

6 Portal Hypertension II

- **Splenic vein** drains blood from spleen
- **Portal vein** is about 5 – 9 cm long. There are a lot of collaterals. These become large and significant during portal hypertension
- **Short gastric vein** drains into the splenic vein. If the splenic vein is thrombosed, the short gastric vein becomes very large, and large varices form on the fundus of the stomach
- Hepatic blood flow is about 1500 mL/min
- **Portal vein and hepatic artery** – the only organ in the body to have a dual blood supply is liver.
- If the hepatic artery is thrombosed, the portal vein cannot compensate. But vice versa is true.

Normal Pressures

- Normal PV pressure = 5 – 10 mm Hg (gradient between portal vein and IVC)
 - Normal portal venous gradient: 1 – 5 mmHg
 - Definition of Portal Hypertension:
 - Port-venous gradient > 5 mmHg = portal hypertension
 - Complications when gradient > 10 – 12 mmHg
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Causes of Portal Hypertension

- Obstruction of portal vein (pre-sinusoidal) or splenic vein
 - SMV thrombosis
 - Portal vein thrombosis or stenosis
 - Compression of portal vein
 - Arteriovenous fistula
- Obstruction within the liver (sinusoidal)
 - Cirrhosis from any cause
 - Severe hepatitis
 - Idiopathic
 - VOD

- Obstruction of hepatic veins and beyond (post-sinusoidal)
 - Budd-Chiari syndrome
 - IVC malformation
 - Constrictive pericarditis
 - **Cirrhosis is the most common (> 90%) cause of portal hypertension.**
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Imaging of Portal & Hepatic Veins

- Ultrasound with duplex
- 3D-CT scan
- MRI
- Venous phase of splenic or mesenteric arteriogram
- HVW carbon dioxide venography

Measurements of Portal Pressure

- Direct pressure
 - Indirect by measuring HVWPG (difference between hepatic venous wedge pressure and free hepatic venous pressure)
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Pathogenesis of Portal Hypertension

- Portal pressure gradient = Blood flow x **Resistance**
- In general, the sinusoids have no resistance in a healthy liver. So you normally need to have a huge increase in bloodflow to get portal hypertension. Unless you get AV fistulas or hepatosplenomegaly.
- **Portal hypertension mostly occurs when you have increased resistance**
- Intrahepatic vascular resistance:
 - Fixed defect (60%)
 - Fibrosis
 - Nodules
 - Thrombosis
 - Dynamic (40%)
 - Smooth muscle
 - Myofibroblasts
 - Stellate cells

- **Upregulation of vasoconstrictors and downregulation of vasodilators**
 - Vasoconstrictors: endothelin, angiotensin, norepinephrine, leukotrienes, and others
 - Vasodilators: nitric oxide, carbon monoxide, and others
- In cirrhosis, there are structural changes and dynamic changes → these increase vascular resistance within liver → causes portal hypertension (backflow) → body creates collateral circulation and those vessels become larger (the blood is bypassing the liver and going through stomach wall, for example) → prevent portal pressure increase
- This is the body's way of compensating for the portal pressure

Common Sites for Collaterals

- Esophageal and gastric
- Less common sites
 - Anorectal varices (hemorrhoidal veins)
 - Caput madusae (PV and epigastric vein through umbilical vein remnant)
 - PV and left renal vein (spontaneous splenorenal shunt)
 - Splenic and coronary vein (gastric varices)
- Pressure would be normal if the collaterals can decompress the portal system. But something else happens in liver disease. After some time, there is **splanchnic (mesenteric vascular system) vasodilation**. That increases bloodflow profoundly.

