PORTAL HYPERTENSION and its COMPLICATIONS

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Appreciation for their contributions

Alvaro Koch

Paul Angulo
OBJECTIVES:
- Describe uniqueness of hepatic vasculature
- Discuss how cirrhosis increases portal venous pressure
- Discuss splenomegaly and resulting thrombocytopenia as a “footprint” of portal hypertension
- Review treatment of esophageal and gastric varices
- Review treatment of ascites, SBP, and HRS
Portal Hypertension does NOT equal Liver Failure
(or need for a Liver Transplant)
CONCEPTS OF LIVER DYSFUNCTION

- **LIVER FAILURE**
  - Decreased organic anion excretion
  - Decreased protein synthesis
  - Altered intermediate metabolism
  - Decreased drug & steroid metabolism
  - Manifestations:
    - Hyperbilirubinemia
    - Low albumin, Prolonged PT
    - High ammonia (PSE), Low glucose
    - Drug sensitive, Feminization

- **LIVER CELL NECROSIS**
  - This is "hepatitis"
  - Manifestations:
    - AST & ALT elevations

- **CHOLESTASIS**
  - Disease process involving biliary system (intra- or extrahepatic).
  - Manifestations:
    - ALP & GGT ("Induced" enzymes)
    - Hyperbilirubinemia, Pruritus

- **CIRRHOSIS**
  - Fibrosis of liver parenchyma leading to portal hypertension
  - Manifestations:
    - Esophageal varices & portal gastropathy
    - Ascites,
    - Hypersplenism -low platelets, low WBC

**EACH OF THE ABOVE CAN OCCUR ALONE,**
..........................................................**BUT USUALLY OCCUR IN SOME COMBINATION**
Normal Vascular Anatomy

Hepatic Artery
- 20-25% blood flow
- Pressure 100 mmHg

Portal Vein
- 75-80% blood flow
- Pressure 4-5 mmHg

Sinusoid

Liver

Coronary vein

Splenic vein

Inferior vena cava

Superior mesenteric vein

Inferior mesenteric vein
Hepatic Microanatomy – Portal Triad

- Portal Vein  
  centripedal
- Hepatic Artery and periductal plexus  
  centripedal
- Bile duct  
  centrifugal

Lymphatics  
(Space of “Mall”)  
“Limiting Plate”
The permeability of the hepatic sinusoid varies in health and disease.

In cirrhosis, the hepatic sinusoid is less leaky.

The normal sinusoid is "leaky".
Cirrhotic Liver

ARCHITECTURAL LIVER DISRUPTION IS THE MAIN MECHANISM THAT LEADS TO AN INCREASED INTRAHEPATIC RESISTANCE

Distorted sinusoidal architecture leads to increased resistance

Portal vein

Ascites fluid

Portal systemic collaterals

Splenomegaly
IN THE NORMAL LIVER, NITRIC OXIDE PLAYS AN IMPORTANT ROLE IN THE REGULATION OF INTRAHEPATIC RESISTANCE

Normally Nitric Oxide (NO) Plays A Major Role in Regulating Intrahepatic Resistance
In Cirrhosis, Nitric Oxide (NO) Activity is Reduced and Vasoconstrictors (VC) are Increased
Portal Hypertension

Sodium and water retention

Vasodilation (SVR)

Shear stress

Bacterial translocation

Ascites

Nitric Oxide

Role of Nitric Oxide in Splanchnic and Systemic Vasodilatation

Hyperdynamic circulation

Plasma volume expansion

Sodium and water retention

Vasodilation (↓SVR)
Vascular disturbances in portal hypertension  
and sites of action of portal pressure-reducing therapies
Classification of portal hypertension

Arterio-portal fistula

Vijay H. Shah and Patrick S. Kamath - 2016
Sleisenger and Fordtran's Gastrointestinal and Liver Disease – 10th Ed, Chapter 92, 1524-1552.
Portal Pressure Measurements

- The hepatic venous pressure gradient (HVPG) is obtained by subtracting the free hepatic venous pressure (FHVP) from the wedged hepatic venous pressure (WHVP):

\[ \text{HVPG} = \text{WHVP} - \text{FHVP} \]

