Portal Hypertension

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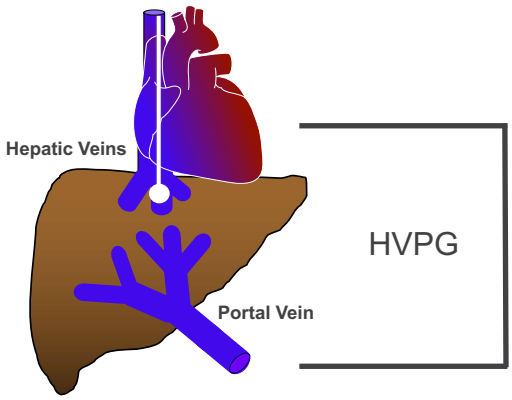
Portal Hypertension – Defined by HVPG



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

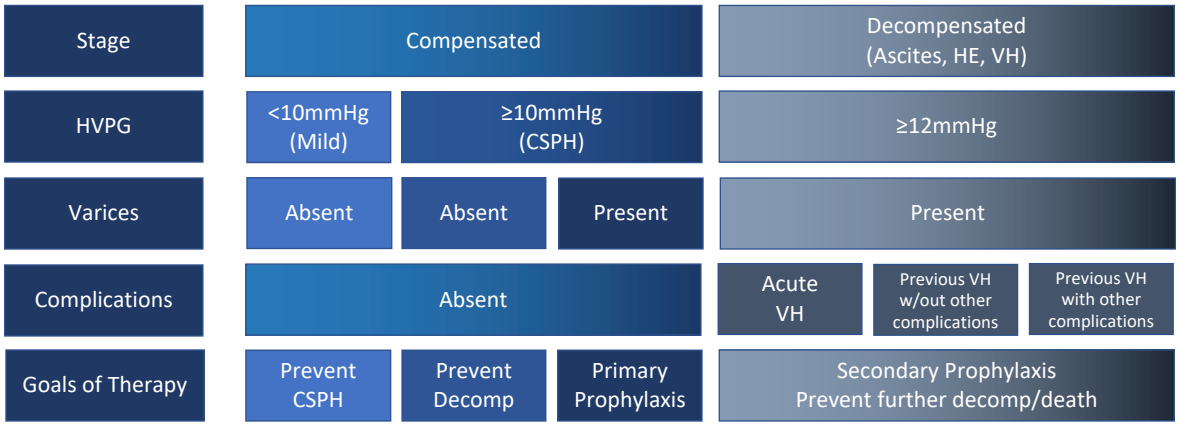
HVPG >5 to <10mmHg = mild portal HTN
HVPG ≥10mmHg = clinically significant portal HTN (CSPH)
HVPG ≥12mmHg = risk of variceal hemorrhage

Garcia-Tsao G. Hepatology 2017;65:310

HVPG & Types of Portal HTN

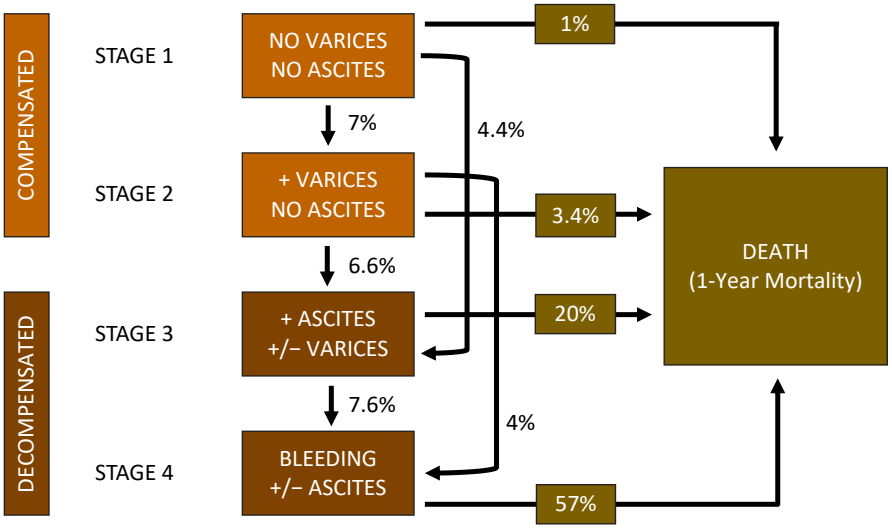
Type of Portal HTN	Wedged Hepatic Vein Pressure	Free Hepatic Vein Pressure	HVPG
Pre-hepatic (portal vein thrombosis)	Normal	Normal	Normal
Pre-sinusoidal (schistosomiasis, noncirrhotic portal HTN)	Normal	Normal	Normal
Sinusoidal (cirrhosis)	⬆	Normal	⬆
Post-hepatic (R heart failure)	⬆	⬆	Normal

