is a disproportionately greater reduction of anticoagulant factors than clotting factors hence they need DVT Px but just use SCDs
        - thrombocytopenia 2/2
            - SM (consider indium-111 tropolone-labeled plts to determine that hypersplenism is the cause, Tx: splenic embolization, TIPS, splenectomy)
            - ITP (measure antiplatelet antibodies)
            - BM suppression from IFN if Tx for HCV, EtOH, etc (get BMBx)
        - dysfibrinogenemia (2/2 decreased/impaired production, Tx: Cryo) & fibrinolysis w/ DIC (2/2 endotoxinemia, etc, Tx: empiric abx and panCx)
    - **Immunosuppression**
        - Reticuloendothelial cells in the liver are responsible for the clearance of endotoxins
        - Pts are relatively immunosuppressed and thus are more prone to infections
            - GNB (E. coli): 1° SBP, 2° UTI, Cholangitis vs GPC (Strept/Staph): 3° PNA, 4° Sepsis, 5° SBE, Cellulitis, TIPSitis

        - RFs: severity of liver dz, UGIB, ascites, poor liver synthetic fxn
        - If pt has one infection then explore other possible ones above!!!
    - **Endocrine Dysfxn**
        - Impaired Glucose Metabolism (cirrhosis: worsening DM b/c of decreased uptake by muscle and reduced glycogen storage in liver and muscle, increased glucagon and insulin resistance, etc VS acute liver failure: hypoglycemia)
        - Adrenal Insufficiency (inadequate hepatic cholesterol production as a result of liver disease may predispose pts to impaired adrenal cortisol synthesis from cholesterol during stress)
        - Impaired Lipid Metabolism (cirrhosis: higher TGL, lower LDL/HDL, dyslipoproteinemia leads to alterations in cellular membrane lipids esp RBC causing echinocytes, in chronic cholestasis there is an increase in all lipids causing xanthomas but interestingly atherosclerosis is rare)
        - Liver is responsible for regulating thyroid hormone binding protein resulting in hypothyroidism, there have been some interesting studies suggesting that mild hypothyroidism is good for cirrhotics b/c thyroid regulates some of the liver functions resulting in less liver bleeding/ascites/HE
        - Some disorders that affect the liver can also affect endocrine organs (esp hemochromatosis w/ iron accumulating in gonads/hypothalamus/pancreas and AIH/PBC/PSC w/ autoimmune attack on thyroid/pancreas)
        - Cirrhosis directly alters the gonadal axis, clearance of sex hormones, changes in binding protein collectively causing high estrogen (b/c increased peripheral conversion) and low testosterone (b/c decreased testicular synthesis): menstrual irregularities, diminished libido, impotence, decreased muscle mass, changes in hair distribution, Spider Angiomata, Palmar Erythema, Dupuytren's Contracture, Gynecomastia, Testicular Atrophy
            - NB in alcoholic cirrhotics the alcohol itself exaggerates these sex hormones effects
            - NB spironolactone can cause painful gynecomastia b/c it displaces androgen from its receptor and by increasing estradiol production
        - Other: Osteoporosis (from cholestasis), Clubbing, Hypertrophic Osteoarthropathy, Muehrcke's Lines (double white nail lines), Terry's Nails (whitish discoloration of the nail with accentuation of the distal pink portion of the nail)

- <u>Sequela of Portal Hypertension</u>
    - General
        - Compensation
            - porto-systemic collaterals enlarge allowing for reversal of blood flow thru collaterals into systemic circulation
        - What is happening?
            - Increased portal blood flow b/c of (1) systemic vasodilation causes increased cardiac output, (2) splanchnic vasodilation, (3) hypervolemia
            - Increased portal resistance b/c of (1) fibrotic liver and (2) smooth muscle contraction
        - Treatment (goal is HVPG <12mm HG or by 20% of pre-treatment value)
            - <u>Decrease Portal Blood Volume</u>
                - **Salt Restriction (<2g/d)**
                - **Diuretics**
                    - Goal weight loss is 0.5kg/d
                    - Always give both lasix and spironolactone to maintain eukalemia
                    - K Sparing Diuretics aka Spironoloactone (Aldactone) starting at 100mg PO Qd (max dose 400mg/d) (b/c hypokalemia precipitates hepatic encephalopathy)
                    - Loop Diuretics aka furosemide (Lasix) starting at 40mg PO Qd (max dose 160mg/d) (generally try to keep this ratio at 100:40) and if severe and in-pt then start w/ Bumex 1mg IV BID then increase to 0.5mg/hr IV to max of 4mg/hr
                    - SEs: hyponatremia, hyperkalemia, hypomagnesemia, encephalopathy, AKI, gynecomastia (switch to Amiloride but less effective than Spironolactone)
                    - Goal: FENA of >10mEq/d and Na:K <1 if not then non-compliant
                - **Serial Therapeutic aka Large Volume Paracentesis/Thoracentesis (LVP/T) w/ albumin replacement Qwk**
                    - If unresponsive to above then considered "refractory ascites"
            - <u>Decrease Portal Blood In-Flow via Splanchnic Arterial Vasoconstriction and Decreasing Cardiac Output</u>
                - Chronically Decrease Cardiac Output (beta-1 receptor) and Increase Splanchnic Arterial Vasoconstriction (beta-2 receptor)
                    - **Non-Cardioselective Beta Blocker – NSBB (Propranolol 10mg PO TID or Nadolol)**
                        - titrate to 25% decrease in HR >50 and SBP >90
                        - taking at night is best
                        - NB Nadolol is better b/c excreted mainly by kidney and less CNS SEs

- Acutely Increase Splanchnic Arterial Vasoconstriction
  - **Somatostatin Analogues (Octreotide)** (refer)
  - **Vasopressin Analogues (Terlipressin)**
    - NB redistributes blood to extra-splanchnic organs including the kidney hence used in HRS
    - SEs: mesenteric ischemic, negative inotropic/chronotropic effects, hyponatremia (analogues have less SEs than vasopressin)

- <u>Decrease Portal Resistance via TIPS, Bypass, Transplant</u>
  - **Meds** (no practical medicine available)
    - **Alpha1-Blockers (ABs)** (rarely used b/c of SEs)
    - **Angiotensin Receptor Blockers (ARBs)** (rarely used b/c of SEs)
    - **Short/Long Acting Nitrates** (rarely used b/c of SEs)
    - **Statins** (newly studied)
    - **Endothelin Receptor Blockers** (under investigation)
  - **Transjugular Intrahepatic Portosystemic Shunt (TIPS)**
    - How
      - catheter is fed thru IJ into IVC, jammed thru the liver into the portal vein followed by placement of stent
      - 95% effective at bringing HVPG to <12mmHg as this decreases r/o EV bleeding
    - Indications
      - Controlled Studies
        - Secondary Prevention of Variceal Bleeding
          - NB Not Primary Prevention b/c mortality is higher when compared to standard Px w/ BB
        - Refractory Ascites (defined as Lasix >160 and Aldactone >400, 50% r/o death at 1yr)
      - Uncontrolled Studies
        - Refractory Tx of Acute Variceal Bleeding
          - NB Not First Line Tx b/c mortality is higher when compared to standard Tx w/ EBL, etc
          - NB lower HVPG are needed for gastric varices
        - PHG
        - Refractory Hepatic Hydrothorax
        - Refractory Hepatorenal Syndrome
        - Refractory Hepatopulmonary Syndrome
        - Moderate Budd Chiari Syndrome (mild can be Tx w/ AC vs severe need transplant)
    - Contraindications (NB MELD Score is used to predict 30d post-TIPS mortality but overall 1yr mortality is dependent on why the TIPS was placed in the first place)
      - Absolute
        - Heart: CHF (TTE)
        - Lung: severe pulmonary hypertension (>45mmHg)
        - multiple hepatic cysts (AB US w/ Doppler)
        - active infection
        - unrelieved biliary obstruction
        - MELD >24
        - TB >4
        - HE Stage IV
      - Relative: central hepatoma, obstructed hepatic veins, PVT, INR>1.5, Plt<20k, moderate pulmonary hypertension, MELD 14-24, TB 3-4, HE Stage II-III, Cr >2.0
    - Complication (first two are the most common)
      - Worsening Liver Function (25%) esp HE (b/c deprives the liver of blood, 1/3 of pts, there is no benefit to prophylactic Tx but it is often done)
      - TIPS Dysfunction: loss of decompression of portal system 2/2 occlusion from thrombus (10%) or psuedointimal hyperplasia (20%), decreased risk w/ covered stents, defined as a recurrence of the problem for which TIPS was placed in the first place and >50% stenosis and HVPG >12, sometimes US will show a

thrombus/stenosis but does miss some cases therefore do a tipsogram, patency can be re-established w/ cath
- Transcapsular Puncture ± Intraperitoneal Bleed & Hemobilia
- Hepatic Infarction
- Fistula
- Sepsis/TIPSitis
- Hemolysis
- Stent Migration

- **Surgical Bypass**
  - Esophageal Transection (rare)
  - Devascularization (rare)
  - Portosystemic Shunt (rare)
    - Portocaval Shunt (side-to-side anastomosis of portal vein and IVC)
    - Mesocaval Shunt (shunt connecting SMV and IVC)
    - Splenorenocaval Shunt (shunt connecting splenorenal vein to IVC)
    - Sugiura Procedure (complex surgery)
  - Peritoneovenous Shunt (developed in 1974 and used for about 10yrs but now rare, plastic tube w/ one way valve is placed in peritoneum and connected to jugular vein allowing removal of fluid, high r/o obstruction, has been shown to not reduce mortality) (rare)
- **Transplant**

- **Ascites** (PEx: + if >1500cc, US: + if >100cc)
  - General
    - "askos" Greek for sack
    - leaks thru Glissen's Capsule
  - 2/2 Portal HTN (SAAG ≥1.1g/dL) ascites is low in albumin
    - **Post-Hepatic** (mainly p/w ascites)
      - Congestive Hepatopathy (refer)
      - Budd-Chiari Syndrome (refer)
    - **Intra-Hepatic** (can p/w both ascites and variceal bleeding, many diseases can have resistance at more than one site)
      - **Postsinusoidal** (High Protein Ascites aka AFTP >2.5g/dL, very leaky)
        - Sinusoidal Obstruction Syndrome / Veno Occlusive Disease (refer)
      - **Sinusoidal** (Mod Protein Ascites aka AFTP 1-2.5g/dL, mod leaky)
        - Chronic Cirrhosis
          - **NB often the AFTP is <1 but after diuresis can be >2.5**
          - NB SBP does not change the AFTP level
          - NB causes of sudden increase in ascites in a stable cirrhotic: SBP, Budd-Chiari Syndrome, HCC, Sepsis, GIB, HRS = any liver change
        - Acute Hepatitis esp Alcoholic Liver Dz, Failure
        - Liver Masses (any type but the most important one is Nodular Regenerative Hyperplasia (NRH) b/c it can present w/ a normal appearing liver on imaging with only Bx being abnormal)
      - **Presinusoidal** (Low Protein Ascites aka AFTP <1g/dL, not leaky)
        - Idiopathic Portal Hypertension (uncommon in US, mainly seen in Asia, most are idiopathic but chronic arsenic, vinyl chloride and vitamin A exposure has been implicated, diagnosed when portal HTN but liver bx is normal, believed to be 2/2 increased endothelin-1)
        - Schistosomiasis (refer)
        - Toxins: Arsenic and Vinyl Chloride
    - **Pre-Hepatic** (mainly p/w variceal bleeding and hyersplenism)
      - Portal Vein Thrombosis (refer)
  - 2/2 NON-Portal HTN (SAAG <1.1 g/dL) ascites is equivalent in albumin
    - Transudative (AFTP <3g/dL, LDH <200, A/S Protein <0.5, A/S LDH <0.6)
      - Any Hypoalbuminemic State (Nephrotic Syndrome)
      - Meig's Syndrome
      - Hypothyroidism
      - All GI tumors
      - Lymphoma (LN obstruction, chylous fluid)
      - Peritoneal Dialysis
    - Exudative (opposite)
      - Malignancy: Peritoneal Carcinomatosis
        - NB 100% + tumor involving peritoneum but only 60% + for HCC or liver mets
        - NB high RBC count suggests malignancy
        - NB high TGL suggests lymphoma b/c lymphatic obstruction

- Infection: TB, Chlamydia w/ Fitz-Hugh-Curtis, Coccidioidomycosis
    - NB TB: high lymphocyte count, high ADA, if suspicious get peritoneal Bx showing "millet seed" and "violin string" sign
- Inflammation: Pancreatitis, Serositis from CTD, Bowel Obstruction/Infarction/Rupture
- Surgery: s/p abdominal surgery w/ extensive RP dissection and lymphatic transection

- Diagnostic Approach
    - 1st Serum - Ascites Albumin Gradient (SAAG) to Determine if Portal HTN vs Not
    - 2nd Ascitic Fluid Total Protein (AFTP), A/S TP, Ascitic Fluid LDH, A/S LDH
    - 3rd Other Tests if Necessary (eg. laparoscopic biopsy of peritoneum, et al)
- Complications
    - **Malnutrition** b/c of early satiety and mucosal gut edema
    - **Hepatic Hydrothorax**
    - **Ab Wall Hernias** but avoid repair until transplant rather use an elastic abdominal binder as a temporizing measure
    - **Spontaneous Bacterial Peritonitis (SBP)**
        - Mechanism
            - (1) mucosal changes in cirrhotics allows for increased translocation of gut bacteria to mesenteric LNs, (2) systemic infection → transient bacteremia → colonization of ascitic fluid
            - cirrhotics especially are at high risk b/c they have low TP and thus low complement levels
        - Epidemiology
            - 20% of cirrhotics at some point develop SBP
            - Once a cirrhotic has one episode there is a 70% recurrence rate the next yr
            - 25% mortality
        - Clinical Manifestations
            - If there are S/S usually fever, AMS, ab pain, decreased BS, TTP w/ guarding and rebound, BUT many times there are no S/S at all just AMS *HENCE ALWAYS R/O IN A CIRRHOTIC PT WHO HAS SHOWN ANY EVIDENCE OF CLINICAL DETERIORATION OF ANY SORT*
        - Diagnosis
            - For every 250 RBC subtract 1 WBC, then take the % of WBC that are neutrophils
            - 15% + Gram Stain
            - 50% + Culture *(INCREASED SENSITIVTY WHEN 10mL OF ASCITIC FLUID IS INOCULATED INTO TWO BLOOD CULTURE BOTTLES AT BEDSIDE)*
            - *Also check B/UCx*
        - Types
            - Spontaneous (no intra-abdominal source)
                - **SBP - Spontaneous Bacterial Peritonitis** (PMN >250 mcl/mm^3 w/ + Cx)
                - **CNNA - Culture Negative Neutrocytic Ascites** (PMN >250 mcl/mm^3 BUT –Cx)
                    - probably from previous abx Tx, inadequate inoculation volume or spontaneously resolving SBP
                - **NNBA – Non Neutrocytic Bacterascites** (+Cx but PMN <250 mcl/mm^3)
                - Pathogens (usually one pathogen)
                    - 70% GNR (esp *E. coli* and *Klebsiella*)
                    - 30% GPC (esp *Strept. pneumonia* and *Enteroccocus*) = becoming more common given the use of prophylactic abx w/ GN activity
            - Secondary (2/2 clear intra-abdominal source)
                - When should you think?
                    - ≥2/3 of Runyon's Criteria: **TP >1g/dL, glu <50mg/dL, LDH >2/3ULN-Serum, bili >6mg/dL and > serum, amylase >5x-serum**
                    - anaerobic polymicrobial except w/ gallbladder rupture
                    - Cx never clears, PMNs do not drop and pt does not improve after 2d abx for suspected SBP
                - What to do if you suspect?
                    - get imaging to assess perforation or loculated infection
                - Tx: emergent surgery
        - Treatment (SBP and CNNA but NNBA is controversial)
            - **Abx**

- If pt is on Px w/ FQ then add vanc b/c of high r/o GP bacteria and don't use FQ
- **1° Rocephin 1g IV Q24hrs x5d to Omnicef 300mg PO BID x5d then life-time Px below**
- **2° Cipro 200mg IV Q48hrs x5d then Cipro 500mg PO BID x5d then life-time Px below**
- **3° Augmentin then life-time Px below**

▪ **Albumin to prevent HRS** (refer below)
▪ Repeat diagnostic paracentesis (don't do LVP or use diuretics) at 2d to document >50% decrease in WBC only if
- (1) no significant improvement
- (2) atypical presentation (non-cirrhotic or unusual bacteria)

o Prophylaxis
▪ Indications
- (1) **Active GIB when In-Pt** (GIB indicates mucosal damage allowing for increased translocation therefore higher risk of not only SBP but also sepsis) = Rocephin 1g IV Q24hrs x7d or Norfloxacin 400mg PO BID x7d
- (2) **AFTP <1g/dL** (less protein means less immune functioning protein to kill bacteria therefore higher risk) or **h/o SBP then Px forever until no more ascites or transplant** = 1° Norfloxacin 400mg PO QD, 2° Bactrim DS PO QOD or Cipro 250mg PO Qd or 750mg PO Qwk

▪ This decreases GN bacteria w/o affecting GP/Anaerobic bacteria thus these are the more common pathogens in these pts
▪ Prophylaxis selects for drug resistant bacteria hence only done for the above indications

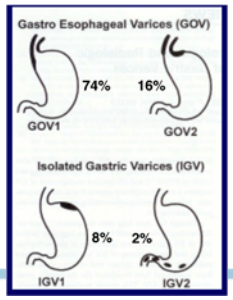
o **Vessels**
▪ **Portal Vein Thrombosis**
- 5% of cirrhotic pts and 25% of cirrhotic pts w/ HCC
- Increased r/o variceal bleeding

▪ **Hypotension**
- if SBP <80 then something is wrong

o **Mucosa/Skin**
▪ **Cellulitis**
▪ **Retroperitoneal Hemorrhage**
▪ **Internal/External Hemorrhoids → Varices**
▪ **Umbilical Caput Medusa w/ Cruveilhier-Baumgarten Venous Hum**
▪ **Portal Hypertensive Gastropathy/Enteropathy/Colopathy (PHG/E/C)**
- Epidemiology: ~50% prevalence, higher risk as varices are obliterated, HP infection, higher risk the duration NOT the severity of liver dz
- Mech: portal HTN leads to congestive injury
- S/S: chronic/mild/slow ooze very rarely acute GIB
- Endoscopy: mosaic pattern of erythema with/without discrete cherry red spots (the presence makes PH severe) outlined by a delicate depressed white network border looking like "snake skin" (PHG proximal stomach vs GAVE distal stomach)
- Bx: mucosal/submucosal vascular ectasia of veins/capillaries w/o inflammation, endoscopically uninvolved areas also show changes, in general DON'T biopsy b/c of theoretical increased r/o bleeding
- DDx: GAVE (similar ectasia but it is more severe w/ the addition of thrombi, spindle cells and fibrohyalinosis), -itis
- Tx: no endoscopic treatments (eg. APC) is effective unless there is very localized active bleeding rather one needs to lower portal HTN (above)

▪ **Gastric Antral Vascular Ectasia (GAVE) or Diffuse Gastric Vascular Ectasia** (refer)
▪ **Esophageal/Gastric/Rectal Varices (E/G/RV) and Ectopic Varices**
- Epidemiology
  - 8%/yr r/o developing varices if cirrhotic
  - 8%/yr r/o small varices turning into large varices
  - 8%/yr r/o bleeding (RF: HVPG >12mmHg)
  - 20% of variceal bleeds die by 6wks 2/2 exsanguination (25%) vs liver failure, infection w/ sepsis and MOF, HRS (75%)
  - 60% of UGIB in cirrhotics is 2/2 varices!!!
  - 40% of pts rebleed w/in 5d
- Classification
  - Gastric

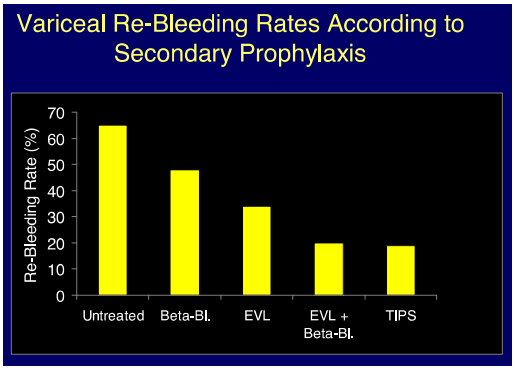
- Types (Sarin Classification)
    - Gastro Oesophageal Varices (GOV) Type 1 (extension of EV along lesser curve, 75%) vs Type 2 (extension of EV along greater curve)
    - Isolated Gastric Varices (IGV) Type 1 (fundus, seen w/ splenic vein thrombosis, highest r/o bleeding) vs Type 2 (body/antrum/pylorus)
        - Isolated Splenic Vein Thrombosis
            - Etiology: pancreatitis (50%), pancreatic cancer (30%)
            - S/S: IGV1 varix bleeding and hypersplenism
            - Dx: b/c it is usually from a pancreatic problem then get a CT
            - Tx: splenectomy



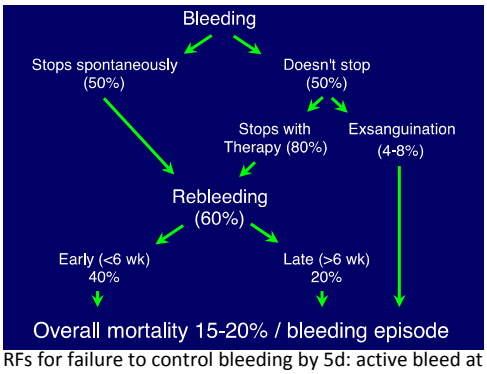
- S/S: only bleed when they are >0.5-1cm unlike esophageal varices which can bleed when smaller this is b/c gastric varices are surrounded by strong gastric mucosa which prevent bursting but when they do bleed it is more severe
    - NB unlike esophageal varices bleeding from gastric varices has been noted in pts w/ HVPG <12mmHg
- Px
    - Primary: no clear data, most start BB
    - Secondary: most start BB but studies show not effective therefor only TIPS
- Tx (in addition to meds below)
    - **GOV1:** 1° EBL, 2° TIPS
    - **GOV2 & IGV1/2:** 1° TIPS 2° Balloon Tamponade
        - NB GOV varices may regress if you Tx EV
        - NB EBL not effective for other parts of the stomach b/c difficult to suck up
        - NB Endoscopic Obturation w/ "glues" (eg. cyanoacrylate polymers) that harden on contact w/ blood are not available in the US in addition there are SEs: infection, ulceration, emboli, endoscope damage
        - NB sclerosants are not effective
        - NB Linton-Nachlas Tube (tube that has a 600mL gastric balloon that essentially fills up the entire stomach, NB the SB tube used for EV have only 250mL gastric balloon, temporarizing measure)
        - NB TIPS (more effective for GOV than IGV)
        - NB Transvenous/Transhepatic Embolization (if CT demonstrates a spenorenal shunt then a catheter can be passed thru R femoral and then R renal vein into the varix, concurrently a catheter is passed percutaneously thru the liver and then portal vein into the varix, balloons are inflated at both catheter ends and sclerosant injected)
        - NB Portosystemic Shunts

- Rectal
    - External hemorrhoids (dilated veins below dentate line) vs internal hemorrhoids (dilated inferior veins above dentate line) vs rectal varices (dilated middle/superior veins way above the dentate line)
- Ectopic (5%)
    - Peristomal***
    - Duodenum
    - Gallbladder

        - Bile Duct
    - Esophageal
        - Grade (not sure these terms are used anymore???)
            - I (small <5mm in diameter / straight / separate / flatten with insufflations)
            - II (medium 5mm in diameter / corkscrew <1/3 of lumen / separate / no flattening with insufflations)
            - III (large >5mm in diameter / corkscrew >1/3 of lumen / confluent / no flattening with insufflations)
        - Location
            - Lower Esophageal have the highest r/o bleeding b/c superficial, high vessel density, etc
- Endoscopy
    - High Risk Red Color Signs
        - Red Wale Sign (longitudinal whip-like marks)
        - Cherry Red Spot
    - Stigmata of Recent Bleed
        - Nipple Sign
        - White Fibrin Plug
        - Red Clot
- S/S
    - Not just overt bleeding but sometimes obscure bleeding presenting w/ other Sx like hepatic encephalopathy
- Screening and Px
    - Screen: all pts w/ cirrhosis need EGD
        - Primary Px (no prior bleed, risk of bleed of 30%)
            - No Varix (risk of developing a varix is 3%/yr) = no Px just Screen Q3yrs
            - Small Varix (risk of developing a larger varix or bleeding is 10%/yr) = no Px just Screen Q1-2yrs
            - Large Varix (risk of bleeding is 15%/yr) = Screen Q1yrs and start NSBB which decreases risk of bleeding to 7%/yr
                - Controversy: EBL for Px
                    - For: decreases first bleed and decrease mortality compared to no Tx
                    - Against: meta-analysis has ACTUALLY NOT shown a clear benefit compared to NSBB
                    - Therefore EBL cannot be advocated for primary Px of large varices (it can be done in pts who are intolerant to NSBB)
        - Secondary Px (had a prior bleed, risk of rebleed of 65%)
            - if EBL then f/u Q2-3wks w/ repeat EBL until obliteration of lower 5cm of esophagus and then rescreen in 3mo, 6mo and Qyr to confirm obliteration
            - in addition NSBB for life



- Tx
    - General



- RFs for failure to control bleeding by 5d: active bleed at EGD, low Hct, high AT, high CTP, infection, HVGP >20, PVT

- Medication
  - Blood Products but only to Hgb 8 no over b/c increases r/o rebleed b/c you engorge the vessels
  - FFP
  - SBP Px (give regardless if ascites present or not, not only decreases infection BUT also decreases rebleeding rate, no one knows why but important to know!!!)
  - Octreotide
  - PPI
  - Tx HE
  - NB no BB until off vasoactive agents
  - NB recent evidence suggests adrenal insufficiency during acute EVB therefore consider steroids
- Endoscopy
  - Early <12hrs
  - Intubation b/c high r/o aspiration b/c lots of blood and encephalopathic
  - EBL (refer) → Sclerotherapy (refer, equally effective to EBL but more complications) → Sengstaken-Blakemore ("SB")
    - Components: gastric balloon, esophageal balloon, gastric suction port (NB called a Minnesota tube if there is an additional esophageal suction port to prevent esophageal content aspiration otherwise place a an NG tube)
    - Mechanism: gastric balloon compresses origin of varyx and esophageal balloon compresses the varix itself
    - Set-Up: always intubate, HOB at 45 degrees, make sure balloons are free of leaks by inflating to max (note pressure at this time), if using an NGT tie it with silk sutures w/ end 3cm above proximal esophageal balloon, pass tube to 50cm mark thru mouth, apply suction to the ports, inflate gastric balloon and if pressure begins to rise above the pressure noted during leak test then the gastric balloon is in the esophagus and is about to perforate it!!!, once in place pull back so that balloon is against the diaphragm, check if continued bleeding from the gastric suction port, if still bleeding then inflate the esophageal balloon, check CXR to ensure correct placement, secure tube w/ football helmet or with weighted pulley, document pressures periodically, once bleeding has stopped based on suction ports then reduce esophageal balloon pressure by 5mmHg Q3hrs until 25mmHg and then stay there for 24hrs, always decrease balloon for 5min Q6hrs to prevent necrosis, can only be used for 24hrs
    - Keep suction on esophageal and gastric ports
    - SEs: VERY dangerous w/ many complications: perforation, aspiration pneumonia, asphyxiation, pain, ulcers/necrosis
- When the above has failed?
  - TIPS
    - Early TIPS aka w/in 24-48hrs if Child C!!!
    - More effective than EBL and NSBB but other issues (refer above)
  - Surgeries (refer)

- **Spleen**
  - **Splenomegaly**

- Thrombocytopenia → Leukopenia → Anemia
- Spleen backs up with blood allowing more time for it to take out cells
- Tx: rarely splenectomy b/c of high r/o sepsis, only removed if there is variceal bleeding and evidence of splenic vein thrombosis

- **Kidney**
  - **Hyponatremia**
    - General
      - Some propose adding Na to MELD by adding 1.59 (135-Na) as the worse hyponatremia the higher the mortality but the problem is you can cheat by having pts drink water
      - Hyponatremia worsens HE and increases short term post-OLT M&M in terms of neurologic fxn
    - Tx (always r/o other SIADH causes esp adrenal insufficiency, etc)
      - Na <130: <2g/d Na diet, decrease diuretics
      - Na <125: free water restrict to <1.5L/d, stop diuretics
      - Na <120: Tolvaptan (PO) vs Conivaptan (IV)
        - Mech: Vasopressin (V12) Antagonist = increases water secretion
        - increases Na by 4/7 at day 4/30
  - **HepatoRenal Syndrome (HRS)**
    - Epidemiology
      - 18/39% at 1/5yr in cirrhotic pts w/ ascites
    - Mechanism
      - Portal HTN & synthetic liver dysfunction → imbalance between multiple vasoactive substances (High: NO, Endothelin-1 vs Low: ?) resulting in systemic (brain, liver, adrenals, muscle, skin) vasodilation → heart is able to compensate by increasing CO (what has recently been appreciated is that cardiac fxn becomes impaired as cirrhosis progresses, specifically there is evidence of impaired repolarization) but eventually as cirrhosis progresses the heart cannot compensate resulting in decreased EABV → increase in multiple neurohormones (RAAS, ADH, sympathetic) leads to increased EABV but in doing so there is disturbed Na+Water/Blood-flow in the kidney (but also there are effects on other organs in the systemic system) →
        - (1) Water>Na Retention → HypoNa <130 AND
        - (2) Renal Vasoconstriction → Functional AKI w/ Cr >2.5
          - NB this is why NSAIDs are bad in cirrhotics b/c they cause additional renal vasoconstriction
          - NB this is a functional renal failure in that the kidneys are normal in terms of morphology
          - NB vasoconstriction also occurs in the liver/brain likely explaining the concurrent development of hepatic encephalopathy and hepatic failure that occurs w/ HRS
      - Type 2 HRS (less severe azotemia over a more indolent course, other organs are fine, median survival 6mos, seen in pts w/ **refractory ascites on high dose diuretics** esp when edema is not present, usually appears **spontaneously**)
      - Type 1 HRS (more severe azotemia over a more rapid course (>50% decrease in CrCl to <20mL/min OR >2x increase serum Cr to >2.5mg/dL in <2wks), generally there is MOF, median survival 2wks, usually appears following a **precipitating event like large volume paracentesis, GIB, SBP or any other type of infection, severe acute alcoholic hepatitis**, etc)
        - NB infection specifically bacterial intestinal translocation to mesenteric LNs plays an instrumental role as bacteria elicit an inflammatory response characterized by increased NO production in the splanchnic tissue, thus it is critically important to r/o infection (pan-Cx, diagnostic paracentesis, CXR, UA, etc) which can be challenging b/c leukocytosis can be blunted b/c of hypersplenism, it has been found that the administration of norfloxacin resulting in selective gut decontamination ameliorates some of the hemodynamic abnormalities seen in cirrhotics
        - NB Type 3 (pts w/ underlying renal dz develop HRS 1/2) and Type 4 (pts w/ ALF developing HRS 1/2)
    - Diagnostic Criteria (must meet every criterion)
      - (1) ESLD w/ Ascites
        - NB ESLD can be 2/2 not just cirrhosis but also acute liver failure, severe alcoholic hepatitis, metastasis
      - (2) Low GFR indicated by Cr >1.5mg/dL
        - NB renal fxn is often overestimated b/c cirrhotics have decreased muscle mass, increased Cr tubular secretion, and decreased conversion of creatine to creatinine

hence pts may have low GFR and one may not know about it (nl Cr in cirrhotics is 0.6-0.8 mg/dL)

- (3) Absence of other Causes of Pre-/Intra-/Post-Renal AKI = HRS is a DOE!!!
  - NB 19% of hospitalized cirrhotic pts get AKI and 68% of these are from a pre-renal condition while only 25% is caused by HRS hence most causes of AKI in cirrhotics is not HRS
  - DDx

	Urine Na	Urine Micro
ATN	>20	Cell Debris
Pre-Renal	<10	Normal
HRS	<10	Normal

    - Pre-Renal: HRS, NSAIDs, hypovolemia (over-diuresis, lactulose diarrhea, bleeding), sepsis, etc
    - Intra-Renal: ATN, HB/CV Glomerulopathies/Vasculitis, Wilson's induced RTA, AD-PCKD, PBC induced lymphocytic interstitial nephritis, etc
    - Post-Renal
- (4) No improvement in GFR despite 1g/kg/d albumin up to 100g/d and withdrawal of diuretics for ≥2d
  - NB some also give a trial of NS but this is not part of the diagnostic criteria
- (5) Normal Kidneys: Normal US (no CKD, no obstruction, etc), $U_{Protein}$ <500mg/d, U_{RBC} <50/hpf
  - Other: Benign Urinary Sediment, $O_{Osm}>P_{Osm}$, no WBC or casts (to r/o GN/Vasculitis, U_{Volume} <500mL/d (oliguria), U_{Na} <10mEq/L off diuretics, hyperosmolar urine, U_{Cr}/P_{Cr} >30
  - NB if you UA is abnormal consider getting a kidney Bx (histologically the kidneys in HRS are normal and in fact there have been cases of these kidneys being successfully transplanted into noncirrhotic recipients)
- NB other diagnostic tests are being developed including the use of Doppler US to measure the "resistive index" aka renal blood flow resistance, the big question is whether this test can identify high risk pts when standard tests of renal fxn are normal

- Prevention
  - IF LVP/SBP AND TB >4mg/dL and Cr >1mg/dL THEN Albumin (1.5g/kg Day#1 then 1g/kg Day#3 up to 150/100g/d)
  - IF AFTP <15g/L AND Child >10 or Na <130 or Cr >1.2 THEN Norfloxacin 400mg PO QD
  - Avoid nephrotoxins including judicious use of diuretics
- Tx
  - Current Tx Paradigm: *Albumin + Splanchnic Vasoconstrictors + LTxE + Prevent Other Causes of AKI → TIPS/ECAD*
    - Most studies looked at Type 1 thus there is limited data on Type 2
    - RRT can be helpful when acting as a bridge to transplant but if not a candidate then don't do except in those with acute reversible liver injury like alcoholic hepatitis
    - Continue intravascular challenge with NS even if at the risk of worsening ascites and withdrawal of diuretics
    - Discontinue/avoid all nephrotoxins
    - Empiric antibiotics
    - Check for adrenal insufficiency
    - Tense ascites can compress renal vessels so consider paracentesis
    - After discontinuation of meds HRS can return but retreatment is effective
    - Various responses: (1) complete (Cr<1.5), (2) partial (decrease in Cr by >50% but still >1.5) , (3) no (decrease in Cr by <50% and still >1.5), (4) relapse after complete
    - Agents w/ Conflicting Evidence: misoprostol, N-acetylcysteine, ACE-I
    - Agents w/ No Benefit: dopamine
  - **Albumin** (1g/kg/d max of 100g/d followed by 20-40g/d to achieve CVP of 10-15cm and only if alb <45g/L and there is no pulmonary edema)
    - Albumin is important b/c it not only expands blood volume but also causes systemic/splanchnic vasoconstriction in its ability to bind vasodilators
  - **Systemic Vasconstrictors**
    - General
      - Why? There is chronic systemic vasodilation which the kidneys sense and as a result cause renal vasoconstriction therefore to reverse then systemic vasoconstrict
      - During the past decade there has been a renewed interest in pharmacologic Tx, trials comparing various constrictors to placebo have

been done but comparisons b/t vasoconstrictors is the next big step, in general most studies are sub-optimal with very few RCTs
        - When using vasoconstrictors you should always monitor pts for possible CV and ischemic complications which have been reported in 12% of pts
    - Midodrine 5-12.5mg PO TID (pure alpha 1 agonist causing systemic vasoconstriction) + Octreotide 100-200mg SC TID (somatostatin analogue causing splanchnic vasoconstriction which keep blood in systemic circulation increased EABV)
        - NB individual use has not been effective
        - NB can be done on floor
    - Norepinephrine 0.5-3mg/hr titrated to increase MAP by 10mm of Hg (alpha 1 agonist > beta 1 agonist), NB done in ICU
    - Terlopressin 1-2mg IV Q4hrs x14d or until HRS has resolved, dose can be doubled Q2d to a max of 12g/d if there is not a >25% decrease in Cr, Tx should be stopped if Cr does not decrease by >50% at 7d of Tx or if there is no change in Cr at 3d
        - **Mechanism: Vasopressin (V1) Agonists = splanchnic vasoconstrictor (NB compare to –vaptans)**
- **TIPS**
    - TIPS is believed to relieve portal HTN which plays a pivotal role in splanchnic vasodilation and increases venous return to the heart promoting increased CO
    - Controversial as all the studies looking at TIPS in HRS were uncontrolled, retrospective, and excluded a large number of pts
    - Only an experimental therapy in Child A/B pts w/ failed Tx above
- **Extra Corporal Albumin Dialysis – ECAD**
    - Dialysis with Molecular Absorbent Recirculating Systems (MARS)
    - Blood is circulated across charcoal anion exchange column
    - This system is also connected to a HD/HP apparatus
    - Allows for the removal of albumin-bound substances
    - Data in HRS is controversial b/c ECAD decreases Cr but it is unclear if this is due to the filtration process or from true improvement in renal fxn
- **Transplant**
    - TOC
    - Transfer to a transplant center
    - Further impairment of GFR may be observed after transplant but this not due to HRS (as pts have regained their ability to excrete water and sodium) rather it is likely 2/2 nephrotoxic effects of calcinuerin inhibitors
    - In general pts transplanted b/c of HRS have more complications, longer hospital stays, and higher mortalities than those who are transplanted for other reasons (3yr mortality is 60% in HRS vs 75% in non-HRS) nevertheless survival is not that bad
    - Pharmacologic intervention prior to transplant has been shown to improve post-transplant survival
    - Every pt should be evaluated given the high mortality of HRS and should be performed as early as possible as renal fxn is a predictor of poor outcome post transplant
    - Improvement in numbers following pharmacologic therapy should not change one's decision to perform liver transplant as prognosis in Type 1 is still very poor
    - The reality is that in most cases pts die b/f they can obtain a transplant b/c of the acuity of HRS

- **CV**
    - **Cirrhotic Cardiomyopathy**
        - New concept
        - Systolic Dysfunction (during rest the heart is hyperdynamic b/c of the peripheral vasodilation resulting in high cardiac output heart failure, during stress the heart is not able to compensate, inotropes/chronotropes don't work as well, TTE will generally be normal) + Diastolic Dysfunction (often unmasked after TIPS, improves after paracentesis, E/A ratio on TTE will be <1) + Electrophysiologic Changes (QT prolongation and arrhythmias 2/2 K channel abnormalities)
        - Always a DOE specifically common cardiac diseases (eg. CAD) and processes that affect both heart and liver (eg. alcohol, hemochromatosis)
        - CM improves after transplant
- **Pulm**
    - **Resp Alkalosis** 2/2 increased nitrogenous compounds which stimulate brainstem
    - **SOB** 2/2 decreased lung volume 2/2 ascites
    - **SOB** 2/2 anemia
    - **SOB** 2/2 muscle wasting

- **Concurrent Primary Liver & Pulmonary Dz: Alpha-1-Antitrypsin Disease, Cystic Fibrosis, Sarcoidosis, Fibrosis from PBC**
- **Hepatic Hydrothorax (HH)**
    - Mechanism: 10% of cirrhotic pts have ascites (sometimes ascites is not present) that leaks thru R>L sided diaphragmatic defects b/c of negative intrathoracic pressure
        - NB 10% will have spontaneous bacterial empyema (SBE) and 40% of these is NOT associated w/ SBP!!! therefore consider in pt who you suspect has SBP b/c of decompensation but their paracentesis is normal!!!
    - Dx: same criteria as SBP BUT must judiciously rule out any secondary cardiac/pulmonary/pleural causes therefore always get a CT & TTE
    - Tx
        - Always: SBE Px and OLTx eval as there is a high mortality
        - General: diuretics, sodium restriction, etc but often not effective therefore most go to TIPS
        - Consider: TIPS, surgical repair of diaphragmatic defect, pleurovenous shunt
        - Avoid: therapeutic thoracentesis b/c high r/o complications, chest tubes b/c hard to remove and pleurodesis b/c high r/o complication
- **PortoPulmonary HTN (PPH)**
    - Definition: portal HTN + pulmonary HTN
    - Epidemiology: F>M, higher w/ autoimmune pts and lower in HCV pts
    - Mechanism: unknown but likely increased pulmonary circulation of substances not cleared by liver that lead to proliferation of pulmonary arterial smooth muscle and endothelium
    - Diagnosis: Mean PAP >25 + Mean PCWP <15 + PVR >240 (start w/ TTE to estimate RVSP and if >40 then right heart cath)
    - Staging
        - mPAP 25-35 (mild) 95% w/ PPS are not clinically apparent
        - mPAP 35-50 (mod)
        - mPAP >50 (severe)
    - S/S: 60% asymptomatic!!! but if symptomatic than usually non-specific including fatigue, SOB, edema out of proportion to degree of ascites
    - Dx: Screen w/ TTE (RVH, TR) and if + then Right Heart Cath (increased PAP, increased PVR, nl PCWP)
        - CXR: enlarged heart
        - Spirometry: normal
    - Tx: normal PAH meds (refer) and liver transplant (similar MELD as if HCC, if mPAP > 35 then contraindicated!!!)
    - DIFFERENCES BETWEEN PPH AND HPS
        - Sx (+ in HPS vs – in PPH)
        - Hypoxia (+ in HPS vs – in PPH)
        - Prognosis (good in HPS vs poor in PPH)
- **Hepatopulmonary Syndrome (HPS)**
    - Mechanism: failure of liver to clear circulating pulmonary vasodilators resulting in loss of hypoxic pulmonary vasoconstriction leading to formation of IPVDs at base of lungs → oxygen in adjacent alveoli cannot diffuse to the center of the dilated vessel → R-to-L shunting
    - Staging
        - PaO2 >80 (mild) 85% w/ HPS are not clinically apparent
        - PaO2 60-80 (mod)
        - PaO2 50-60 (severe)
        - PaO2 <50 (very severe)
    - Diagnostic Triad
        - (1) Cirrhosis
        - (2) Increased Aa gradient (>15 mm of Hg) on RA
            - Markers for Chronic Hypoxia: clubbing & cyanosis
            - DOE/SOB
            - **platypnea** (paradoxic increase in SOB when upright and improvement when supine) - **orthodeoxia** (paradoxic deoxygenation when upright and improvement when supine) **syndrome** why? 2/2 preferential perfusion of IPVDs at lung bases when pt is upright
            - **Nl spirometry and CXR**
        - (3) Intra-Pulmonary Vascular Dilatations (IPVDs)
            - Markers for IPVDs
                - spider telengectasia
                - hyperdynamic circulation (CO >7L/min)
            - Diagnosis of IPVDs
                - TEE w/ Bubble Study (agitated saline aka air bubbles >20microns are injected into a peripheral vein, in normal heart only the R

chambers opacify but if shunting exists then both chambers opacify, if opacification of L chambers occurs in <3 heart beats then the shunt is in the heart and if it occurs after >6 hearts beats then shunt is in the lung as in IPVDs)
    - Other tests: Technitium-99m Labeled Macroaggregated Albumin Scan (normal pulmonary capillaries are <10microns and when you give labeled albumin which are >20microns they should not pass thru pulmonary capillaries unless a shunt exists and if there is (>6%) then you can detect albumin in other organs particularly brain) and Pulmonary Angiogram (shows spider like abnormalities in the lung, used to assess if embolization is a possibility)
    - NB CXR is non-specific and non-sensitive
    - NB no studies that look at CT, MRI, PFTs
    - NB autopsy can show IPVDs on injection
- Tx
    - Supportive Tx like oxygen, mednebs, treating other pulmonary problems
    - Liver transplant is the definitive Tx, however the presence of HPS is an indicator for increased M&M from transplant, MELD exception points (similar MELD as if HCC)
    - Decrease pulmonary vasodilators (all investigational)
        - Decrease NO Production by Endothelial Cells: methylene blue inhibits guanylate cyclase transiently helps, nitro-L-arginine methyl ester (NAME) inhibits NO synthase has mixed results, norfloxacin
        - Decrease VEGF: pentoxifylline
    - Occlude IPVDs w/ embolization if they are large enough to be visualized on angiography
- Prognosis: 5yr survival of 23-63% with median survival of 24-87mo depending on coexisting medical conditions and age