Portal Hypertension
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Portal Hypertension – Defined by HVPG

Hepatic Veins

Portal Vein

HVPG

Wedged hepatic vein pressure (balloon inflated)
- Free hepatic vein pressure (balloon deflated)
= Hepatic Venous Pressure Gradient (HVPG)

HVPG >5 to <10mmHg = mild portal HTN
HVPG ≥10mmHg = clinically significant portal HTN (CSPH)
HVPG ≥12mmHg = risk of variceal hemorrhage
HVPG & Types of Portal HTN

<table>
<thead>
<tr>
<th>Type of Portal HTN</th>
<th>Wedged Hepatic Vein Pressure</th>
<th>Free Hepatic Vein Pressure</th>
<th>HVPG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-hepatic (portal vein thrombosis)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Pre-sinusoidal (schistosomiasis, noncirrhotic portal HTN)</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Sinusoidal (cirrhosis)</td>
<td>↑</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>Post-hepatic (R heart failure)</td>
<td>↑</td>
<td>↑</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Clinical Stages of Cirrhosis

- **Compensated**
  - <10mmHg (Mild)
  - Absent
  - Prevent CSPH

- ** Decompensated (Ascites, HE, VH)**
  - ≥10mmHg (CSPH)
  - Present
  - Prevent Decomp
  - Prevent Decomplasia

- **Goals of Therapy**
  - Secondary Prophylaxis
  - Prevent further decomp/death
  - Prevent VH w/out other complications
  - Previous VH w/other complications
### Decompensation & Mortality Risk

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>1-Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1</td>
<td>Compensated, No Varices, No Ascites</td>
<td>7%</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Compensated, + Varices, No Ascites</td>
<td>6.6%</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Compensated, + Ascites, +/- Varices</td>
<td>7.6%</td>
</tr>
<tr>
<td>Stage 4</td>
<td>Decompensated, Bleeding, +/- Ascites</td>
<td>57%</td>
</tr>
</tbody>
</table>

**DEATH** (1-Year Mortality)

- 1%
- 4.4%
- 3.4%
- 20%
- 4%
- 57%

*D'Amico G. J Hepatol 2006;44:217*

### HVPG & Bleeding Risk

**Variceal Bleeders** (n=49) vs **Non-Bleeders** (n=44)

- **HVPG ≥12 mmHg**
- **p < 0.001**

**Reduction of HVPG:**
- Bleeding POR 0.17 (0.09-0.33)
- Mortality POR 0.39 (0.19-0.81)

Screening & 1° Prophylaxis for Varices

Patient Characteristics
- Cirrhosis
  - No Prior Screening
- Compensated Cirrhosis
  - No Varices
- Compensated Cirrhosis
  - Small Varices
- Decompensated Cirrhosis
  - +/- Small Varices
- Medium/Large Varices

Screening Interval
- At Time of Diagnosis
- 2 yrs (ongoing injury)
  - 3 yrs (quiescent)
  - At Time of Decomp
- 1 yr (ongoing injury)
  - 2 yrs (quiescent)
  - At Time of Decomp
- Yearly

1° Prophylaxis
- NSBB if high risk stigmata
- NSBB if small varices
- NSBB or EVL (no EGD after NSBB)

1° Prophylaxis - Key Points
- Low risk for development of varices = liver stiffness <20 kPa & platelets >150,000 (AASLD, Baveno VI)
- No role for NSBB in preventing formation of varices
- NSBB (propranolol, nadolol, carvedilol)
  - β-1 adrenergic blockade = ↓ heart rate, ↓ cardiac index
  - β-2 adrenergic blockade = ↓ splanchnic flow via unopposed α-adrenergic vasoconstriction
  - Carvedilol = NSBB + weak α-1 blockade (↓ hepatic resistance)
  - Goal HR 55-60; maintain SBP ≥90
- EVL = q 2-8 wks until eradication, then at 3-6 mo, then q 6-12 mo
- No role for combination NSBB + EVL in 1° prophylaxis
- TIPS not recommended
Acute Bleeding & 2° Prophylaxis