Clinical Stages of Cirrhosis



Garcia-Tsao G. Hepatology 2017;65:310

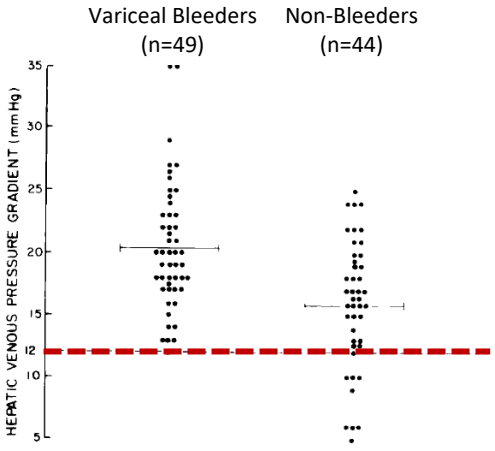
Decompensation & Mortality Risk



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

HVPG & Bleeding Risk

HVPG ≥12 mmHG

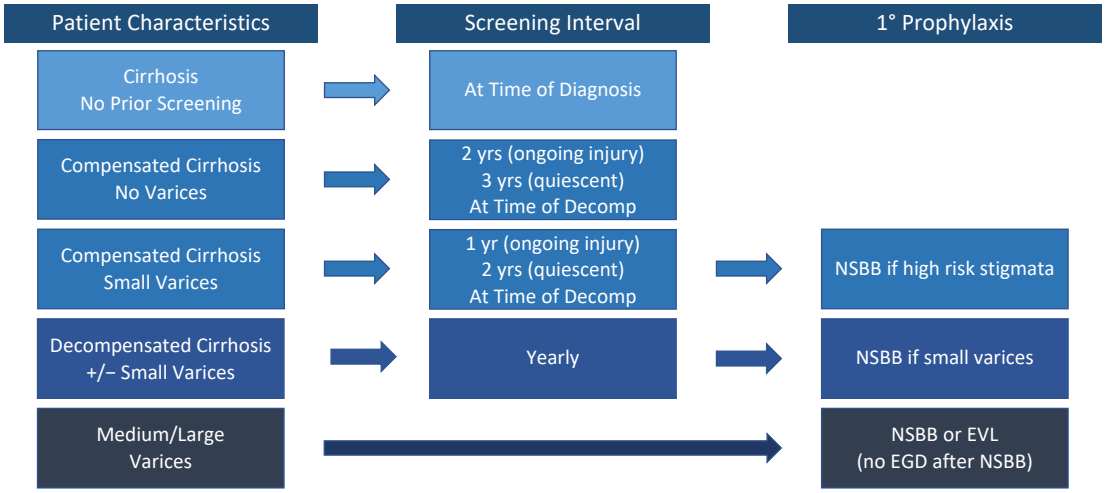


p < 0.001

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

Garcia-Tsao G. Hepatology 1985;5:419. D'Amico G. Gastroenterology 2006;131:1611

Screening & 1° Prophylaxis for Varices



Garcia-Tsao G. Hepatology 2017;65:310. de Franchis R. J Hepatol 2015;63:743

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-adrengeric 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

Garcia-Tsao G. Hepatology 2017;65:310. de Franchis R. J Hepatol 2015;63:743

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

Garcia-Tsao G. Hepatology 2017;65:310

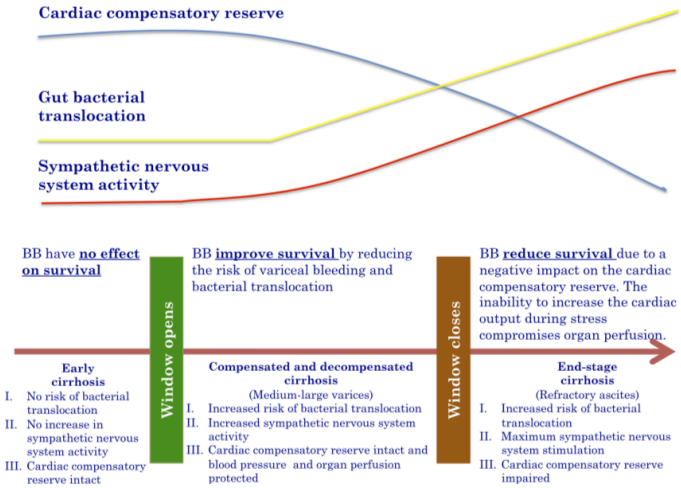
Beta Blockers – Treatment Considerations

- 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

Large volume paracentesis
Variceal hemorrhage
SBP/infections

Reiberger T. J Hepatol 2017;66:849

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

  If NSBB d/c, resume EVL
- Carvedilol → caution w/ renal insufficiency, hypotension

Krag A. Gut 2012;61:967. Reiberger T. J Hepatol 2017;66:849. Garcia-Tsao G. Hepatology 2017;65:310.

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

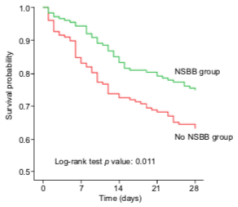
• Benefit

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

Reiberger T. J Hepatol 2017;66:849. Kim S. Liver Transpl 2017;23:733. Serste T. Hepatology 2010;52:1017. Serste T. J Hepatology 2011;55:794. Serste T. Liver Int 2015;35:1974. Mandorfer M. Gastroenterology 2014;146:1680. Leithead J. Gut 2015;64:1111. Mookerjee R. J Hepatol 2016;64:574. Bossen L. Hepatology 2016;63:1968.

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



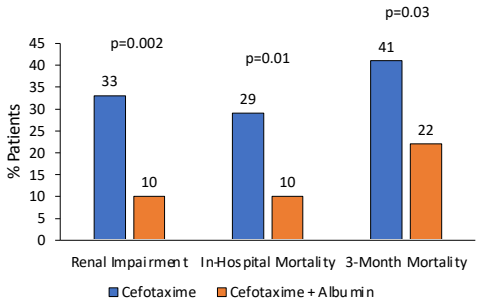
Tergast T. Aliment Pharmacol Ther 2019;50:696. Kumar M. Hepatol Int 2019;13:800. Mookerjee R. J Hepatol 2016;64:574. Reiberger T. J Hepatol 2013;58:911

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 3rd 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



Sort P. NEJM 1999;341:403

SBP Antibacterial Prophylaxis

Candidates for 1° 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

2° SBP Prophylaxis

All patients with history of prior SBP

2° Prophylaxis:
Prospective, double-blind, placebo controlled trial
↓ recurrent SBP from 68% to 20% within 1 year

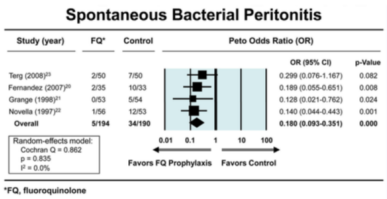
Antimicrobial agent (daily dosing preferred)

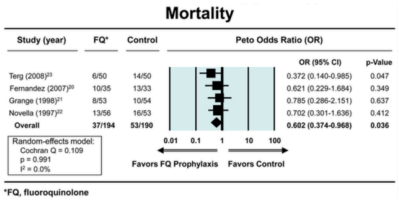
- fluoroquinolone (norfloxaxin, cipro 500mg daily)
- trimethoprim/sulfamethoxazole (160/800mg)

Gines P. Hepatology 1990;12:716.

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

Loomba R. Clin Gastroenterol Hepatol 2009;7:487

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, NASCELD)
  - Emerging data; limited
- Important to restrict prophylaxis to those who meet high-risk criteria

Fernandez J. J Hepatol 2019;70:398. Bajaj J. Am J Gastroenterol 2019;114:599

Hepatic Hydrothorax

- Occurs in appox 5% of patients with cirrhosis + ascites
- Spontaneous bacteria empyema (SBE)
  - Diagnosis: PMN >500 cells/mm^3 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

Riggio O. J Hepatol 2005;42:674.

Negative Effects of Proton Pump Inhibitors

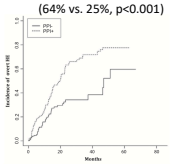
- Potential effects:
  - Bacterial translocation
  - Altered microbiota
  - Bacterial overgrowth
- PPI therapy & cirrhosis:
  - ↑ dose/duration of PPI = ↑ risk of HE
  - minimal HE → overt HE
  - ↑ mortality
- Avoid unnecessary PPI therapy

Risk of Subsequent Hepatic Encephalopathy Among Patients With Cirrhosis, Stratified by PPI

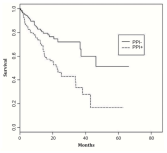
	Risk of hepatic encephalopathy		
	Users, n (%)	Nonusers, n (%)	OR (95% CI)[a]
Pantoprazole	120 (10.3)	42 (3.6)	**2.05 (1.39–3.03)**
Lansoprazole	193 (16.6)	100 (8.6)	**1.40 (1.05–1.87)**
Omeprazole	125 (10.7)	64 (5.5)	**1.38 (1.03–1.96)**
Esomeprazole	176 (15.1)	95 (8.1)	**1.35 (1.01–1.71)**
Rabeprazole	57 (4.9)	28 (2.4)	1.43 (0.87–2.34)

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)



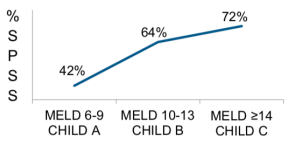
Survival ↓ in PPI (41% vs. 81%, p<0.001)

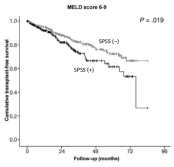


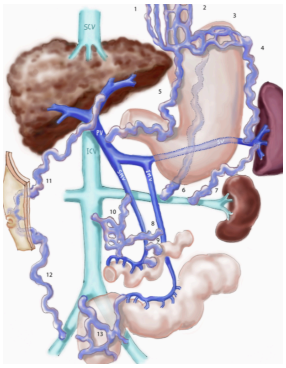
Tsai C. Gastroenterology 2017;152:134. Nardelli S. Hepatology 2019;70:640.

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

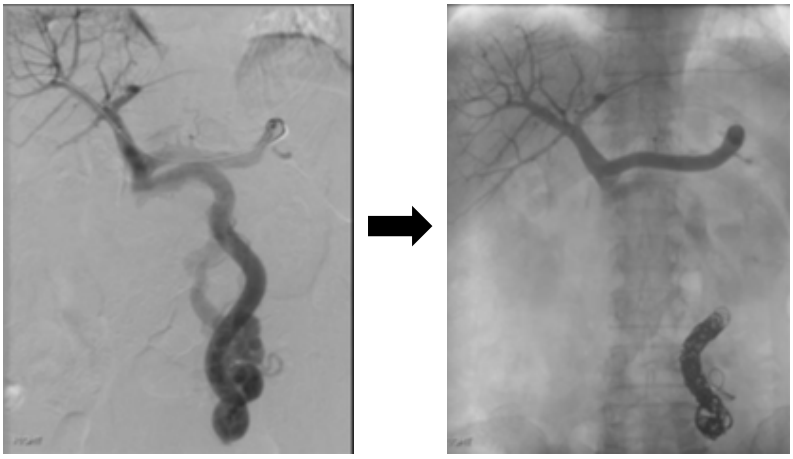






Simon-Talero M. Gastroenterology 2018;154:1694. Guillaume M. Gastroenterology 2018;154:1569

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%

Laleman W. Hepatology 2013;57:2448. Lynn A. Liver Transpl 2016;22:723.