- The FHVP acts as an internal zero to correct for extravascular, intraabdominal pressure increases (e.g., ascites)
Normal HVPG is 3-5 mmHg

Inferior vena cava
Hepatic veins

Sinusoidal pressure = 5 mmHg

Portal vein
PVP = 6 mmHg

WHVP = 5 mmHg

HVPG* = 5 - 2 = 3 mmHg

FHVP = 2 mmHg
HVPG is Increased in Sinusoidal Portal Hypertension

Sinusoidal pressure = 20 mmHg

Blocked inter-sinusoidal communications (poor pressure dissipation)

Portal vein
PVP = 20 mmHg

Sinusoidal pressure = 20 mmHg

WHVP = 20 mmHg

Hepatic veins

HVPG = 18 mmHg

FHVP = 2 mmHg
Use of Hepatic Vein Pressure Gradient in the Differential Diagnosis of Portal Hypertension

<table>
<thead>
<tr>
<th>Type of Portal Hypertension</th>
<th>WHVP</th>
<th>FHVP</th>
<th>HVPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehepatic</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Presinusoidal</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Sinusoidal</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Postsinusoidal</td>
<td>Increased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Posthepatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>Increased</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>—</td>
<td>Hepatic vein cannot be cannulated</td>
<td>—</td>
</tr>
</tbody>
</table>
Natural History of Chronic Liver Disease

Development of complications:

- Ascites, SBP and HRS
- Variceal hemorrhage
- Encephalopathy
- Jaundice

Chronic liver disease → Compensated cirrhosis → Decompensated cirrhosis → Death

Liver Transplant
AN INCREASE IN PORTAL VENOUS INFLOW SUSTAINS PORTAL HYPERTENSION

Splenomegaly leads to Thrombocytopenia

85 – 90% of thrombocytopenia is due to splenic sequestration
10 – 15% is due to decreased hepatic thrombopoietin production

BUT LOW PLATELETS ARE A “FOOTPRINT” OF PORTAL HTN AND NOT USUALLY A CLINICAL PROBLEM
SUMMARY OF THE PATHOGENESIS OF PORTAL HYPERTENSION

VARICES – Why do they Form?

Cirrhosis

↑ Resistance to portal flow

Portal pressure

↓ Splanchnic arteriolar resistance

↓ Portal blood inflow

Varices
Varices Increase in Diameter Progressively

- No varices
- Small varices
- Large varices

Merli et al. J Hepatol 2003;38:266
Drugs Used in the Treatment of Portal Hypertension

Drugs That Decrease Portal Blood Flow

Nonselective \( \beta \)-adrenergic blocking agents

\((\text{But we avoid with refractory ascites and low BP})\)
- Propranolol (bid dosing)
- Nadolol (qd dosing and fewer side effects)
- Carvedilol (also \( \alpha \)-antagonist – don’t exceed 12.5 bid b/c hypotension)

Somatostatin and its analogs (octreotide, lanreotide, vapreotide)
Vasopressin and terlipressin (…latter not available in US)

Drugs That Decrease Intrahepatic Resistance

\( \alpha_1 \)-Adrenergic blocking agents (e.g., prazosin – but causes hypotension)
Angiotensin receptor blocking agents (but can lead to renal failure)
Nitrates (rarely used anymore due to side effects)
Endoscopic Variceal Band Ligation

- Bleeding controlled in 90%
- Rebleeding rate 30%
Transjugular Intrahepatic Portosystemic Shunt

- Hepatic vein
- Portal vein
- Splenic vein
- Superior mesenteric vein

TIPS
Algorithm for the **Primary Prophylaxis** of esophageal variceal hemorrhage in patients with cirrhosis

![Algorithm Diagram]
Predictors of hemorrhage:

- Variceal size
- Red signs
- Child B/C

Variceal hemorrhage


Varix with red signs
Algorithm for **Acute Bleeding** esophageal varices

1. **Acute bleeding from esophageal varices**
   - Resuscitation
   - Vasoactive agent (e.g., octreotide)
   - Antibiotic (e.g., norfloxacin)
   - Transfusion to hematocrit value of 24%