Acute Management:
- EGD w/in 12 hrs of admission once hemodynamically stable
- PRBC transfusions w/ goal hemoglobin 7-9
- Antibiotic prophylaxis (up to 7 days): IV ceftriaxone 1g/24hr
- Vasoactive therapy: octreotide (somatostatin analogue) x 2-5 days
- Initiate NSBB after octreotide discontinued
- Consider “early” TIPS w/in 72 hrs if decomp (CTP B/C) w/ active bleeding on EGD
- Rescue therapy = TIPS
- Post-TIPS: stop octreotide, no need for NSBB or EVL

2° Prophylaxis = NSBB + EVL

Beta Blockers – Treatment Considerations

- β adrenergic blockade = ↓ HVPG when splanchnic vasodilation & hyperdynamic circulation is present (CSPH)
- Hyperdynamic circulation = adrenergic-mediated ↑ cardiac output is compensatory to ↓ effective circulatory volume
- Risk: NSBB may impair HR increase during circulatory challenge
NSBB – Window Hypothesis

• NSBB do not provide benefit:
  • Compensated cirrhosis
  • No varices

• NSBB are beneficial:
  • CSPH (HVPG ≥10 mmHg)
  • Medium/large varices (1° prophylaxis)
  • Variceal hemorrhage (2° prophylaxis)

• Consider reduce/discontinue NSBB:
  • Refractory ascites
  • SBP <90 or MAP <80
  • Serum Na <130
  • AKI or HRS
  • Sepsis
  • SBP
  • Hemorrhagic shock
  • Carvedilol → caution w/ renal insufficiency, hypotension

If NSBB d/c, resume EVL

NSBB – Risk vs. Benefit

**Risk**

• Refractory ascites (*prospective cohorts*)
  • ↑ mortality; ↑ paracentesis-induced circulatory dysfunction

• SBP
  • ↑ mortality; ↑ AKI/HRS

• Ascites (waitlist registrants); severe alcoholic hepatitis
  • ↑ AKI

**Benefit**

• Variceal hemorrhage (1° & 2° prophylaxis)
• Cirrhosis + ascites
  • ↓ waitlist mortality; ↓ hospitalization
• Severe/refractory ascites (*Post-hoc, sativaptan RCTs*) – no effect on mortality
• ACLF (*limited data*)

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NSBB & Short-term Benefit in ACLF

- Pre-existing NSBB therapy - retrospective
  - N=349, ACLF (EASL-CLIF consortium, CANONIC study)
  - ↓ short-term mortality, ↓ ACLF grade

- Carvedilol – prospective RCT, initiated at ACLF presentation
  - N=136, ACLF, no/small esophageal varices, HVPG ≥12 mmHg
  - ↓ short-term mortality, ↓ AKI, ↓ SBP, ↓ ACLF grade

- NSBB may have beneficial effect on gut motility/permeability & systemic inflammation (↓ SIRS)
- Mean arterial BP may define benefit of NSBB in ACLF:
  - ↓ MAP (≤ 82 mmHg) = ↓ benefit


Ascites

- New onset ascites = diagnostic paracentesis
- No role for platelets/FFP prior to paracentesis
- First-line therapy: Na-restricted diet, spironolactone +/- furosemide
- Avoid: NSAIDS, ACE-inhibitors, ARBs
- IV albumin for large volume paracentesis (>4-5L):
  - 6-8g/L fluid removed
SBP – Treatment

- Diagnosis: PMN > 250 cells/mm$^3$
- IV 3$^{rd}$ gen. cephalosporin + IV albumin (1.5g/kg on day 1 + 1.0g/kg on day 3)
- x 5 days therapy
- Empiric therapy if high suspicion
- Follow up paracentesis at 48hrs if:
  - Nosocomial
  - Recent β-lactam exposure
  - Atypical organism
  - Atypical response to therapy

