

The Kidney in Liver Disease

Jeff Kaufhold MD FACP

Nephrology Assoc. of Dayton

Oct 2018

Objectives

- 1. Understand new evidence in the pathophysiology of Hepatorenal syndrome
- 2. Review current treatment guidelines and some over the horizon treatments.

Outline

- Associations between kidney disease and liver disease
- Causes of Acute renal failure and liver disease
- Pathophysiology of Hepatorenal Syndrome
- Current Treatment
 - Octreotide/Midodrine Therapy
 - Terlipressin Therapy
 - Head Out Water Immersion
- Extracorporeal Liver Dialysis
- References

Associations

- Kidney Disease
- PCKD
- IgA Nephropathy
- Membrano-proliferative GN (MPGN)
- Membranous GN
- Liver Disease
- Liver Cysts and Fibrosis
- Cirrhosis
- Cirrhosis
- Hepatitis B

Associations

- Kidney Disease
- Membrano-proliferative GN (MPGN)
- Membranous GN
- Cryoglobulinemia
- Liver Disease
- Cirrhosis
- Hep C
- Hepatitis B
- Hep C
- Hep C

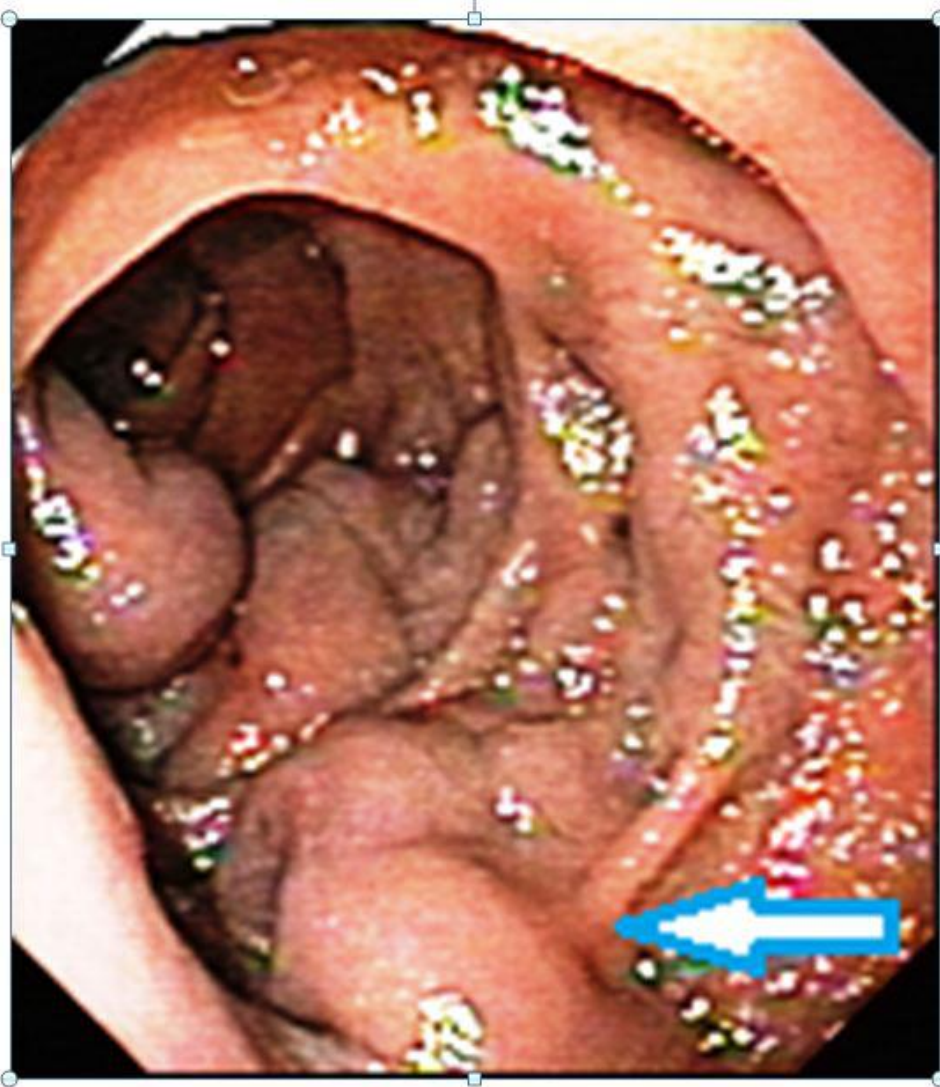
Associations

- Patients with Diabetic nephropathy also have higher incidence of presence of Hep C, and worse prognosis from Hep C
- Patients with Hep C are more likely to develop Diabetes (type I) due to treatment with Interferon.

Abnormal Liver Physiology

- Fibrosis
- VEGF
- Accumulation of Nitrogenous Wastes
- Increased Portal Pressure - ascites and hypersplenism
- Telangiectasias and Varices
- Hepatic Encephalopathy
- Increased substrate for Nitric Oxide Synthase (Nos)

Esophageal Varices



Nitric Oxide

- **Functions:**
 - Regulate BP – potent vasodilator
 - Neurotransmitter
 - Suppress Pathogens
- **Studies describe Pathophysiology in:**
 - Pregnancy/Pre-eclampsia
 - Hypertension
 - Hepatic Failure

Endothelin

- Function:
 - Most potent vasoconstrictor
- Studies describe broad range of Pathophysiologic conditions.
 - Hypertension
 - Pulmonary Hypertension

Why is this Important?

- Inhibitors and Antagonists being developed which you will use soon
- You already use some:
 - Nitroprusside
 - Isordil/NTG
 - Viagra
- Endothelin receptor antagonists:
 - Bosentan, Ambrisentan

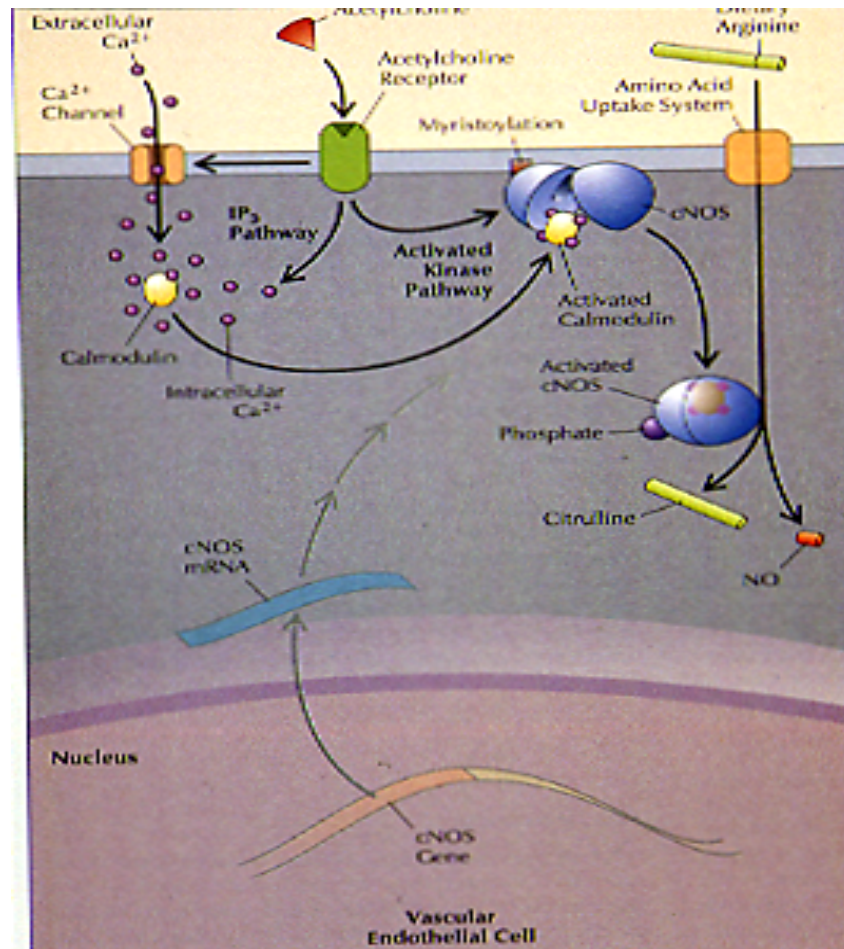
Nitric Oxide - NO

- Uncharged molecule - can go anywhere
- Unpaired electron - highly reactive
- Chemical generation:
 - Arginine + O₂-----> NO + Citrulline
NOS*
 - *Nitric Oxide Synthase

Enzyme Production

- Nitric Oxide Synthase (NOS)
 - Two Types
 - Constitutive
 - vasodilator
 - neurotransmitter
 - Inducible
 - Free radical scavenger
 - Pathogen killer

NITRIC OXIDE



Nitric Oxide

- Targets:
 - Vascular Smooth Muscle
 - Neurons
 - Pathogenic bacteria
- Effects:
 - Vasodilator
 - Feedback for ET-1
 - Neurotransmitter
 - Free Radical/Killer