Noncirrhotic Portal Hypertension

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 telangectasia (Osler-Weber-Rendu)
Schistosomiasis
PBC & PSC
Nodular regenerative hyperplasia/obliterative portal venopathy
Vasculitidies
Right heart failure
Idiopathic

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

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

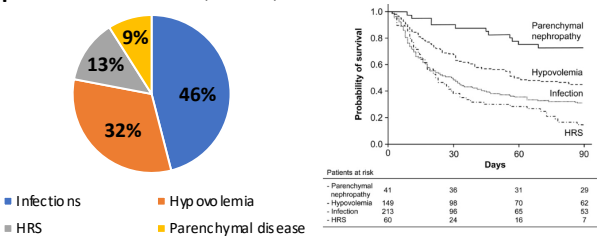
Management
- Specific to etiology & presentation
- Anticoagulation
- EVL, NSBB, diuretic therapy, TIPS
- Liver transplantation

Fiel M. Semin Diag Pathol 2019;36:395. Da B. Current Opin Gastroenterol 2018;34:140

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)

Consecutive hospitalized patients, cirrhosis & renal failure (n=463)



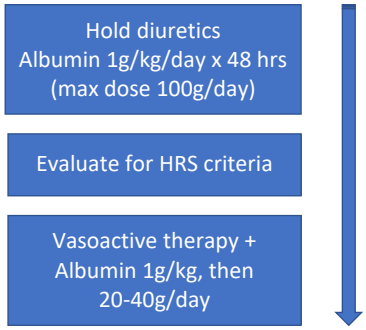
Martin-Llahi M. Gastroenterology 2011;140:488. Desai A. J Hepaotl 2020;Epub

Hepatorenal Syndrome: AKI vs. HRS

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

Angeli P. J Hepatol 2015;62:968

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

Angeli P. J Hepatol 2015;62:968. Singh V. J Hepatol 2012;1293. Piano S. Clin Gastroenterol Hepatol 2018;16:1792

Hepatopulmonary Syndrome

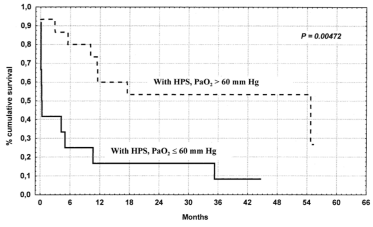
- Signs/symptoms: cyanosis/clubbing, platypnea, orthodeoxia
- Screening: pulse oximetry, SaO2 <96% *(specificity 84%, low sensitivity 28%)*
- Contrast enhanced TTE ("bubble" echo)
  - Late appearance of bubbles (≥3 cycles) in L atrium indicates intrapulmonary vasodilation, extracardiac shunting
  - Optional: 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

Krowka M. Transplantation 2016;100:1440. Forde K. Hepatology 2019;69:270.

HPS – Risk Assessment & Management

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

HPS Stage	PaO2 (mmHg)
Mild	≥80
Moderate	60 to <80
Severe	50 to <60
Very severe	<50



- 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

Schenk P. Gastroenterology 2003;125:1042. Krowka M. Transplantation 2016;100:1440

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

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

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

POPH Severity	mPAP (mmHg)
Mild	25 to <35
Moderate	35 to <45
Severe	≥45

Krowka M. Transplantation 2016;100:1440. Raevens S. Liver Transpl 2013;19:602

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

Krowka M. Transplantation 2016;100:1440. Krowka M. Liver Transpl 2000;6:443

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