Gines P. NEJM 1999;341:403

SBP Antibacterial Prophylaxis

Candidates for 1$^{\circ}$ SBP Prophylaxis
- Low protein ascites (<1.5 g/dL)
- Impaired renal function (creatinine ≥1.2 or BUN ≥25 or serum Na ≤130)
  (OR)
- CTP ≥9 AND bilirubin ≥3

Antimicrobial agent (daily dosing preferred)
- fluoroquinolone (norfloxacin, cipro 500mg daily)
- trimethoprim/sulfamethoxazole (160/800mg)

2$^{\circ}$ SBP Prophylaxis
- All patients with history of prior SBP
- Prospective, double-blind, placebo controlled trial
- ↓ recurrent SBP from 68% to 20% within 1 year

1° SBP Prophylaxis

- Meta-analysis, 4 RCTs; 297 patient-years follow-up
- Fluoroquinolone prophylaxis vs. placebo
- Low protein ascites (<1.5 g/dL)

- Number needed to treat (NNT) to prevent: 1st SBP episode = 7
  Bacteremia = 6
  Mortality = 12


Consequences of SBP Prophylaxis?

- Most frequent organisms historically associated with SBP = gram-negative enteric bacteria
- Increasing prevalence of gram-positive & multidrug resistant bacteria
  - MDR may be associated with SBP prophylaxis failure, ACLF
  - Up to 38% MDR in culture-positive infections associated with ACLF, including 14% with SBP (European, CANONIC study)
  - 35% with ACLF on 1°/2° SBP prophylaxis presented with SBP (N. America, NASCELDM)
  - Emerging data; limited
- Important to restrict prophylaxis to those who meet high-risk criteria

Hepatic Hydrothorax

• Occurs in approx 5% of patients with cirrhosis + ascites
• Spontaneous bacteria empyema (SBE)
  • Diagnosis: PMN >500 cells/mm³ or positive culture
  • Can occur in the absence of SBP
• Chest tube insertion contraindicated (high mortality)
• First-line therapy: Na-restricted diet, diuretics
• Consider TIPS for refractory cases

Hepatic Encephalopathy

• Identify precipitating factors
  • GI bleed, infection, hypokalemia, volume depletion, medications
• Blood ammonia level not required
• Treatment: lactulose; rifaximin to prevent overt HE recurrence
• Avoid protein restricted diet
• New onset post-TIPS:
  • No role for lactulose/rifaximin for prevention
  • Prospective RCT, incidence 33%
  • No difference treatment vs. placebo
Negative Effects of Proton Pump Inhibitors

- Potential effects:
  - Bacterial translocation
  - Altered microbiota
  - Bacterial overgrowth
- PPI therapy & cirrhosis:
  - ↑ dose/duration of PPI = ↑ risk of HE
  - minimal HE → overt HE
  - ↑ mortality
- Avoid unnecessary PPI therapy

Prospective cohort; n=310 (cirrhosis, no overt HE)
Mean follow up 14.1 ± 12.3 months
Overt HE incidence ↑ in PPI (64% vs. 25%, p<0.001)
Survival ↓ in PPI (41% vs. 81%, p<0.001)

Spontaneous Portosystemic Shunts & HE

- Assess for spontaneous portosystemic shunts (SPSS) in refractory HE
- Retrospective cohort study, n=1729; prevalence of large SPSS = 28%
- Most common = splenorenal shunt
- Size of SPSS increases with MELD score
  - ↑ SPSS size = ↑ HE
  - Presence of SPSS may affect survival in low MELD groups
  - CSPH + SPSS = ↑ decompensating events

Prospective cohort; n=310 (cirrhosis, no overt HE)
Mean follow up 14.1 ± 12.3 months
Overt HE incidence ↑ in PPI (64% vs. 25%, p<0.001)
Survival ↓ in PPI (41% vs. 81%, p<0.001)
SPSS Embolization for Refractory HE