Mechanisms of Splanchnic Vasodilation

- Increased levels of vasodilators due to inadequate clearance or due to shunting
 - Glucagon
- Increased production of NO in mesenteric vascular bed
 - Endothelial shear due to increased portal flow?
 - Response to circulating constrictors
 - Endotoxemia
- Prostaglandins
- Carbon monoxide

Consequences of Splanchnic Vasodilation

- Increased portal blood flow and hence increased portal hypertension (pressure)
- Causes less blood to be in the systemic circulation → hypovolemia & decrease in systemic blood pressure (hypertensive patients become normotensive and normotensive patients become hypotensive)

- Hypovolemia and decrease in systemic pressure leads to a cascade of events including **upregulation of vasoconstrictors, sodium retention, decrease in renal blood flow and finally renal failure (hepatorenal syndrome)**
- This all activates many substances in the body, and that's what causes renal failure in these patients

Formation of Ascites → KNOW THESE!!

- Increased resistance → Portal hypertension
- Splanchnic vasodilation → even higher portal pressure
- Increase in capillary permeability (lymph and serum oozes out of vessels and fluid forms in abdomen)
- Renal changes
 - Upregulation of RAA system (due to hypovolemia)
 - Upregulation of sympathetic system (peripherally they are vasodilated, but the kidney is vasoconstricted)
 - Decreased GFR
 - Increased atrial natriuretic peptide (ANP)
- This causes **ascites** to form → fluid in abdomen
- **Antidiuretic hormone** is upregulated, so the body is conserving more water than you need to. So there is hemodilution and Na^+ stops dropping (hyponatremia). So although total body sodium is very high, the patients will be hyponatremic. As disease progresses further, the person develops renal failure (hepatorenal syndrome). If creatinine goes above 1.5, this is **hepatorenal syndrome**.

Hepatorenal Syndrome

- No intrinsic renal disease here, mainly because of decrease in renal cortical bloodflow, increase in RAA
- Low GFR (creatinine > 1.5 or 24 hour creatinine clearance < 40 mL/minute)
 - Make sure the patient:
 - Absence of shock, ongoing infection, dehydration, current use of nephrotoxic drugs
 - Absence of improvement in GFR after hydration with 1.5 L of isotonic saline or colloids and discontinuation of diuretics
 - Proteinuria < 500 mg/24 hours, no U/S evidence of obstructive uropathy or parenchymal renal disease
- Type 1 – rapidly progressive, usually seen in type II HRS
- Type 2 – slowly progressive renal failure

Complications of Portal Hypertension

- **Gastro-esophageal variceal bleeding**
- **Ascites**
- **Hepatorenal syndrome**
- **Hepatic encephalopathy** (toxins from intestine are not cleared by liver, so they go to brain and cause problems)
- Hepatopulmonary syndrome & portopulmonary hypertension
- Bacteremia
- Hypersplenism
- Impaired drug metabolism

Signs of Portal Hypertension

- Gynecomastia because they lose secondary sexual characteristic
- Large blood vessels in abdomen (caput medusae)
- Asterixis (flapping tremors in hand due to hepatic encephalopathy)
- Edema
- Splenomegaly
- Ascites
- Confusion

Variceal Bleeding

- The pressure is so high that these are like torrential bleeding
- What can we do for this? You have to screen patients with advanced cirrhosis to look for these collaterals:
 - Prevention of 1st bleeding (primary prophylaxis)
 - Treatment of acute bleeding
 - Prevention of rebleeding (secondary prophylaxis)
- **Varices do not bleed unless HVWPG (hepatic venous wedge pressure gradient) exceeds 12 mm Hg**
- One-third of patients with cirrhosis die from bleeding if they do bleed
- 6-week mortality with bleeding is around 20 – 40% and it is dependent on severity of liver disease (Child A 10 – 20%, Child C about 70%)

Objectives of Primary Prophylaxis

- To prevent the first variceal bleeding in high-risk subjects (because mortality with first bleed is so high)
- To reduce or prevent bleeding related morbidity and mortality
- *Treatment should be relatively inexpensive, readily available, and have minimal complications*

Risk Factors for Bleeding

- Large varices
- Varices with red signs
- Advanced cirrhosis
- High portal pressure gradient (HVWPG)