NO in Pregnancy: Progesterone

- Stimulates Nitric Oxide Synthase
 - Leads to systemic Vasodilation
 - Which causes lower BP,
 - Which stimulates Aldosterone
 - Which leads to volume expansion
 - Which increases GFR/RBF
- Decreased response to Angiotensin

ENDOTHELIN

Clinical Aspects

- ET plays a role in
- ATN
- Contrast nephrotoxicity
- Cyclosporine nephrotoxicity
- Endotoxic shock
- Hypertension and pulmonary hypertension
- Chronic renal failure

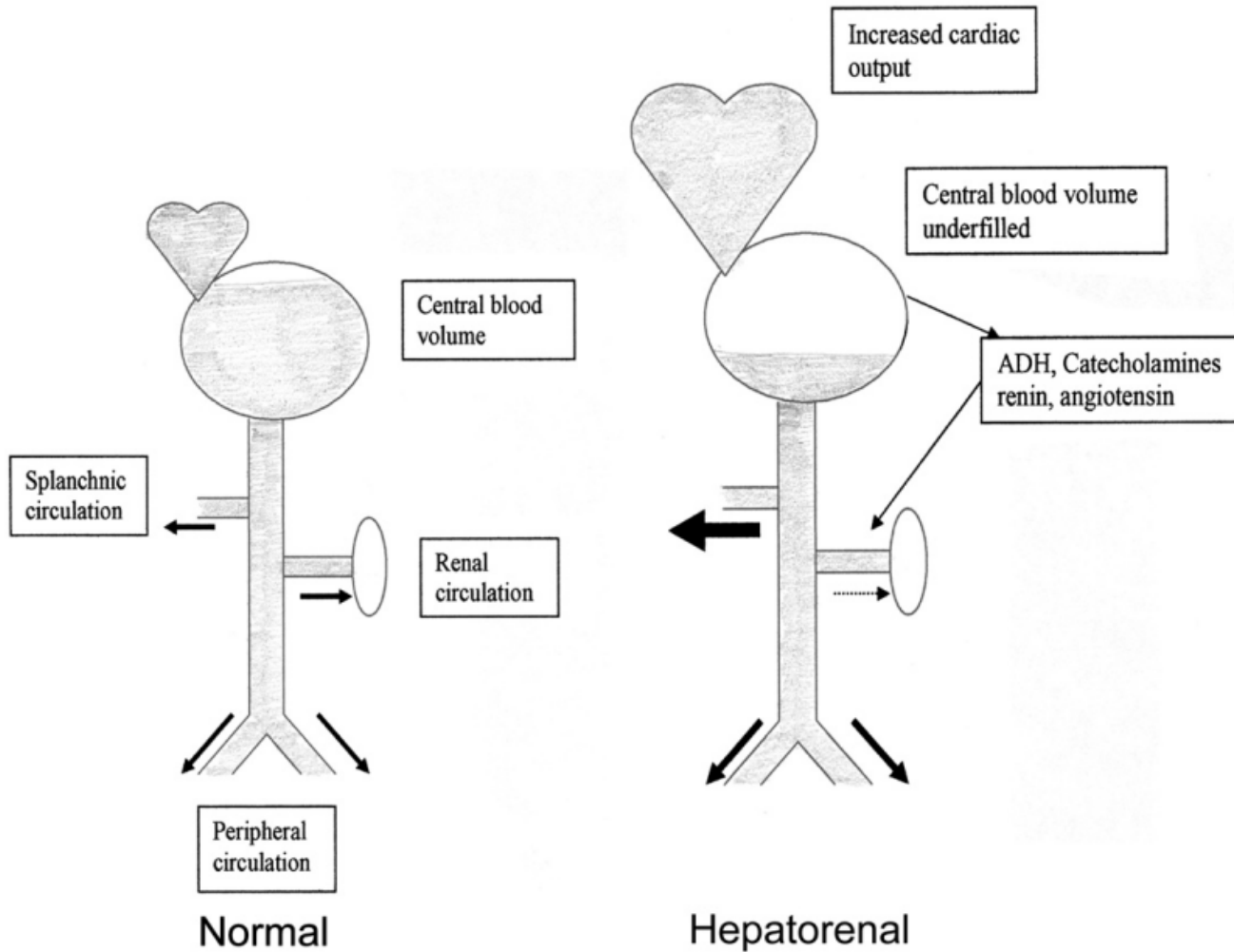
Clinical Aspects of N.O.