Consider in selected patients
- MELD >11 less likely to benefit
- Potential for ↑ portal HTN (ascites, ↑ varices)
- 48% - 92% with durable response
- ↓ hospitalizations in 67% - 75%

Noncirrhotic Portal Hypertension

Presentation
- Splenomegaly, variceal hemorrhage, ascites
- Hepatic encephalopathy (SPSS)
- ± Thrombocytopenia
- Normal hepatic synthetic function

Diagnosis
- Transjugular liver biopsy
- HVPG normal ± ↑ portal venous pressure

Management
- Specific to etiology & presentation
- Anticoagulation
- EVL, NSBB, diuretic therapy, TIPS
- Liver transplantation

Causes of Noncirrhotic Portal Hypertension
- Budd-Chiari syndrome
- Extrahepatic portal vein/mesenteric thrombosis
- Infiltrative malignancy
- Hepatic sarcoidosis
- Sinusoidal obstruction syndrome (veno-occlusive disease)
- Congenital hepatic fibrosis
- Cystic fibrosis
- Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu)
- Schistosomiasis
- PBC & PSC
- Nodular regenerative hyperplasia/obliterative portal venopathy
- Vasculitides
- Right heart failure
- Idiopathic
Cirrhosis & Renal Failure

- **Infections** are a major cause of AKI.
- Mortality risk based on etiology:
  - HRS (OR 6.88)
  - Bacterial infection (OR 2.61)
  - Hypovolemia (OR 2.32)

- AKI is a defining feature of ACLF.
- In 2004-2016, 22% of cirrhosis hospitalizations = AKI (large-scale data, US; >3.6 million)
  - AKI increased 15% to 30% from 2004 to 2016
  - Hospitalization for AKI = ↑ risk of death (OR 3.75)

**Hepatorenal Syndrome: AKI vs. HRS**

<table>
<thead>
<tr>
<th>ICA-AKI Criteria</th>
<th>HRS-1 Criteria (HRS-AKI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline SCr within previous 3 months; if not available, baseline at time of presentation</td>
<td>Cirrhosis and ascites</td>
</tr>
<tr>
<td>Increase in SCr ≥0.3 mg/dL within 48 hours, or SCr increase by ≥50% from baseline within prior 7 days</td>
<td>Criteria for ICA-AKI met</td>
</tr>
<tr>
<td><strong>Stage 1</strong>: Increase SCr ≥0.3 mg/dL, or ≥1.5-fold to 2.0-fold from baseline</td>
<td>No response after 48 hrs of diuretic withdrawal + albumin 1 g/kg/day; response defined by regression of AKI to lower stage</td>
</tr>
<tr>
<td><strong>Stage 2</strong>: Increase SCr ≥2-fold to 3-fold from baseline</td>
<td>Absence of shock or nephrotoxic drugs</td>
</tr>
<tr>
<td><strong>Stage 3</strong>: Increase SCr &gt;3-fold from baseline, or SCr ≥4.0 mg/dL with increase ≥0.3 mg/dL, or initiation of RRT</td>
<td>Absence of structural kidney injury elements:</td>
</tr>
</tbody>
</table>
  - Proteinuria (>500 mg/day) |
  - Microhematuria (>50 RBC/HPF) |
  - Normal renal ultrasonography |
HRS - Management

- Assess for infection, SBP; low threshold for antibiotic therapy
- Specific treatment options
  - Albumin + midodrine/octreotide
  - Albumin + norepinephrine (if in ICU; goal MAP increase 10 mmHg)
  - Albumin + terlipressin (if available)
- TIPS (limited data, caution with clinical decomp)
- Nephrology consultation, CRRT if needed
- Transplant evaluation if candidate