Primary Prophylaxis

- Pharmacological therapy
 - **Non-selective β -blocker (e.g. propranolol)**
 - Reduces portal pressure by reducing cardiac pressure
 - Reduces portal influx by antagonism of β -blocker receptors on splanchnic vessels
 - Reduce collateral blood flow by increasing resistance in collaterals
- Endoscopic treatment
 - Endoscopic banding (clots blood \rightarrow thrombosis \rightarrow collaterals disappear)
- If patient cannot tolerate the β -blocker, endoscopy can be used
- Although banding reduces bleeding much more than beta-blockers, they do not decrease the mortality, so β -blockers are preferred. Only patients intolerant of β -blockers get endoscopic banding.
- Current recommendations
 - Non-selective β -blockers reduce both bleeding and mortality
 - Banding reserved for high risk patients who cannot tolerate β -blockers

Acute Variceal Bleeding Resuscitation

- If somebody does have a big bleed, make sure there is:
 - Airway protection & oxygen if there is any sign of desaturation
 - Adequate replacement of blood
 - IV antibiotics (reduce the re-bleeding rate and reduce mortality)

- Avoid nephrotoxic drugs

Acute Variceal Bleeding

- Give **octreotide** (mimics somatostatin) or **somatostatin** infusion if there is a strong index of suspicion. These help to decrease bleeding.
 - **Glypressin** (like vasopressin) is comparable to both drugs
- Endoscopy to confirm the diagnosis only after stabilizing the patient
- Endoscopic treatment successful in 85 – 90% of active bleeders
- Repeat endoscopic treatment once more if bleeding continues after one session of endoscopic treatment + pharmacologic therapy

When There is Uncontrolled Variceal Bleeding

- Balloon tamponade to stabilize the patient (inflate balloon in cardia)
- TIPS (shunt between portal vein and hepatic vein which decompresses the portal system) shunt is the treatment of choice for uncontrolled bleeding

Secondary Prophylaxis

- To avoid the second bleeding
- Combination treatment
 - Endoscopic banding until variceal vessels are obliterated
 - Non-selective β -blockers lifelong
- **TIPS (transjugular intrahepatic porto-systemic shunt)** or surgery for rebleeding
 - Go through neck vein and get into the hepatic vein → make a track within the liver and get into the portal vein. Put a balloon between the hepatic vein and portal vein in the liver → inflate the balloon and employ a self-expanding metal stent that allows communication between hepatic & portal veins → very effective at reducing portal pressure
 - Blood here is bypassing the liver, so some of the toxins from the intestine are kept in the blood → can cause **hepatic encephalopathy** (especially ammonia). If it weren't for this side effect of this treatment, this would be first-line therapy

Management of Ascites

- Identifying the cause
- Sodium restriction
- Combination of **loop diuretic** (furosemide) and **aldosterone antagonists** (spironolactone) → conserves K^+ and doesn't require K^+ supplementation
- Paracentesis to take fluid out from peritoneal cavity

Refractory Ascites

- Significant ascites due to cirrhosis that require repeated paracentesis despite sodium restriction of 2000 mg/day, and maximal, tolerated diuretic therapy (furosemide 120 – 160 mg and spironolactone 400 mg daily)
- Once patients develop this, mortality is very high
 - 1 year-mortality: 25% - 79%
- Complications:
 - Spontaneous bacterial peritonitis (SBP)
 - Respiratory compromise (fluid pushing up on diaphragm)
 - Rupture of umbilical hernia
 - Hepatorenal syndrome
 - Discomfort

Treatment Options for Refractory Ascites

- Repeated paracentesis + IV albumin
- TIPS (for portal hypertension)
- Liver transplantation

Conclusions for Management of Refractory Ascites

- Medical therapy and periodic large volume paracentesis should be the first-line therapy
- TIPS should be reserved as a second-line therapy for patients with good synthetic functions (less advanced disease) → because of risk of hepatic encephalopathy
 - Response and survival rate are both unpredictable
 - TIPS is more expensive than medical therapy
 - TIPS does not improve quality of life

Hydrothorax

- Fluid in the pleural cavity
 - 5 – 12% of patients with portal hypertension get this
 - Less effective when compared to refractory ascites
 - In a study of 40 patients, hydrothorax resolved in 71% with 1-year survival of 64%
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Hepatic Encephalopathy

- **Less functioning liver mass + lots of collaterals bypassing the liver.**
- The intestine produces a lot of toxins, ammonia being the most important.
- The intestinal motility is reduced in liver disease, so all the toxins go through the portal system, and the liver cannot clear the toxins due to shunts or due to less functioning liver mass. → this gets into the CNS → astrocytes start swelling up and not functioning well → leads to confusion

Increased Blood Ammonia

- Ammonia is most important toxin for hepatic encephalopathy
- Causes astrocyte swelling
- Causes increased osmolality within astrocytes, altered neuronal electrical activity, and may have multiple more speculative pathogenic mechanisms

Other Pathogenic Mechanisms

- Multiple other pathogenic mechanisms may exist, and there are multiple additional putative toxins
- Pathogenic changes may lead to activation of inhibitory (**GABA**, serotonin) and impairment of excitatory (glutamate, catecholamines) neurotransmitter systems, resulting in **enhanced neural inhibition**.

Common Precipitating Factors for Recurrent Hepatic Encephalopathy

- Has there been a change in general condition or diet?
- Look for:
 - GI bleeding
 - Infection (especially spontaneous bacterial peritonitis)
 - Excessive dietary protein intake (which can precipitate it)
 - Constipation (delayed motility → more ammonia absorbed → use a laxative)
 - Electrolyte abnormalities (decreased potassium, increased or decreased sodium)
 - Azotemia, dehydration, over-diuresis
 - Sedative use (would be cleared slower in liver disease)
 - Hepatic insults (viral infection, toxic damage, surgery, hepatocellular carcinoma, new portal vein thrombosis)

DDx for Hepatic Encephalopathy (other than liver disease) (Don't need to know)

- Intracranial lesions (hemorrhage, infarct, tumor, abscess)

- Infections (meningitis, encephalitis, sepsis)
- Metabolic encephalopathy (hyper or hypoglycemia)
- Alcohol-related disorder (intoxication, withdrawal, Wernicke's encephalopathy)
- Drug toxicity (sedatives or psychoactive drugs)
- Postictal encephalopathy
- Primary neuropsychiatric disorders
- Use **West Haven Criteria** to grade the level of hepatic encephalopathy. Grade 1 is trivial lack of awareness, shorted attention span, impaired performance in addition. Grade 4 is coma.

Treatments for Hepatic Encephalopathy

- Protein restriction → falling out of favor
- Use **lactulose**, an indigestible sugar (treatment of favor)
 - Lactulose is a non-absorbable, synthetic disaccharide that has multiple effects on gut flora and, therefore, several potential MoA's.
 - Its most obvious effect is as laxative; it serves to **decrease the gut production and absorption of ammonia**
 - Lactulose dosing should be titrated to 3 – 4 loose bowel movement a day. Due to erratic dose-response curves, patients are often both over and under-dosed.
 - Too much lactulose = lots of diarrhea = fluid and electrolyte depletion and your patients despise you
 - Too little lactulose = no therapeutic effect
 - Lactulose can be given per NG tube or as an enema as needed.
- Poorly-absorbed antibiotics
 - Poorly absorbed oral antibiotics to decrease the population of urease + gut bacteria
 - The "classics" are metronidazole (Flagyl) and neomycin
 - Alternative choices include vancomycin and rifaximin (being newly re-discovered)

Liver Transplantations

- 5-year survival for liver transplantation is up to 80%
- Decisions about transplantation for patients are made exclusively based on MELD score, not how long they are on the transplant list.
- With transplant, most patients can reverse the hepatorenal syndrome (because there is no **INTRINSIC** damage to the kidney).