- Cirrhosis
 - decreased BP, low SVR, angiogenesis
 - NOS inhibitors work, sort of.
- Pregnancy
 - reduced response to angiotensin
 - natural inhibitor of NOS found in pre-eclampsia

Theories for Fluid retention in Liver Failure

- Overfill - measured circulating volume is UP due to problems with portal hypertension, but doesn't explain why there is too much aldosterone
- Underfill Leads to too much aldosterone, but doesn't correlate with measured volume
- There must be a better reason!

Pathophysiology



Theories for Fluid retention in Liver Failure

- The vasodilation caused by excess Nitrous Oxide leads to poor perfusion of tissues, leading to stimulation of aldosterone and ADH. This is the concept of Reduced Effective Circulating Volume (ECV) or Reduced Effective Arterial Blood Volume (EABV).

Hemodynamic Insults of Cirrhosis

- Increased nitrogenous wastes like ammonia, amino acids, lead to increased production of Nitric Oxide, which leads to:
 - Vasodilation, Lower BP
 - Stimulates Aldosterone and ADH production
 - Edema accumulation
 - Hyponatremia

Causes of ARF in Liver Disease

- Volume depleted due to Nausea, diarrhea, diuretic use
- Septic - ATN
- Interstitial Nephritis from antibiotics or other drugs
- Drug induced from NSAID or ACE use
- Hepatorenal Syndrome

Hepatorenal Syndrome

- Syndrome where Compensated Cirrhosis becomes decompensated
 - Marked by Very Low BP,
 - Increased ammonia with encephalopathy
 - Usually pt is pancytopenic/
thrombocytopenic as portal pressures rise
causing hypersplenism
 - Acute Renal Failure

ARF in HRS

- Creatinine climbs over 2 with bland UA
- Pt usually poorly responsive to diuretics
 - Develops edema, ascites
 - Low urine sodium (low FENA)
- Hyponatremia due to increased stimulus for ADH
- Hyperkalemia due to ARF and spironolactone use
- Should rule out adrenal insufficiency (low BP, low sodium, high K)

What makes Cirrhotic patient Decompensate?

- Sepsis usually
 - Endotoxin leads to stimulation of Inducible Nitric Oxide Synthase, and worsens vasodilation, low BP, decreases EABV further.
- GI Bleed
 - Increases nitrogenous wastes/substrate for Nos.

Proofs of Concept

Hepatorenal syndrome

- Can improve BP, Perfusion pressure, renal blood flow, Urine output with:
 - Head Out Water Immersion (HOWI)
 - Uniform compression of peripheral vasculature
 - Agents which antagonize Nos
 - LNAME, LNMMA other substituted Arginine substances.
 - Midodrine and Octreotide