- Early HRS diagnosis/treatment = ↑ response to terlipressin
- Response to terlipressin determined by ACLF grade
  - ↑ Severity of ACLF grade/organ failure = ↓ response

Hold diuretics
Albumin 1g/kg/day x 48 hrs (max dose 100g/day)

Evaluate for HRS criteria

Vasoactive therapy +
Albumin 1g/kg, then 20-40g/day

Hepatopulmonary Syndrome

- Signs/symptoms: cyanosis/clubbing, platypnea, orthodeoxia
- Screening: pulse oximetry, SaO2 <96% (specificity 84%, low sensitivity 28%)
- Contrast enhanced TTE (“bubble” echo)
  - Late appearance of bubbles (≥3 cycles) in L atrium indicates intrapulmonary vasodilation, extracardiac shunting
  - Optional: lung perfusion scan, 99mTc macroaggregated albumin (MAA) to assess contribution of HPS-induced hypoxemia if coexisting cardiopulmonary disease
- Assess for clinically significant 1° pulmonary disease
HPS – Risk Assessment & Management

• ABG determines severity; HPS = AaPO2 >15 mmHg (>20 mmHg if age >64)

<table>
<thead>
<tr>
<th>HPS Stage</th>
<th>PaO2 (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>≥80</td>
</tr>
<tr>
<td>Moderate</td>
<td>60 to &lt;80</td>
</tr>
<tr>
<td>Severe</td>
<td>50 to &lt;60</td>
</tr>
<tr>
<td>Very severe</td>
<td>&lt;50</td>
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</tbody>
</table>

• Management:
  • Supplemental O2 if PaO2 <60 mmHg
  • Coil embolization in selected cases
    • Type I (precapillary PA dilation)
    • Type II (discrete pulmonary AV fistulas)
  • TIPS (± benefit)
  • Liver transplantation

Hepatopulmonary Syndrome & Transplant

• Requirement for MELD exception points
  • Ascites, varices, splenomegaly, or thrombocytopenia
  • Shunt documented by contrast (bubble) echo or lung scan
  • PaO2 <60 mmHg on room air
  • No clinically significant 1° pulmonary disease
Portopulmonary Hypertension

• Screening: TTE (*frequently asymptomatic*)
  • RVSP <30 mmHg = NPV of 100%, but low PPV
  • If RVSP ≥50 mmHg → R heart cath
• Diagnosis: Right heart catheterization
  • mPAP ≥25 mmHg
  • PVR >3 Wood units (>240 dynes)
  • normal PCWP ≤15 mmHg
  • Volume overload: ↑mPAP, ↓ PVR, ↑ PCWP
• Mean PA pressure determines severity
• ↑ mortality without treatment

<table>
<thead>
<tr>
<th>POPH Severity</th>
<th>mPAP (mmHg)</th>
</tr>
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<tbody>
<tr>
<td>Mild</td>
<td>25 to &lt;35</td>
</tr>
<tr>
<td>Moderate</td>
<td>35 to &lt;45</td>
</tr>
<tr>
<td>Severe</td>
<td>≥45</td>
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Portopulmonary Hypertension - Treatment

• Treatment:
  • Avoid TIPS, NSBB
  • Prostacyclin analogues
  • Endothelin receptor antagonists
  • Phosphodiesterase type-5 (PDE-5) inhibitors
• Liver transplant candidacy
  • Requires therapy to achieve mPAP <35 mmHg
  • ↑ Post-operative mortality if poorly controlled
    • mPAP >35 mmHg = 50% mortality
    • mPAP >50 mmHg = 100% mortality
    • mPAP 45-50 mmHg absolute contraindication to transplant
Portopulmonary Hypertension & Transplant

- Requirement for MELD exception points
  - Initial mPAP, PVR, transpulmonary gradient
  - Documentation of treatment
  - Post-treatment:
    - mPAP <35 mmHg
    - PVR <400 dynes sec/cm5 (or) <5.1 Wood units

https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf