ICU MANAGEMENT OF ACUTE ON CHRONIC LIVER FAILURE

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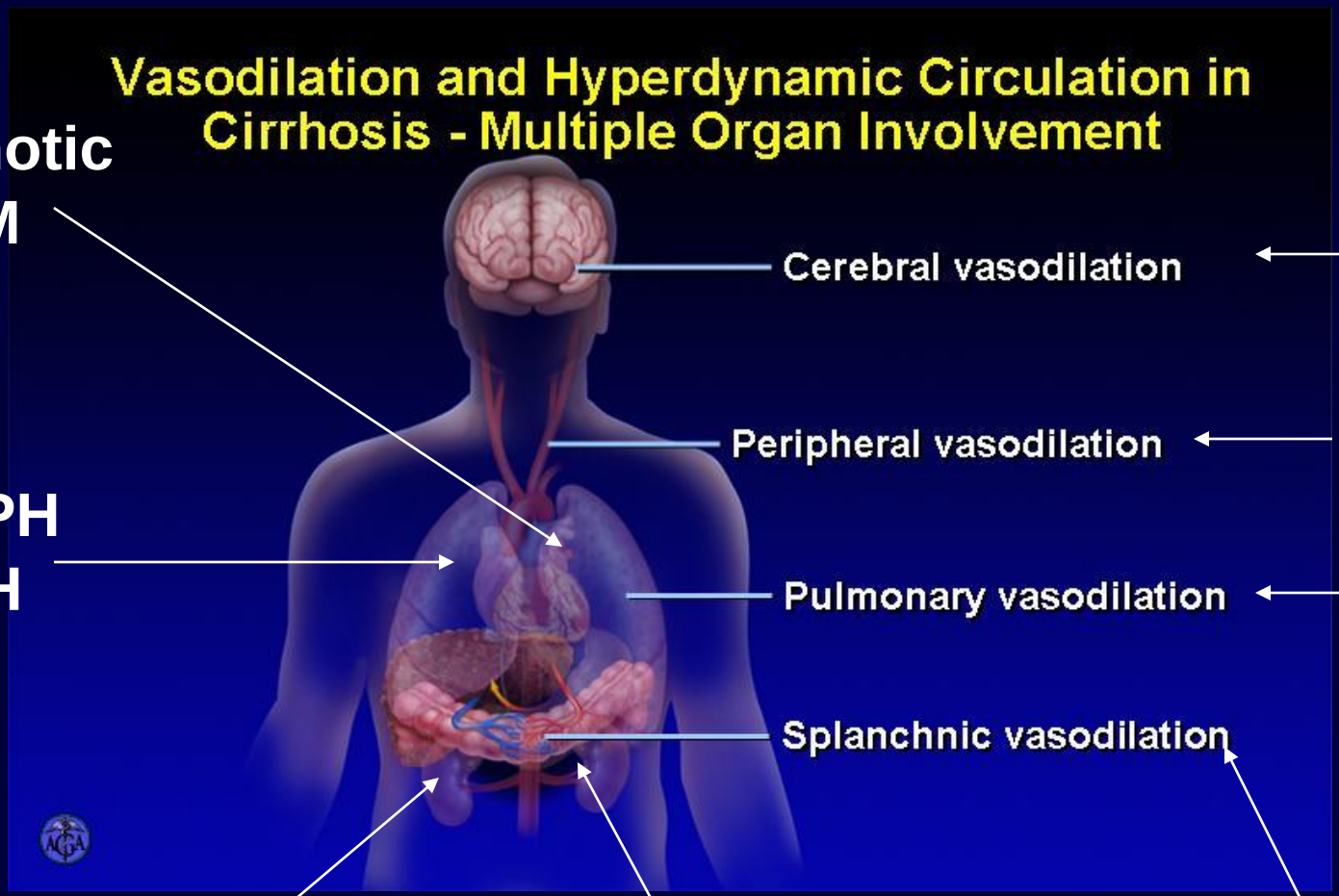
Disclosures: None

Acute on Chronic Liver Failure (ACLF)



Cirrhotic CM

HE

Shock

PPH

HH

HPS

HRS

Ascites/ SBP

Variceal Bleeding

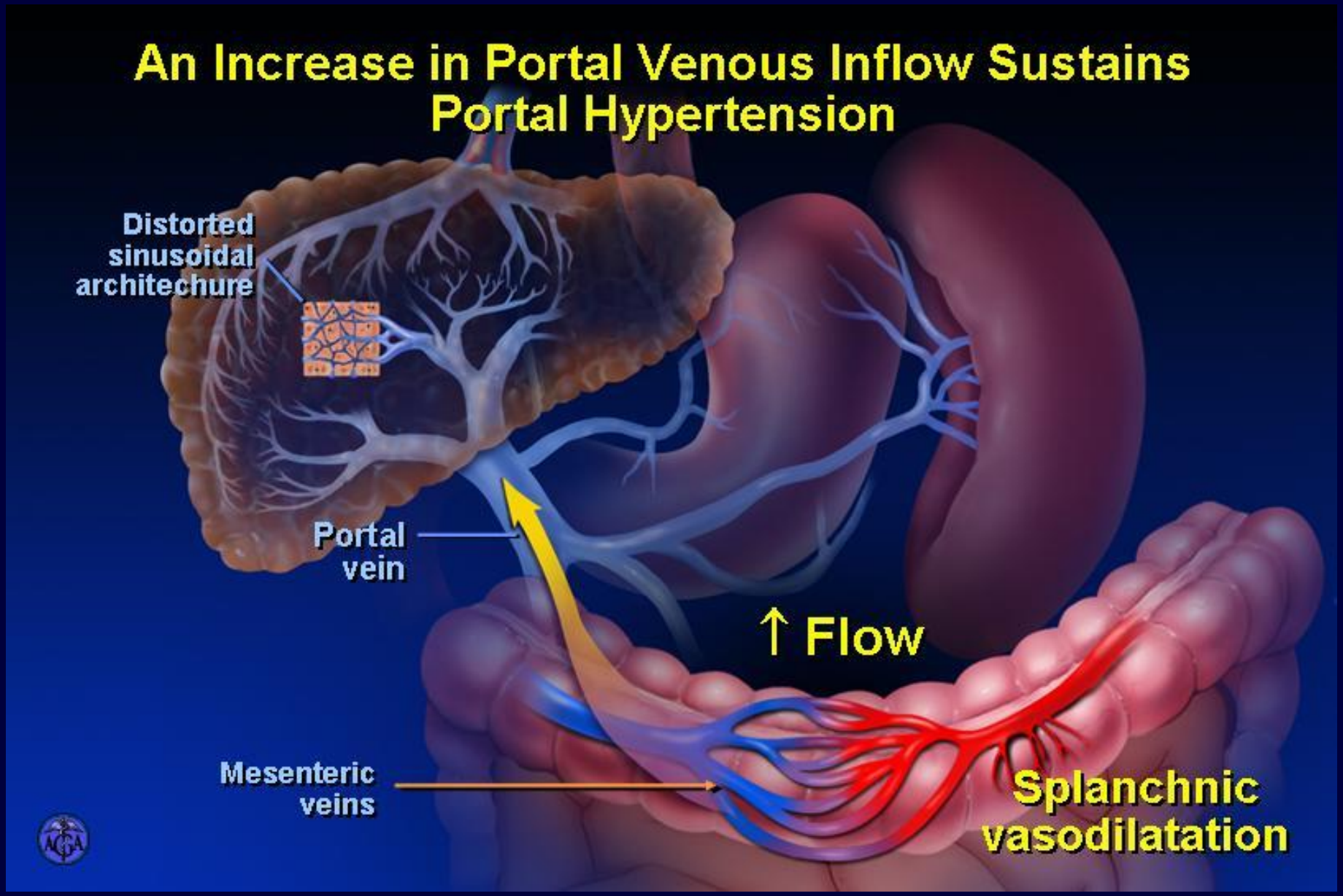
Mechanisms of Portal Hypertension

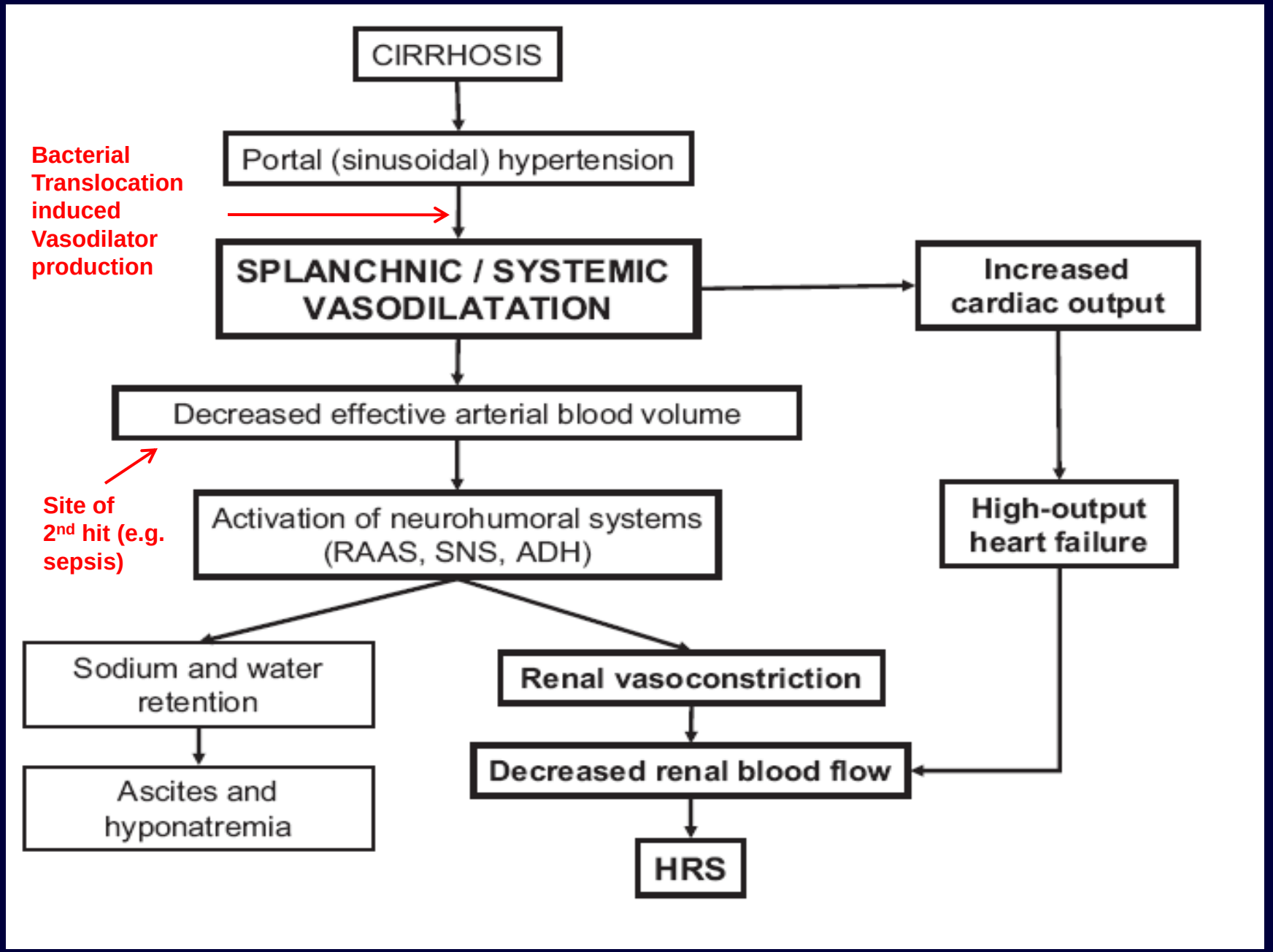
- Pressure (P) results from the interaction of resistance (R) and flow (F):

$$P = R \times F$$

- Portal hypertension can result from:
  - **increase in resistance** to portal flow and/or
  - **increase in portal venous inflow**

An Increase in Portal Venous Inflow Sustains Portal Hypertension




CIRRHOSIS
Portal (sinusoidal) hypertension
Bacterial Translocation induced Vasodilator production
SPLANCHNIC / SYSTEMIC VASODILATATION
Increased cardiac output
Decreased effective arterial blood volume
Site of 2nd hit (e.g. sepsis)
Activation of neurohumoral systems (RAAS, SNS, ADH)
High-output heart failure
Sodium and water retention
Renal vasoconstriction
Ascites and hyponatremia
Decreased renal blood flow
HRS

HEPATIC ENCEPHALOPATHY (HE) (1)

- Neurologic & psychiatric dysfunction in the presence of chronic or acute liver failure
- Potential Mechanism includes conversion of Ammonia to Glutamine that induces altered neuro-transmission and astrocyte swelling
- Chronicity of liver disease in ACLF allows the development of extrahepatic mechanisms of ammonia fixation (e.g. muscle), thereby limiting the degree of hyperammonemia in ACLF compared to ALF
- Clinically graded from Stage I to IV reflecting progression from mild confusion to coma; elevated intracranial pressure rare in ACLF (in contrast to ALF)
- HE in chronic and acute liver failure differs in disease manifestation, therapy and prognosis

HEPATIC ENCEPHALOPATHY (2)

- **Precipitants of HE** in chronic disease
  - Dehydration /GI Bleed / *Infection*/ Electrolyte derangements/ TIPS

- **Diagnosis:** Ammonia level not sensitive for initial diagnosis; can be used serially to gauge response to therapy

- **Treatment:**
  - Elective intubation for G3/4 HE for airway protection
  - If Mechanical Ventilation necessitates sedation, minimize sedation and use non-benzodiazepine therapy (propofol, dexmedetomidine)
  - Reversal of precipitating factor (e.g. antibiotics for SBP)
  - Elimination of nitrogenous sources from the GI tract; medications include Lactulose (PO/PR), Rifaximin, Metronidazole.
  - No role for therapy targeted at decreasing cerebral edema (in contrast to ALF)

HEMODYNAMIC CHALLENGES (1)

- Baseline abnormal cirrhotic hemodynamics characterized by low MAP mediated by splanchnic and peripheral vasodilation (*How should hypotension/ shock be defined ?)*

- Assessment of fluid/ intravascular status challenging in the critically ill cirrhotic
  - Static indices of preload (e.g. CVP , PCWP) inadequate, especially in the setting of mechanical ventilation and tense ascites
  - Utilization of pulse contour analysis based devices (e.g. Lidco, Vigileo) and Echocardiography should be considered.

- Utility of lactate and central venous saturation in guiding fluid and vasoactive agent therapy compromised by abnormal pre-shock values.

- Minimal insults in vascular tone/ volume due to septic/ hypovolemic insults can result in hypotension/ shock, and decreased perfusion to end organs and extracorporeal circuit.

HEMODYNAMIC CHALLENGES (2)

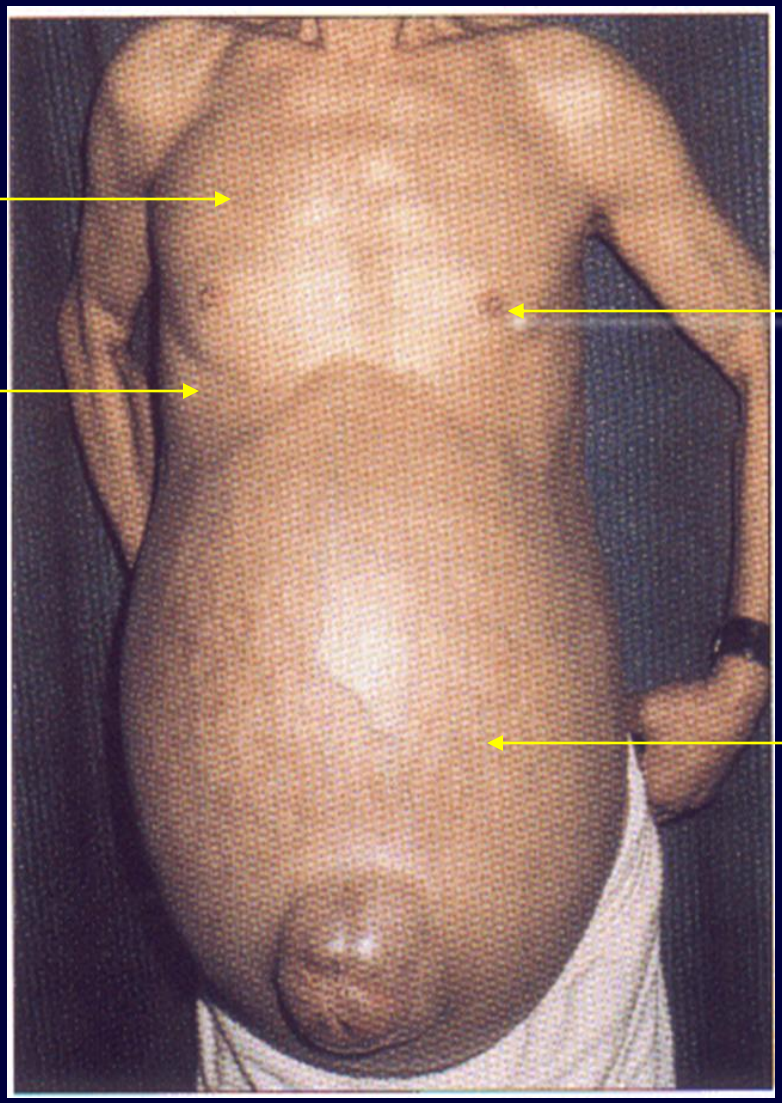
- Evidence of abnormal myocardial function (cirrhotic cardiomyopathy), characterized by systolic & diastolic dysfunction, and impaired b-adrenergic receptor function

- In the setting of tense ascites, cardiac preload can be compromised by IVC compression due to abdominal compartment syndrome; role for therapeutic paracentesis.

- Evidence for high incidence of adrenal insufficiency in septic shock in the setting of cirrhosis (*Tsai et al. Hepatology 2006*). Consider stress dose steroids in septic shock refractory to initial vasoactive agent support.

- Prior evidence of POPH may necessitate placement of Swan Ganz catheter to evaluate pulmonary artery pressures, and Echo to monitor R heart function

Unique Pulmonary Derangements in Cirrhosis



Portopulmonary Hypertension (PAH)

Hepatic Hydrothorax

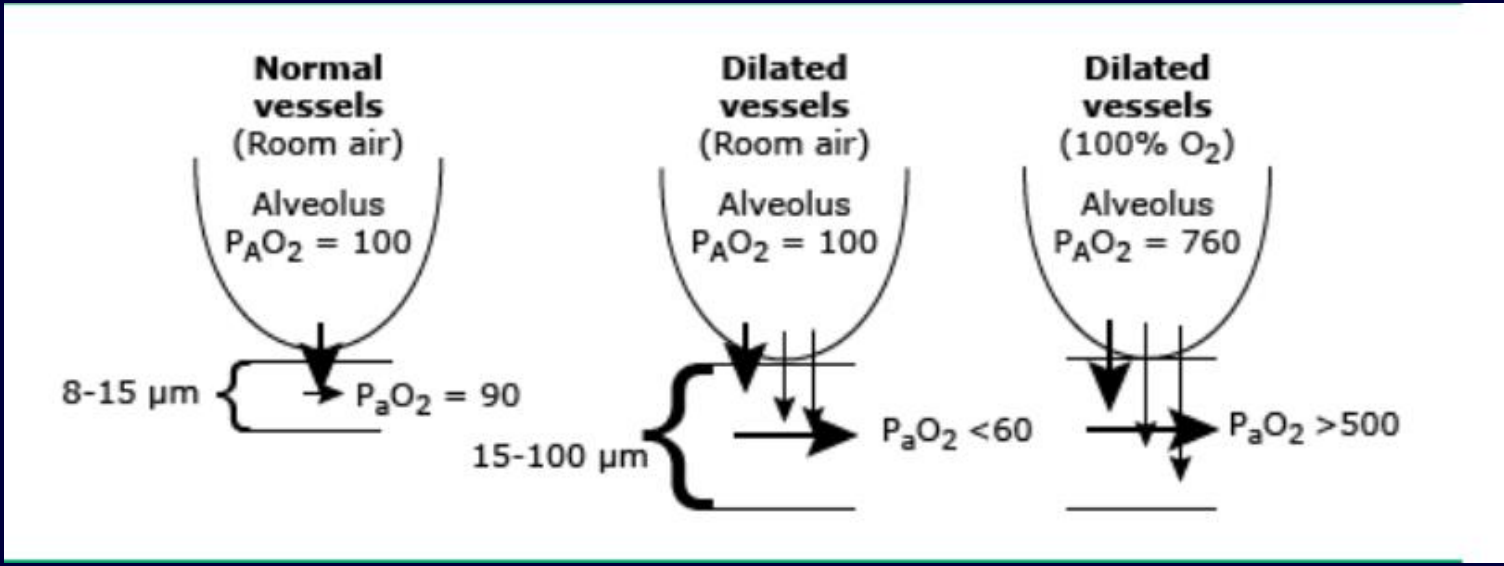
Hepatopulmonary Syndrome (hypoxemia)

Ascites induced Restrictive Lung Mechanics

HEPATOPULMONARY SYNDROME (HPS): Pathophysiology

- Hypoxemia due to diffusion impaired transfer of oxygen from the alveoli to the vasculature secondary to pathologic pulmonary vascular dilation.

- Pathologic pulmonary vasodilation proposed to be due to vasodilators (e.g. NO) emanating from the hepatic venous drainage into the IVC



HPS: Clinical Manifestations

- Hypoxemia in the absence of a radiographic lesion on chest imaging

- Characterized by platypnea (dyspnea when upright) and orthodeoxia (desaturation when upright) due to West Zone 3 (basilar) predominance of vascular dilations

- Prevalence: 10-32 % (retrospective data sets)

- Effect on mortality: Increased mortality compared to non HPS cirrhotics (median survival: 2 vs 7 years), with significantly worse mortality if RA PO_2 < 50mm Hg. [1] (*MELD exception of 22 for RA PO_2 < 60mm Hg*)

1. Swanson et al. Hepatology 2005; 41: 1122

HPS: Diagnosis and Therapy

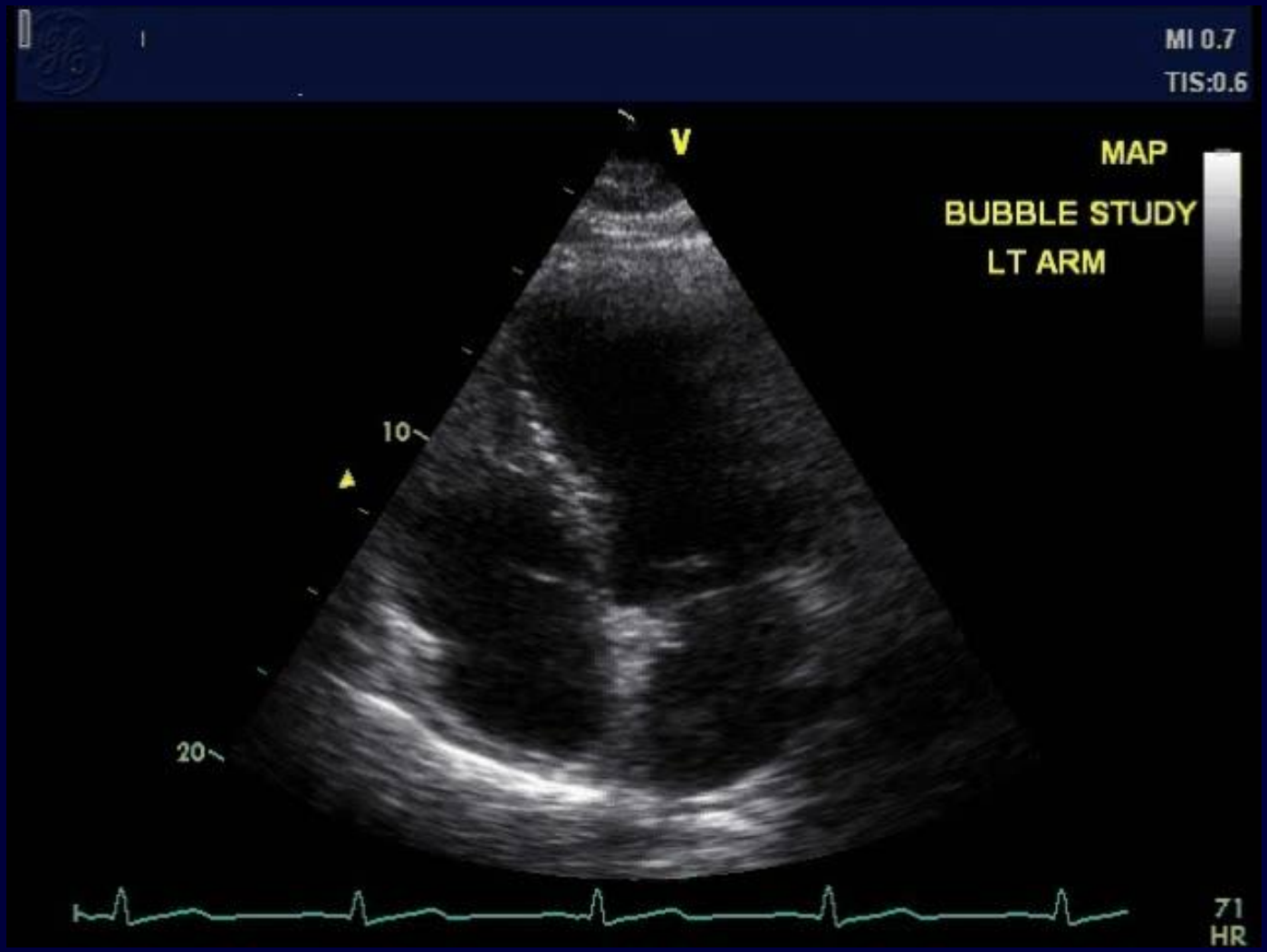
Diagnosis:

- Rule out parenchymal/ pleural lung disease by Chest CT
- PFTS demonstrate isolated low DLCO
- **Documentation of *late bubbles* on TTE in 4-6 cardiac cycles**

Therapy:

- Increasing alveolar PO_2 by supplemental O_2 overrides diffusion limitation
- Coil embolization in rare cases of radiographically visible pulmonary AVMs
- Liver transplantation (LT) typically reverses hypoxemia in weeks to months irrespective of severity of pre-LT hypoxemia

Echo Diagnosis of HPS



- Pre LT: RA PO_2 45mm Hg, requiring 7L NC O_2
- 7 months post LT: liberated from O_2

Portopulmonary HTN (PPHTN) :
Pathophysiology and Clinical Manifestations

- A form of pulmonary arterial hypertension that is histologically identical to idiopathic P. HTN

- Pathophysiology: putative mechanisms : vascular injury/inflammation mediated by serum factors abnormally persisting in hepatic outflow vs shear stress due to hyperdynamic circulation

- Prevalence: 4 to 16% (retrospective data sets)

- Symptoms/ signs:
  - Dyspnea, angina, exacerbation of ascites, LE edema
  - In critical illness, acute cardiac or pulmonary insults can exacerbate pre-existing PPHTN by increasing RV afterload, thereby increasing the risk of acute RV failure.

PPHTN: Diagnosis and Therapy

- **Diagnosis:**
  - Initial study: Transthoracic Echocardiography
    - Estimated RVSP > 50 mm Hg triggers RHC
  - RHC: mPAP > 25 mm Hg and PVR ((mPAP – PCWP)/ CO) > 240 dynes/ s /cm $^{-5}$
  - Target mPAP for *LT candidacy : < 35 mm Hg (similar evaluation prior to TIPS)*

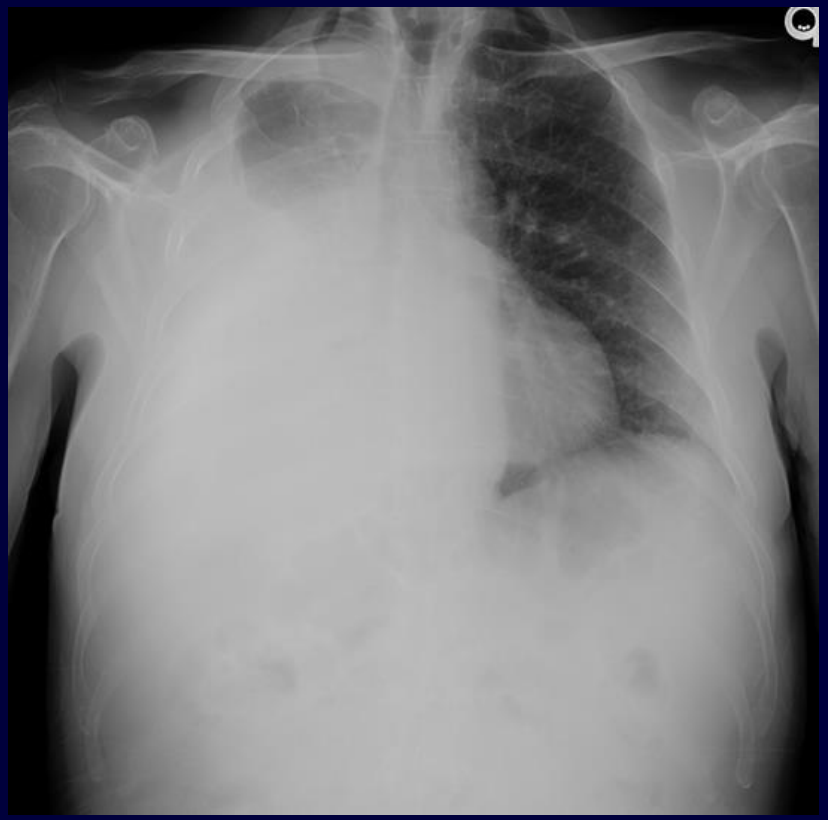
- **Treatment:**
  - Monitoring of RV function with TTE and RHC.
  - Therapy with dobutamine and milrinone (for ionotropy) and IV epoprostenol (for pulmonary vasodilation).
  - Low tidal volume ventilation to decrease RV afterload.
  - Chronic IV Epoprostenol, with goal to decrease mPAP < 35 mm Hg for LT candidacy. Emerging role for co-therapy with ERAs
  - Liver transplantation: varying degrees of reversal of PPHTN after transplant (in contrast to HPS)

Treatment of PPHTN:
Effect of Epoprostenol on RHC data

• RA	9		14
• RV	80/15		53/17
• PA	82/33 (49)	→ Epoprostenol 18 months	52/23 (32)
• PW	13		22
• CO	6.3		11
• PVR	452		76

HEPATIC HYDROTHORAX:
Pathophysiology & Clinical Manifestations

- Transudative pleural effusion (R> L) due to translocation of ascites across the diaphragm
- Can present in the absence of ascites if diaphragmatic defect large
- Characteristic symptoms of a pleural effusion; large effusions may necessitate MV
- Can be complicated by spontaneous bacterial empyema (ANC > 250/cc); perform diagnostic thoracentesis as part of infectious workup



Hepatic Hydrothorax (HH): Treatment

- Maximize combination diuretic therapy with furosemide and spironolactone as tolerated by renal function.
- Serial Thoracentesis if pulmonary status does not necessitate mechanical ventilatory support
- In the event of HH induced respiratory failure requiring initiation or persistence of mechanical ventilation, consider small bore (10/12 F) pleural catheter with *gravity drainage* *(large bore suction drainage contraindicated)*
- TIPS for refractory hydrothorax if no contraindications (e.g. MELD > 22, severe HE, PPHTN)
- Consider Pleurex catheters for cases in which TIPS is contraindicated, while the patient awaits transplant or for palliation

GI: Variceal Bleeding Initial Management

- Large bore IV access; Arterial Line
- Intubation for airway protection and for shock
- Optimization of platelets and coagulation parameters
- Monitor core temp to prevent cold coagulopathy
- Interventional Radiology Consult for possible TIPS; pre-procedure hepatic imaging and **TTE**
- Access to Blakemore Tube
- NG tube placement; large bore to facilitate endoscopy

VARICEAL Bleeding: Treatment

Pharmacologic:

- Splanchnic Vasoconstrictors (Octreotide/ Terlipressin)
- Antibiotics ; shown to decrease mortality and rebleeding

Endoscopic:

Esophageal varices: endoscopic band ligation. Gastric varices: TIPS

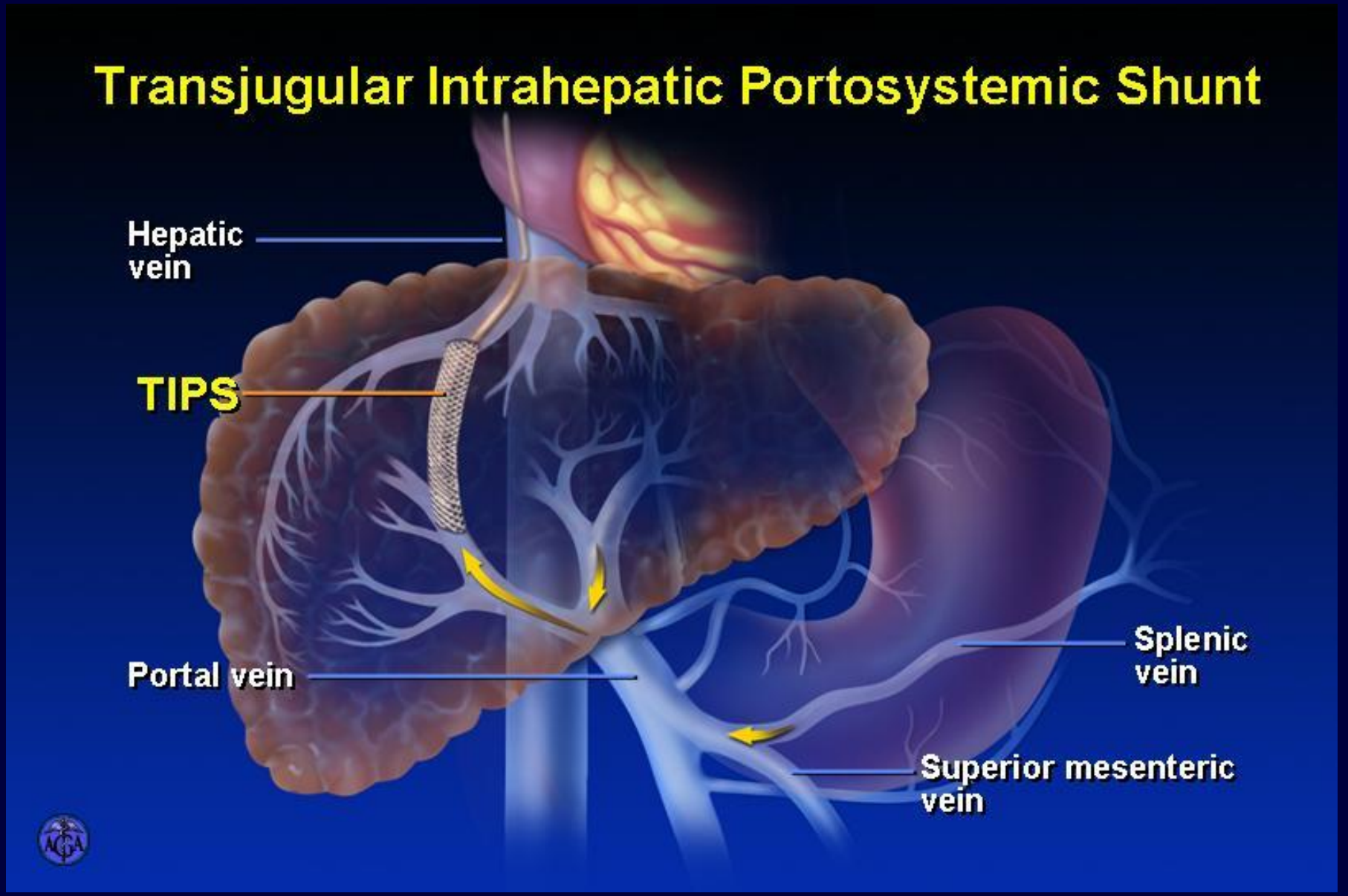
Balloon Tamponade:

Gastric and esophageal balloon tamponade for bleeding refractory to endoscopic therapy, with a goal to bridge to TIPS

TIPS:

Effective salvage hemostatic therapy. Monitor for hepatic decompensation in high MELD patients (MELD > 20)

Transjugular Intrahepatic Portosystemic Shunt



Ascites & Spontaneous Bacterial Peritonitis (SBP)

- Peritoneal fluid accumulation secondary to renal fluid retention and portal hypertension; Serum to Ascites Albumin Gradient (SAAG) > 1.1

- Massive ascites can potentially cause restrictive lung mechanics and abdominal compartment syndrome

- Ascitic fluid predisposes to Spontaneous Bacterial Peritonitis (SBP), characterized by peritoneal infection (ANC > 250/cc) in the absence of a perforated viscus. Organisms include gram positive and negative bacteria, and fungi

Ascites/ SBP: Treatment

- **Ascites**
  - Diuretics (combination of spironolactone & furosemide; ratio of 100: 40 to maintain eukalemia)
  - Paracentesis; IV albumin with large volume taps (> 5L) to prevent hypotension and HRS
  - TIPS
- **SBP**
  - Emergent Antibiotics for acute event (Cefotaxime/ Zosyn)
  - Albumin 1.5g/kg Day 1 and 1g/ kg Day 3 to decrease the incidence of HRS
  - Prophylactic antibiotics indefinitely to prevent recurrence (FQ)

RENAL CHALLENGES

- Tenuous baseline cirrhotic hemodynamics predisposes to development of AKI in the setting of *minimal* cardiovascular insults
- Recent multi-center European study identified AKI as most common extrahepatic injury in ACLF and major contributor to mortality (*Moreau et al. Gastro 2013*)
- Infection, and in particular SBP, classic trigger for T1 HRS (*Follo et al. Hepatology 1994*)
- Renal dysfunction can compromise platelet qualitative function; role of DDAVP
- Concomitant AKI in the setting of liver failure can cause a rapidly progressive anion gap metabolic acidosis, necessitating consideration for early CRRT

HEPATORENAL SYNDROME (HRS)

- Functional renal injury (Cr > 1.5g/dl or CrCl < 40ml/ min) in the presence of decompensated cirrhosis (*definition being revised based on AKIN guidelines*)
- Diagnosis based on exclusion of other causes (e.g ATN, pre-renal azotemia, post renal etiology)
- Characterized by no improvement in renal function after fluid challenge and withdrawal of diuretic therapy
- Bland urinary sediment
- Urine Na < 10mmol/ L; FeNa <1

Treatment of HRS

- Treatment
  - Splanchnic vasoconstrictors (e.g octreotide, terlipressin) + Albumin
  - Octreotide and Midodrine combination therapy
  - Norepinephrine
  - Renal replacement therapy
  - Liver Transplantation (OLT); if dialysis initiated for > 6 weeks, consider candidacy for combined Liver & Kidney transplant

- Prognosis

  Poor in the absence of OLT; Creatinine now used in defining severity of liver disease and prioritizing LT recipients (MELD score : INR, Bili, Cr)

METABOLIC ABNORMALITIES

- Anion gap Metabolic Acidosis due to combined etiologies of hypoperfusion, hepatic and renal dysfunction
  - Anticipate rapid onset of severe metabolic (lactic) acidosis in the setting of shock due to increased production and decreased hepatic clearance
  - Expedited combined interventions of fluid resuscitation, MV, CRRT and THAM/ bicarbonate infusions
- Hypoglycemia secondary to decreased hepatic gluconeogenesis and glycogenolysis; associated with advanced stages of severe liver failure. Ominous prognosis
- Hyponatremia due to excess TBW
  - Precipitant for HE
  - Evolving role for aquaretics for renal free water excretion (e.g. tolvaptan)

ID / Antibiotic Issues

- Consider the decompensated cirrhotic an immuno-compromised host
- Common triggers of septic physiology in cirrhotics include SBP, UTI, pneumonia and cellulitis
- Early administration of empiric antibiotics for clinical suspicion of infectious insult/ hypotension
- Consider empiric double coverage for gram negative bacteria for worsening septic hypotension/ shock
- Have low threshold for anti-fungal coverage for empiric treatment of septic shock refractory to initial empiric anti-bacterial therapy

Management of ACLF: Summary

- Elective intubation for G3/4 hepatic encephalopathy. No indication for pharmacotherapy targeted at decreasing intracranial hypertension
- Early consideration for TIPS consultation in the setting of variceal bleeding refractory to endoscopic therapy
- Active search for infectious trigger, with low threshold for empiric antibiotics including antifungal therapy
- Anticipate rapid onset of lactic acidosis, and the need for CRRT
- Monitor for abdominal compartment syndrome due to tense ascites
- Include Hepatorenal Syndrome in the differential diagnosis of AKI