Liver Disease:

Anatomy:

Key Liver Functions:

- Removing metabolic waste products, hormones, drugs and toxins
- Producing bile acids for digestion
- Processing lipids, carbohydrates and proteins
- Storing glycogen, vitamins and minerals
- Maintaining normal blood sugar
- Synthesize proteins (albumin, clotting factors)
- Produce immune factors
- Removing senescent RBCs from circulation
- Excreting bilirubin

Circulation

- Venous blood is returned to the heart by either: Portal system or Systemic system
- **Portal venous system**: drains from spleen and all gastrointestinal organs from distal esophagus to rectum
  - Portal blood is directed by portal vein to the liver where it is filtered before returning to the heart via inferior vena cava
- **Systemic (Caval) system**: blood from rest of body drains back to heart via superior and inferior vena cava
  - In healthy people, little blood exchange between these two systems (pressure is approximately equal in both systems)
- **Portosystemic anastamosis**: abnormal venous return when blood flows the wrong way through these connections
  - Blood from the portal system that should flow through the liver ends up avoiding the liver and goes backward to join the systemic circulation due to PORTAL hypertension

1. **Cirrhosis**: late stage of chronic progressive hepatic fibrosis (scarred)
   - *chronic injury leads to production of protein in extracellular space and disrupts the hepatic architecture and flow of blood to liver*
   - **Etiology/Risk factors:**
     - Chronic alcohol consumption
     - Hepatitis (B, C, D or autoimmune)
       - Risk factors for Hep C: IVDU 1980/early 90s → blood contaminated
       - Risk factors for Hep B: Mother not being vaccinated → passed to children at birth; endemic region
     - Metabolic liver diseases (hemochromatosis, Wilson's disease, α-1 antitrypsin deficiency, nonalcoholic steatohepatitis aka "fatty liver")
     - Medications: Acetaminophen, Herbal products, Alcohol, Isoniazide, Methyldopa, Methotrexate, Phenothiazine, Estrogen and anabolic steroids, Black cohosh, Jamaican bush tea
     - Cholestatic liver diseases (primary or secondary biliary cirrhosis, primary sclerosing cholangitis, Budd-Chiari syndrome, severe CHF and constrictive pericarditis)
     - Cancer
     - Cryptogenic (unknown cause)
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<thead>
<tr>
<th>Signs/symptoms</th>
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<tbody>
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<td><strong>Vitals</strong></td>
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<th>Labs</th>
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<td>↑ INR</td>
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<td>↓ albumin</td>
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<td>↑ bilirubin</td>
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<tr>
<td>unconjugated bilirubin = yellow</td>
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<td>➔ negative prognostic indication</td>
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<td>↓↑ bilirubin, ↑ worse prognosis</td>
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<td>Hgb – Liver ➔ Bilirubin</td>
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<table>
<thead>
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<th>AST, ALT</th>
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<td>Markers of hepatocellular damage</td>
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<td>GGT, ALP</td>
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<td>Related to biliary issues</td>
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In ESRD, AST + ALT can be normal

- Child-Pugh Classification: Correlates with one-year survival in non-surgical patients
- MELD score: Used to prioritize liver allocation for transplantation
  - ↑ MELD score is associated with ↑ severity of hepatic dysfunction and ↑ 3-month mortality risk
  - View LFTs in PAIRS:
    - Hepatocellular damage/inflammation: AST, ALT
      - AST/ALT ratio
        - >1: alcoholic liver disease (often >2), drug-induced injury, malignancy, cirrhosis, non-liver disease
        - AST and ALT require vitamin B6 as co-factor
        - ALT is more dependent on B6 for its synthesis
        - <3x ULN - can recheck in 1-3 months if asymptomatic
        - >3x ULN - correlate with history/clinical picture or consider further investigations if asymptomatic
        - Statins may ↑ AST/ALT 3x ULN
    - Cholestatic: ALP, GGT
      - causes: gall stone, abdominal masses, pregnancy, primary biliary cirrhosis, systemic sepsis, medications
      - General pattern:
        - ALP (>4x normal) and bilirubin are elevated
        - Sometimes, ALP is raised in isolation with a normal bilirubin
        - IF GGT is also elevated, liver is the most likely source
        - IF GGT is normal, source is likely non-hepatic
      - GGT: high sensitivity but non-specific
        - limited usefulness in isolation - raised in ANY liver disease (hepatocellular or cholestatic)
    - Useful indicators of hepatic function: albumin and INR
      - Albumin: has a long half life so may not be reduced in acute liver injury
Treat Underlying Causes:

I. Drug causes of hepatocyte injury:

II. Overview of some conditions associated with LFT abnormalities:

Fatty Liver (steatohepatitis):

- Non-alcoholic fatty liver disease:
  - suspected with risk factors (associated with metabolic syndrome, insulin resistance, diabetes and hyperlipidemia)
  - Hepatocellular predominant pattern
  - U/S shows echogenicity
  - AST/ALT <1 (ratio increases as fibrosis advances)
  - Mild to moderate increase in aminotransferases

Acute viral hepatitis:

- Hep A, B, C, D, E, CMV, EBC
- AST/ALT peak before jaundice, more gradual decrease after
- Greater increase in serum bilirubin levels
- Jaundice: Hep A (70%), Hep B (33-50%), Hep C (20-33%)
- Always check history and exposure
- If suspect acute viral hepatitis, check: Hep A IgM, Hep B IgM, Hep BsAg, HCV antibodies + HCV RNA test if negative for other tests

Chronic hepatitis:

- may present with LFTs within normal range
- pattern: AST/ALT ~100’s, decreased albumin
- Chronic Hep B: Usually transmitted via sexual contact of IV drug use
  - <5% develop chronic infection after acute infection
  - Significant risk of developing liver damage (i.e. cirrhosis, liver failure, liver cancer)
- Chronic Hep C:
  - usually transmitted by blood transfer (e.g. IVDU, sharing of needles)
  - >80% develop chronic hepatitis after acute infection
  - Carriers at risk of developing liver damage

Ischemic/Hypoxic Acute Liver Damage:

- Very high aminotransferase levels (often >50-75x ULN)
- Peaks and decreases rapidly
- LDH raised 80% (ALT/LDH <1)
- Rarely jaundiced
- *Closely monitor bilirubin and INR for risk of hepatic failure!*

Clinical Pearls:

- Normal LFTs do not exclude liver disease
- Degree of abnormalities in LFTs not always indicative of disease severity (not prognostic)
  - E.g. improve LFTs does not necessarily indicate that condition is getting better and hepatic damage is not there
- Drugs may confound or modify LFT patterns - consider discontinuation of hepatotoxic agents
- Always interpret with consideration of clinical context and underlying etiology

**Goals of Therapy:**

- Slow or reverse the progression of liver disease
- Preventing superimposed insults to the liver
- Manage symptoms and laboratory abnormalities
- Preventing, identifying and treating the complications of cirrhosis
- Identifying medications that require dose adjustments or should be avoided entirely
- Determine the appropriateness and optimal timing for liver transplantation

**Portal Hypertension:**
Portal Pressure > Caval Pressure – this can lead to varices

Pathophysiology of esophageal varices:

- Distal portion (lower 1/3) of esophagus sends its blood inferiorly to join the portal system (rest is caval system)
- In portal hypertension, portal blood will be shunted to the caval system until pressures are equal ⊴ portosystemic anastamosis
  - This leads for vessels to dilate and form varices
  - Varices can form in external surface and internal surface of esophagus – these swollen vessels may rupture and cause leakage of blood – s/s: black, tarry stool (due to breakdown of RBC cells in GI tract)
- Presence correlates with Child-Pugh Score: 40% in Class A and 85% in Class C
- Gold standard for diagnosis: Endoscopy

**Risk Factors:**

- Large (>5mm) varices
- Hepatic venous portal gradient >12 mmHg
- Child-Pugh B/C
- Red wale marks (higher risk of bleeding)
**Treatment:**

**A. Pre-Primary Prophylaxis**

- **GoT:** prevent varices (i.e. treat underlying cause)
  - RCT (N=213) – Timolol vs. Placebo – NSS with 1° Endpoint (presence of varices or variceal hemorrhage) + 2° Endpoint (ascites and/or hepatic encephalopathy, transplantation and death) AND ↑ risk of serious AEs
  - Non-selective BBs cannot be recommended to prevent development of varices
  - Repeat *esophagogastroduodenoscopy* in 3 years unless evidence of decompensation

**B. Primary Prevention**

- **Primary Prophylaxis – Small varices**
  - RCT (N=161), nadolol vs. Placebo – benefit for occurrence of large varices at 5 years and cumulative probability of being free of variceal bleeding...BUT NSS for death
    - Benefit lost if variceal growth observed
  - Non-selective BBs should be used in patients who are high risk for bleeding
  - Non-selective BBs can be used in patients who are low risk for bleeding
  - Repeat esophagogastroduodenoscopy every 2 years in patients who have not chosen to take BBs

- **Primary Prophylaxis – Medium/Large varices**
  - Propranolol/Nadolol vs Placebo
    - NNT = 7 for mean weighted bleeding rate at 2 years and NNT = 15 for mortality rate from bleeding
  - Non-selective BB or EVL are recommended in patients with high risk for bleeding while BBs preferred first line in patients not at high risk for bleeding
    - Non-selective BBs should be adjusted to max tolerated dose, follow up EGD not necessary
    - EVL should be repeated every 1-2 weeks until obliteration and EGD should be done 1-3 months afterwards, and then every 6-12 months
  - Nitrates, shunt therapy or sclerotherapy not recommended for primary prophylaxis

**Summary - Treatments:**

- **β-blockers**
  - Non-selective BB: propranolol 10mg TID OR nadolol 20-40mg BID
  - ↓ blood flow by ↓ BP and constricting arteries
  - Target: 55-66 BPM or <25% ↓ in HR (from study vs. Placebo)
  - GoT: prevent bleed (no mortality benefit but prevent 1st bleed)

- **Endoscopic band ligation:** constricts varices
  - Better than BB but not routinely done as invasive
  - Nitrates (don’t use if >50 yo as leads to lead in liver disease patients)

**C. Event – bleeding**

Gi Bleed + variceal bleed (possible s/s: vomit blood) – need to protect from both types of bleed

Upon initial presentation, the diagnosis is often Gi bleed NYD

∴ 80mg pantoprazole IV bolus then 8mg/hr IV x 72 hrs (or PO equivalent) and octreotide – then patients will get scoped

GoTs: Hemodynamic resuscitation, Prevention and treatment of complications, Treatment of bleeding

- **Hemodynamic resuscitation**
  - IV fluids to maintain BP and organ perfusion
  - Transfusion of pRBC’s to replace blood loss (target Hb 80)
  - +/- Transfuse platelets/plasma

*Be careful of fluid overload from resuscitation: could lead to rebound portal hypertension and a rebleed
*Monitor serum calcium if large volumes of blood replaced (hypocalcemia from citrate in pRBCs)

- **Complications:**
  - Patients may be intubated to protect their airway if lost massive amounts of blood
  - Aspiration Pneumonia – it is unclear if intubation or insertion of an NG tube lowers the risk of aspiration
  - Prevention of infection