2. Upper endoscopy
   - Variceal ligation (or sclerotherapy)

3. **Bleeding controlled**
   - Repeat endoscopic therapy

4. **Bleeding controlled**
   - Balloon tamponade
   - Secondary prophylaxis (see Fig. 92-15)

5. **Child-Pugh class B**
   - or **C**
   - or **MELD score >18 with transfusion requirement for >4 units of RBCs**

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Vijay H. Shah and Patrick S. Kamath - 2016
Sleisenger and Fordtran's Gastrointestinal and Liver Disease – 10th Ed, Chapter 92, 1524-1552
Algorithm for the **Prevention of Recurrent** variceal bleeding (secondary prophylaxis).

Vijay H. Shah and Patrick S. Kamath - 2016
*Sleisenger and Fordtran's Gastrointestinal and Liver Disease* – 10th Ed, Chapter 92, 1524-1552
A. Active bleeding from a gastric varix (arrowhead) can be seen.  
B. Bleeding from the varix (straight arrow) is controlled following injection.
Algorithm for the management of **Bleeding Gastric Varices** in patients with portal hypertension

Vijay H. Shah and Patrick S. Kamath - 2016
Sleisenger and Fordtran's Gastrointestinal and Liver Disease – 10th Ed, Chapter 92, 1524-1552
ENDOSCOPIC IMAGES OF MILD AND SEVERE PORTAL HYPERTENSIVE GASTROPATHY

Mild

Severe

Mosaic pattern

Mosaic pattern + red spots

Carpinelli et al. Ital J Gastroenterol Hepatol 1997; 29:533
Types of Gastric Antral Vascular Ectasia

Typical GAVE “watermelon stomach”

Diffuse GAVE
## Comparison of Portal Hypertensive Gastropathy (PHG) and Gastric Antral Vascular Ectasia (GAVE)

<table>
<thead>
<tr>
<th>Feature</th>
<th>PHG</th>
<th>GAVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Proximal stomach</td>
<td>Distal stomach</td>
</tr>
<tr>
<td>Mosaic pattern</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Red color signs</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Findings on gastric mucosal biopsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombi</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Spindle cell proliferation</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Fibrohyalinosis</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Treatement</strong></td>
<td>If bleeding:</td>
<td>Endoscopic therapies:</td>
</tr>
<tr>
<td></td>
<td>β-Adrenergic blocking agent</td>
<td>APC, HALO, Band ligations</td>
</tr>
<tr>
<td></td>
<td>?TIPS</td>
<td>(TIPS of no value)</td>
</tr>
</tbody>
</table>

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Sleisenger and Fordtran's Gastrointestinal and Liver Disease – 10th Ed, Chapter 92, 1524-1552
Ascites
Spontaneous Bacterial Peritonitis
and
Hepatorenal Syndrome
Cirrhosis is the Most Common Cause of Ascites

- Cirrhosis
- Peritoneal malignancy
- Heart failure
- Peritoneal tuberculosis
- Others
  - Pancreatic
  - Budd-Chiari syndrome
  - Nephrogenic ascites
Natural History of Cirrhotic Ascites

- **Portal Hypertension**
  - No Ascites
  - HVPG <10 mmHg
    - Mild Vasodilation
- **Uncomplicated Ascites**
  - HVPG <10 mmHg
    - Moderate Vasodilation
- **Refractory Ascites**
  - HVPG >10 mmHg
    - Severe Vasodilation
- **Hepatorenal Syndrome**
  - HVPG >10 mmHg
    - Extreme Vasodilation
Cirrhosis

Hepatic venous outflow block

Sinusoidal pressure
(HVPG ≥ 10-12 mmHg)

Ascites

Sodium and water retention

Arteriolar resistance (vasodilation)

Effective arterial blood volume

Activation of neurohumoral systems (renin, angiotensin, aldosterone, ADH)
Cirrhosis

↓

Arteriolar resistance (vasodilatation)

↓

Effective arterial blood volume

↓

Activation of neurohumoral systems
(aldersterone, renin, angiotensin, epinephrine, antidiuretic hormone)

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sodium retention

↓

ascites

renal vaso-constriction

↓

hepatorenal syndrome

water retention

↓

hyponatremia
Initial Workup of Ascites
Diagnostic Paracentesis

**Routine**
- PMN count
- Every tap!!
- Gram Stain
- Culture

**Albumin / Tot Protein**
- ? cirrhotic ascites

**Glucose, LDH**
- + PCR for TB
- ? secondary infection

**Optional**
- Amylase
- Cytology
  - +Chylomicron screen
  - 5cc Red Top to Spec Chem 7-1550
- ? pancreatic ascites
- ? malignant ascites
- ? SBP
The Serum-Ascites Albumin Gradient (SAAG) Correlates With Sinusoidal Pressure

$$r = 0.73$$
Ascites Can Be Characterized by Serum-Ascites Albumin Gradient (SAAG) and Ascites Protein

- **Peritoneal pathology**
  - Malignancy
  - Tuberculosis

- **Sinusoidal hypertension**
  - Cirrhosis
  - Late Budd-Chiari

- **Source of ascites**
  - Hepatic sinusoids
    - "Capillarized" sinusoid
      - Ascites protein < 2.5
    - Normal "leaky" sinusoid
      - Ascites protein > 2.5
    - Sinusoidal hypertension
    - Post-sinusoidal hypertension
      - Cardiac ascites
      - Early Budd-Chiari
      - Veno-occlusive disease
  - Peritoneum
    - Peritoneal lymph
      - Ascites protein > 2.5
    - Peritoneal pathology
      - Malignancy
      - Tuberculosis
Medical Management of Ascites

- **Sodium restriction (2 gm) most important**
  
  Must restrict Na in **IV fluids**, too
  
  Careful patient education (get Dietary Consult)

- **Prolonged bedrest never good**

- **Start appropriate diuretics:**
  
  K+-sparing (e.g. spironolactone) – start at 100mg/d
  
  +/- Loop diuretic (furosemide)

- **NSAIDs must be avoided**

- **Stop ACE inhibitors and ARBs**

- **Follow electrolytes and creatinines**

- **Can do LVPs electively**
Definition and Types of REFRACTORY Ascites

Occurs in ~10% of cirrhotic patients

- **Diuretic-intractable ascites** 80%
  Therapeutic doses of diuretics cannot be achieved because of diuretic-induced complications

- **Diuretic-resistant ascites** 20%
  No response to maximal diuretic therapy (400 mg spironolactone + 160 mg furosemide/day)

- Most of the time the patient is not following Na+ restriction

Arroyo et al. Hepatology 1996; 23:164
Management Options for Refractory Ascites

- Large Volume Paracentesis
- Transjugular Portosystemic Shunt
- +Peritoneal-Atrial (LaVeen or Denver) Shunts
Large Volume Paracentesis for Refractory Ascites

Cirrhosis

- Intrahepatic resistance
- Sinusoidal pressure

Ascites

- Sodium and water retention

- Activation of neurohumoral systems

LVP + Albumin

Arteriolar resistance (vasodilation)

Effective arterial blood volume
MUST USE ALBUMIN AFTER LVP - (6g albumin/L removed if >5 L)

LVP Without Albumin Leads to Increases in Renin, Renal Failure and Hyponatremia

![Plasma renin activity (ng/mL/h)](chart)

- **Before Albumin**: 4 ng/mL/h
- **After Albumin**: 8 ng/mL/h
- **Before No albumin**: 12 ng/mL/h
- **After No albumin**: 20 ng/mL/h

**Post-paracentesis circulatory dysfunction (PCD):**

- **Before No albumin**: p<0.1
- **After No albumin**: p<0.1

**Renal failure / Hyponatremia**

- **Before No albumin**: ns
- **After No albumin**: 20%

Gines et al., Gastroenterology 1988; 94:1493
Cirrhosis

- Intrahepatic resistance
- Sinusoidal pressure

TIPS FOR REFRACTORY ASCITES

- Arteriolar resistance (vasodilation)
- Effective arterial blood volume
- Activation of neurohumoral systems
- Sodium and water retention

Ascites
Spontaneous Bacterial Peritonitis (SBP) is the Most Common Infection in Cirrhotic Patients

- SBP
- UTI
- Pneumonia
- Procedure-related
- Spontaneous

Fernández et al., Hepatology 2002; 35:140
Mortality Associated with SBP has been Decreasing by Early Diagnosis and Treatment
Diagnosis and Management of Spontaneous Bacterial Peritonitis

**Diagnostic Paracentesis**

- **PMN>250?**
  - **NO**
    - **Culture Positive?**
      - **NO**
        - **TREATMENT NOT INDICATED**
      - **YES**
        - **Repeat Paracentesis**
  - **YES**
    - **Culture Positive?**
      - **NO**
        - **TREATMENT NOT INDICATED**
      - **YES**
        - **PMN>250?**
          - **NO**
            - **TREATMENT NOT INDICATED**
          - **YES**
            - **TREATMENT INDICATED**
Treatment of SBP

- Antibiotics for initial empiric therapy
  - i.v. cefotaxime, amoxicillin-clavulanic acid
  - oral ofloxacin (uncomplicated SBP)
  - avoid aminoglycosides

- Give albumin if Tbili >4.0, creat >1.0
  - 1.5g/kg day 1 and 1g/kg day 3.
  - Prefer 25% albumin b/c of volume and Na load

- Minimum duration of antibiotics: 5 days

- Re-evaluation if ascitic fluid PMN count has not decreased by at least 25% after 2 days of treatment
Hepatorenal Syndrome:

Cirrhosis

- Intranepathic resistance
- Sinusoidal pressure
- Refractory ascites

Systemic arteriolar resistance

Effective arterial blood volume

Activation of neurohumoral systems

- Sodium and water retention
- Refractory ascites

Renal vasoconstriction

Worsening Liver Disease

Vasodilators
- LVP w/o albumin
- Infection

Diuretics
- Diarrhea
- Hemorrhage

Hepatorenal Syndrome:

Worse;

- Diuretics
- Diarrhea
- Hemorrhage
Two Types of Hepatorenal Syndrome

Type 1
- Rapidly progressive renal failure (2 weeks)
- Doubling of creatinine to >2.5 or halving of creatinine clearance (CrCl) to <20 ml/min

Type 2
- More slowly progressive
- Creatinine >1.5 mg/dL or CrCl < 40 ml/min
- Associated with refractory ascites

Arroyo et al., Hepatology 1996; 23:164
Survival in Different Types of Hepatorenal Syndrome (HRS)

Gines et al., Lancet 2003; 362:1819
Management of Hepatorenal Syndrome

- Stop all nephrotoxic agents (ACEIs, ARBs, NSAIDs, diuretics)
- Antibiotics for infections
- IV albumin—bolus of 1 g/kg/day on presentation (maximum dose, 100 g daily). Continue at dose of 20-60 g/d to maintain CVP between 10-15 cm H₂O
- Vasopressor therapy (in addition to albumin):
  - Midodrine and octreotide—begin midodrine at 2.5-5 mg orally 3 times daily and increase to a maximum dose of 15 mg 3 times daily. Titrate to an MAP increase of at least 15 mm Hg; begin octreotide at 100 µg subcutaneously 3 times daily and increase to a maximum dose of 200 µg subcutaneously 3 times daily, or begin octreotide at a 25-µg IV bolus and continue at a rate of 25 µg/hr
  - OR
  - Norepinephrine—0.1-0.7 µg/kg/min as an IV infusion. Increase by 0.05 µg/kg/min every 4 hr and titrate to an MAP increase of at least 10 mm Hg. Duration of vasopressor treatment is generally a maximum of 2 weeks until reversal of hepatorenal syndrome or liver transplantation

Evaluation for liver transplantation if a candidate

Moises Ilan Nevah and Michael B. Fallon 2016
Sleisenger and Fordtran's Gastrointestinal and Liver Disease, Chapter 94, 1577-1590
Thank You for Your Attention

Questions?