- **Prophylactic Antibiotics (misnomer – s/b "empiric treatment" as treating a possible infection NYD in the setting of upper Gi bleed):**
  - *Often think that variceal bleed will ↑ translocation and that infection will ↑ cytokines released and may cause varices to bleed
  - Cirrhotic patients with upper Gi bleeding
    - High risk of developing severe bacterial infections – associated with early recurrence of variceal hemorrhage and a greater mortality
Antibiotics can also improve survival even if a cirrhotic patient is having a non-variceal related GI bleed
- Short-term prophylactic antibiotics
  - Decreases the rate of bacterial infections
  - Increase survival
- Norfloxacin 400mg po BID x 7 days
  - Alternative – ciprofloxacin BID (PO or IV)
- Ceftriaxone 1g IV daily x 7 days (minimum of 5 days)
  - MA: ↓ mortality, rebleeding, hospital LOS, bacterial infections
  - In acute setting – also ↓ UTIs, ↓ SBP, ↓ pneumonia
  - Ceftriaxone + Fluoroquinolone (10 days vs. 5 days – no difference)
  - keep for > 5 days if looks like need longer treatment

- Control of Bleeding
  - Vasoactive Medications
    - Splanchnic vasoconstriction: ↓ blood flow to all splanchnic organs; thereby, leading to a decrease in portal venous inflow and to a decrease in portal pressure
    - Vasopressin: directly vasoconstricts mesenteric arterioles
      - Benefit of bleeding cessation may be outweighed by increased mortality due to extrasplanchnic vasoconstrictive properties and resultant myocardial, cerebral, bowel and limb ischemia
    - Terlipressin: synthetic analog of vasopressin
      - Mortality benefit over placebo
      - Unavailable in Canada
    - Somatostatin and analogs
      - Inhibits the release of vasodilator hormones such as glucagon, indirectly causing splanchnic vasoconstriction and ↓ portal inflow
        - Somatostatin (250mcg bolus then 250mcg/hr infusion)
        - Octreotide (50mcg bolus then 50mcg/hr infusion) until patient is clinically stable and at least for 72 hours and bleed-free >24 hours and up to 5 days (only studied for this duration)
        - MOA mimics natural somatostatin by inhibiting serotonin release and the secretion of gastrin, VIP, insulin, glucagon, secretin, motilin, and pancreatic polypeptide – constricts splanchnic arteries
      - Duration: 3-5 days (where the risk of rebleeding is the highest)
      - No benefit for mortality if used as monotherapy
      - Endoscopic band ligation/variceal ligation: stop blood flow by banding – 1st choice
        - Only banding the ones that are bleeding
    - Endoscopic sclerotherapy
      - like superglue – but can cause ulceration, bleeding and esophageal perforation – 2nd line after EVL
      - Transjugular intrahepatic portosystemic shunt (TIPS) if EVL fails twice
      - Balloon tamponade – temporary (24 hours) measure until definitive therapies can be arranged
        - Not a safe option – more for helping you buy time until you can do something else
    - Pharmacologic therapy (e.g. octreotide) in combination with endoscopic therapy (e.g. EVL) vs. endoscopic therapy alone
      - MA of 8 trials: improved control of initial bleeding and 5 day hemostasis in combination group but no differences in mortality

D. Secondary prophylaxis: after having varices that bleed – bleeding has stopped and no bleeding x 24 hours
- Untreated patients following variceal bleed within 1-2 years of index hemorrhage
  - Rebleeding rate = 60%
  - Mortality = 33%
- If required shunt surgery or TIPS procedure to control index bleed do not require secondary prophylaxis
  - RCT (N=91) TIPS vs. ISMN + propranolol – TIPS better or variceal rebleeding, bleeding from any source, de novo encephalopathy...but NSS for death
- BBs: ↓ rebleeds AND ↓ mortality (in 2° prevention but not 1° prevention)
  - NNT ~ 9 for rebleed and NNT is good for mortality reduction
- Endoscopic band ligation
  - Typically will have columns of esophageal varices - want to band the whole column of varices even if not bleeding (may have to be done in several sessions)...doesn't prevent reformation but will reduce the risk
- Even if getting rid of varices on surface, need to also treat the underlying cause.
  - Non-selective BB + EVL is the best option
  - Non-selective BB should be adjusted to max tolerated dose, follow up EGD not necessary
  - EVL should be repeated every 1-2 weeks until obliteration and EGD should be done 1-3 months afterward and then every 6-12 months
- TIPS should be considered for recurrent variceal bleeds despite combination pharmacological therapy

Is there a right time to stop BBs?
The recommendation to stop BB at a certain point is based on a retrospective observational study – there is likely a window that BB is useful but also some point where it is probably harmful (↓ BP which is associated with mortality)
- MAP < 82 is the mortality predictor

If there are indications for BB – would try to keep it as long as possible
- For this population, would never get BB doses very high (e.g. for HF) ∴ if withdraw the BB, wouldn’t have significant tachycardia and since usually withdrawing due to hypotension, reflex hypertension upon withdrawal is not much of a concern
If have SBP – may stop...but if SBP resolved and patient has recovered and is stable, would consider a BB again if indicated

Ascites: fluid in gut due to backflow of veins leading to accumulation of fluid in the peritoneal cavity

Peritoneal Cavities:
The space within the abdomen that contains the intestines, the stomach, and the liver. It is bound by thin membranes.
Clinically detected when >3L of fluid has accumulated
Low albumin (oncotic agent) ↓ oncotic pressure = leak ↓ plasma leaves the vessels

Pathophysiology: Multi-factorial

- Severe portal hypertension lead to splanchnic arterial vasodilation and ↓ peripheral resistance
  - ↑ nitric oxide by spleen → systemic/splanchnic vasodilation → ↓ effective arterial blood volume
- Systemic hypotension triggers activation of RAAS
  - ↑ sodium and water retention
  - Vasoconstriction
- Splanchnic vasculature unaffected by RAAS, instead becomes vasodilated increasing hydrostatic pressure
- Leakage of fluid into peritoneal cavity which is perpetuated by ongoing RAAS activation

Goals of Therapy:

- Improve QOL – less abdominal discomfort, SOB, improved mobility
- May protect against SBP
- ↓ risk of tense ascites – associated with abdominal cellulitis, hernia, diaphragmatic rupture
- Less energy used to heat ascitic fluid

Non-pharmacologic measures:

- Fluid restrict (1-1.5L/day) and salt restrict (<2g/day + no added salt)
  - Often patients have hyponatremia – don’t usually want to treat with salt but with fluid restriction
  - No fluid restriction unless sodium <125 mmol/L (hyponatremia often asymptomatic)
  - Vaptans (for hyponatremia) – not clinically beneficial in ascites
- Cessation of alcohol use – reversible component to alcohol liver disease!
  Class C – if stop drinking → by 3 years, most would still be alive

Pharmacological treatments:

- Spironolactone 100mg OD
  aldosterone: hormone :: onset of action is longer (1-2 weeks)
  10 to 4 ratio
- Furosemide 40mg OD
  Losix added as works faster but required higher doses (some studies had patients on 1400mg furosemide)

Goal weight loss: 0.5kg/day

- Usual starting dose 100:40mg
- For guidance: Titrate q3-5 days to max 400:160mg
  - 400:160mg thought to be a good balance between diuresis and hypoK+
- If ↑ furosemide – will have more rapid diuresis but run the risk of hypokalemia and intravascular depletion ∴ may ↑ furosemide if more edema going on and then move back if edema is resolving

- May lean towards spironolactone monotherapy if out-patient and can’t monitor (e.g. K+) since diuresis onset is slower and not as effective

Alternatives:

- Amiloride (K+ sparing diuretic) if tender gynecomastia from spironolactone (but not studied in this setting)
- Eplerenone has not been studied in ascites
- Avoid HCTZ combo with spironolactone/furosemide (↑ risk of hyponatremia)
- Remove up to 1kg (volume) per day if peripheral edema

Avoid/use with caution:

- NSAIDs (azotemia: abnormally high levels of nitrogenous products) – unless risk is outweighed (e.g. ischemic heart disease)
  - e.g. ASA 81mg daily can be kept if strong cardiac indication
- ACEI (BP lowering)
  Many patients with liver disease have systemic hypotension, despite having portal hypertension. Although fluid may be accumulating in peritoneal cavities (i.e. ascites), intravascularly – may be hypovolemic and relying on their baseline RAAS tone
Mortality associated with hypotension ∴ don’t want to block the compensating mechanism with RAAS against nitric oxide 
∴ with use of ACEI = also ↑ risk for renal failure as hypovolemia = little renal function reserve to rely on

Tense ascites:

- Initial 5L paracentesis (can be done without colloid infusion)
  - Paracentesis is a procedure to take out fluid that has collected in the belly (peritoneal fluid)
  - Does not correct underlying problem (sodium retention)
  - Also initiate sodium dietary restriction and diuretics to excrete sodium

Refractory ascites (e.g. patients with uncontrolled ascites on 400:160mg spironolactone/furosemide):
Once patients become refractory to routine medical therapy, 21% die within 6 months

- Ensure compliance to diet
- Consider discontinuing beta blockers: shown to ↓ survival in these patients
- Add midodrine 7.5mg PO TID
  - MOA: α1-agonist - ↑ arteriolar and venous tone resulting in a rise in standing, sitting and supine and diastolic BP in patients with orthostatic hypotension
  - To aid in maintaining BP while increasing diuretic doses
- Last line – serial therapeutic paracentesis, liver transplant, TIPS, peritoneovenous shunt

Abdominal paracentesis, always send cultures, gram stain, cell counts, chemistries!

**Spontaneous Bacterial Peritonitis (SBP):** Spontaneous infection of the ascitic fluid in the absence of an identified intra-abdominal source of infection or inflammation

- Common complication in patients with ascites

Pathophysiology: Multiple mechanisms proposed

- Primary mechanism: bacterial translocation from gut
  - Low protein ascites has diminished antimicrobial activity
  - Failure of immune system to destroy bacteria
  - Translocation mechanism may be due to swelling and stretching: bacteria from GI tract can pass through tight junctions in the cell to the peritoneum
- Most commonly gram-negative enteric bacilli
  - E. Coli
  - Klebsiella species
- Pneumococci – don’t often see strep pneumoniae as a gut bacteria but as it is an encapsulated bacterium and we lack the immune component in ascitic fluid, this needs to be covered

Risk Factors:

- Albumin < 10 or Protein < 15 in ascitic fluid
  - a lot of immune components are proteins (e.g. complements, immunoglobulins) ∴ protein or albumin content – is a surrogate marker for amount of immune protein in the ascitic fluid
  - Huge volume of fluid + no immune component = huge source of infection

Complications:

- High Mortality – severe underlying liver disease is usually a progenitor to the development of SBP
  - Inpatient non-infection-related mortality rates: 20-40%
  - If the patient survives that hospitalization, one-year and two-year mortality rates for those with SBP are 70 and 80%, respectively
- High recurrence rate

Prophylaxis: No mortality benefit

Treatment:

- Empiric treatment when:
Symptoms present, regardless of PMN count
- Ascitic PMN > 250 cells/mm³ (x 10⁶/L) or WBC > 500 cells/mm³ (x 10⁶/L)

**Cefotaxime 2g IV q8H**
- Or similar 3rd generation cephalosporin
- Alternative: ciprofloxacin (if they haven’t been receiving a FQ for prophylaxis)
  - But...MLegal says *never* use ciprofloxacin for empiric treatment as does not cover strep
- (Previously ampicillin + tobramycin but less mortality with cefotaxime)

**Culture directed therapy** – would want to do a diagnostic tap!
- Can narrow treatment after sensitivities known
- Culture negative neutrocytic (elevated PMN) ascites also warrants treatment (same mortality as SBP)
  - *Even if cultures are negative – there are follow up studies that show that growth may be seen later on : would continue antibiotics*
- Duration
  - 5 days (just as good as 10 days) cefotaxime – but monitor to see if need more than 5 days
  *Even a single dose of an effective broad spectrum drug causes the culture to produce no growth if paracentesis is repeat 6 hours after the dose is given*

**Albumin**
- 1.5g Albumin/kg body weight within 6 hours of detection and 1g/kg on day 3
- Give if:
  - sCr > 88 umol/L
  - BUN > 30mg/dL
  - Or total bilirubin >4mg/dL

Secondary =/= SBP

**Secondary: ascitic infection from an intra-abdominal source (e.g. periappendiceal abscess or perforation)**
- Requires antibiotics AND surgery (for source control) usually
- < 5% of ascitic infection

**Distinguishing features:**
- Often grow fungi and enterococcus
- PMN count can be in 1000s
- Ascitic fluid glucose <50mg/dL
- Ascitic fluid LDH elevated
- Ascitic fluid total protein >1g/dL
- Regardless – would start patients on antibiotics – but may need to broaden coverage if have abscess

**Secondary Prevention:** Recurrence is up to 69% in one year!

**Antibiotics:**
- Septra DS i tab daily
  - Risk: hyperK+
- Ciprofloxacin 500mg po daily
  - Cipro OK for prophylaxis as in ascitic fluid may be able to take out the small amount of Strep
  - NNT ~3 for 1-2 years since rate of recurrence is so high – since highly beneficial for SBP prophylaxis
- May not need broad spectrum abs if presenting since trying to prevent the couple of organisms that be translocating
  (Daily regimens are preferred over intermittent/once weekly dosing, which has been associated with development of resistance)

**Hepatic Encephalopathy:** metabolic disorder of the CNS leading to a wide range of neuropsychiatric symptoms and which is associated with hepatic insufficiency and liver failure

**Fluctuating** condition – *patients often present to the hospital at their worst. -> literature shows lactulose is beneficial...but difficult to tell if it is just the course of their condition*

**Pathogenesis:** Multifactorial

- Ammonia – by product protein metabolism by GI bacteria
  - Normally absorbed and metabolized by liver to urea then excreted renally
Accumulates in cirrhosis and enters CNS
- Amino acid balance (leading to change in neurotransmitters?)
- Gamma-aminobutyric acid

Presentation:
- Asterixis AKA “flapping tremor” – most characteristic neurological abnormality
  - May be severe enough that they can’t raise arms
  - Best to have them close their eyes to avoid them trying to actively hold their hands back
  - Even by pushing their hands back, may feel and detect fine tremors
- Fetor Hepaticus: Peculiar sweetish, musty, pungent order to breath thought to be caused by circulating unmetabolized mercaptans
  - May have garlic-like smell

Categorization:
- Underlying disease
  - Type A: acute liver failure
  - Type B: portosystemic bypass with no intrinsic hepatocellular disease
  - Type C: cirrhosis with portal hypertension or systemic shunting
- Time Course
  - Episodic, Recurrent (<6 months between bouts), Persistent

Severity:

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<th>Physical Sign</th>
<th>Stage I Prodrome</th>
<th>Stage II Impending Coma</th>
<th>Stage III Stupor</th>
<th>Stage IV Coma</th>
<th>Stage V Coma</th>
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<tr>
<td>Mental status</td>
<td>Alert</td>
<td>Sleepiness</td>
<td>Somnolence</td>
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<td>Behavior</td>
<td>Restless, irritable, disoriented speech</td>
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<td></td>
<td>None</td>
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<tr>
<td>Spontaneous motor activity</td>
<td>Uncoordinated with tremor</td>
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Precipitating Factors:

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<tr>
<th>Excess Nitrogen Load</th>
<th>Fluid and Electrolyte Abnormalities</th>
<th>Drug-Induced Central Nervous System Depression</th>
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<tbody>
<tr>
<td>Blandering from gastric and esophageal varices</td>
<td>Hypokalemia</td>
<td>Sedatives</td>
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<tr>
<td>Peptic ulcer</td>
<td>Alkalosis</td>
<td>Tranquilizers</td>
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<td>Excess dietary protein</td>
<td>Hypovolemia</td>
<td>Narcotic analgesics</td>
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<td>Anemia or kidney failure</td>
<td>Excessive diarrhea</td>
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<td>Deteriorating hepatic function</td>
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<tr>
<td>Infection: tissue necrosis</td>
<td>Excessive vomiting</td>
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<td>Constipation</td>
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Treatment:
- Control precipitating factors
  - ~90% of patients can be treated with correction of the precipitating factors
- Treat only overt hepatic encephalopathy (OHE)
  - May choose to treat even with minimal as may affect QOL and cognition (discuss with patient)
  - Mortality benefit only present for treatment of OHE (not for MHE) but when removed high risk bias trial, mortality benefit was NSS
- Primary prevention for OHE not required...unless severe cirrhosis patients with high risk
- Secondary prevention of OHE is recommended (if develop OHE, ↑ risk of developing future episodes of OHE)
- Lactulose:
  - Proposed MOA: catabolized by colonic bacteria, which produces lactic acid and acetic acid → ↓ pH
Favours NH₃ (ammonia) $\rightarrow$ NH₄⁺ (ammonium – mnemonic: larger word :: 4 and +)

- NH₄⁺ trapping (cannot pass through gut walls) $\rightarrow$ reduces plasma ammonia
  - Dose: 25mL (16.7g) po Q1-2h until 2 soft/loose BMs/day
  - Then change to maintain 2-3 soft/loose BMs/day

**Rectal administration:**
- Retention enema: 200g (300mL) via rectal balloon catheter; retain for 30-60 minutes, may repeat q4-6h
  - Basically: giving PO lactulose (diluted and qs to a certain volume) rectally
- **May have to be used** – *e.g. if patient has severe HE and is guarding their airway and unable to take PO*
  - **But not sustainable** – *and may want to use NG tube instead*
- **Check orders** – often doctors will write PO/PR – but the frequency is different Q1-2h vs. Q4-6h

**Risks of lactulose overuse:**
- Aspiration
- Dehydration
- Hypernatremia
- Severe perianal skin irritation
- Sores if immobile

*Overuse can even precipitate HE*

- **Rifaximin:** (half rifampin, half erythromycin)
  - MOA: antibiotic – alters gut flora
  - Dosing: 550mg po BID or 400mg po TID
  - Costs: “$40 per day (gastroenterologists may have drug cards for reimbursements)
  - **Treatment:** NSS in efficacy of treatment when compared to non-absorbable disaccharides...BUT less diarrhea and abdo pain
    - Option if patient cannot tolerate lactulose
  - **Secondary Prevention:** Rifaximin 500mg po BID vs. Placebo x 6 months (>90% of pts were on lactulose) ↓ recurrence of HE but NSS for mortality and ↑ risk of Cdiff infection

*Some literature (“bad” literature) showing some evidence with PO vancomycin or metronidazole at C. diff doses in improving encephalopathy but neither are therapies to give long term for recurrent or secondary prevention*

- **Ammonia levels**: elevation of ammonia does not correlate with staging or level of severity of symptoms
  - An elevated level does not require treatment if the patient is asymptomatic
  - Not necessary to follow levels with treatment – just monitor your patient’s symptoms

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**Management Summary**

- **Ascites**
  - spironolactone:furosemide 100:40 mg daily. Na⁺<2g/day
- **Spontaneous Bacterial Peritonitis**
  - cefotaxime 2g IV q8h x 5 days, then prophylaxis
- **Variceal bleed**
  - Octreotide inf x 3-5 days & EVL, ceftriaxone 1g IV QD x 7 days
- **Prevention of Varices**
  - **Pre-Primary**: repeat EGD q3y
  - **Primary (small)**: low risk (none), high risk (BB) repeat EGD q2y
  - **Primary (medium/large)**: BB or EVL & repeat EGD
  - **Secondary**: BB or EVL or TIPS if recurrent despite meds
- **Hepatic Encephalopathy** *(overt)*
  - Tx: lactulose 25 mL q1-2h until 2 BM, then titrate to 2-3 BM/d
  - **Primary Prevention**: no prophylaxis
  - **Secondary Prevention**: lactulose titrate to 2-3 BM/d