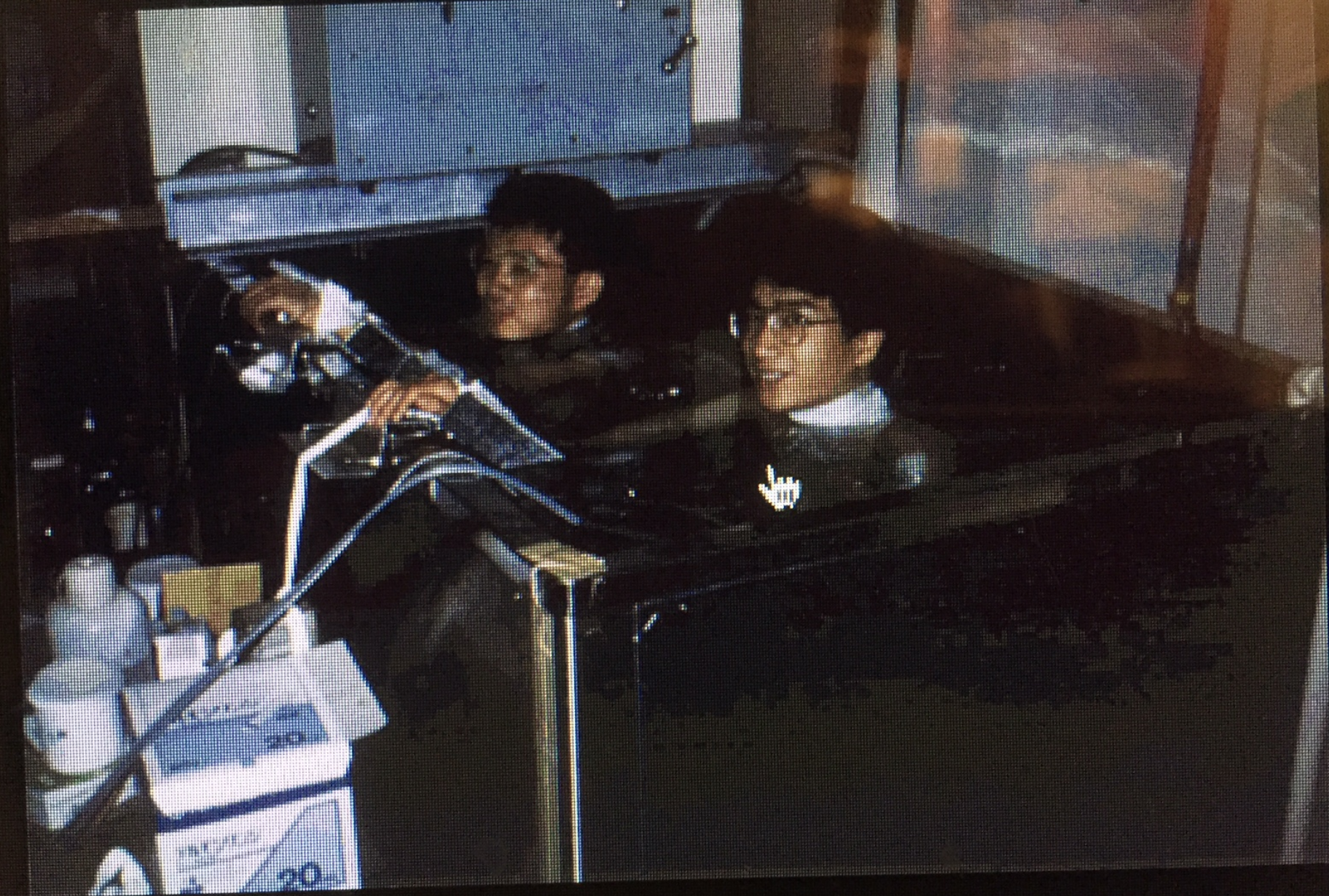
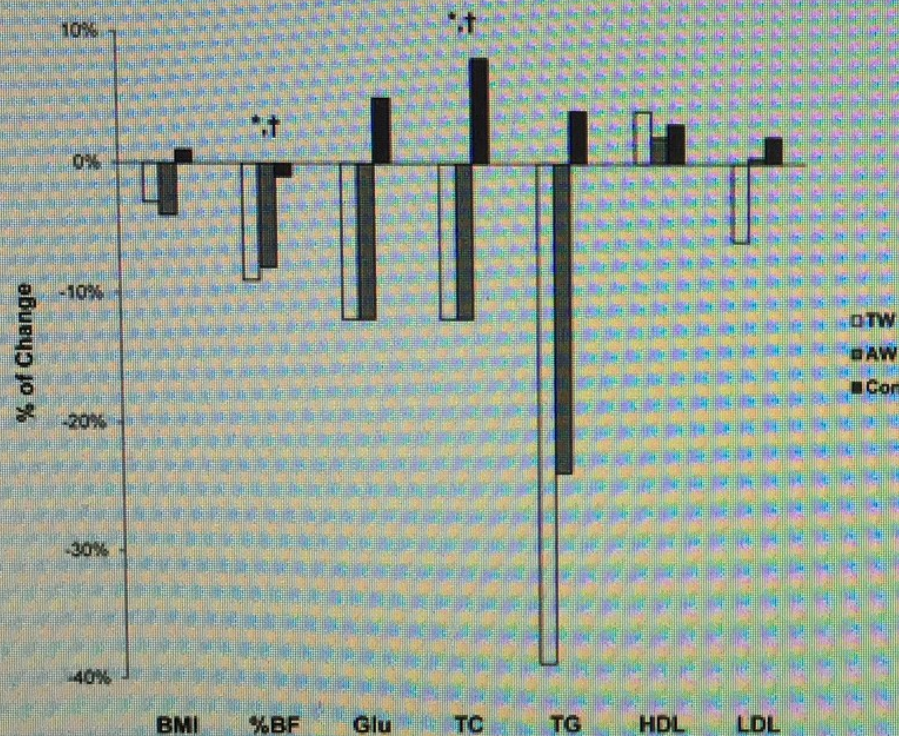


Fig. 1



Comparison of the change in body composition, blood lipid level, and blood glucose level. *Difference between the treadmill/track walking (TW) and control (CON) groups. †Difference between the aqua walking (AW) and CON groups

Treatment of HRS

- Head Out Water Immersion (HOWI)
 - Good for outpts to prevent problems
 - I tell my patients to go swim at the YMCA 2-3 times a week.
- Agents which antagonize Nos
 - Not used due to increased risk of Variceal hemorrhage!
- Midodrine and Octreotide
 - Used for inpts with HRS, diuretic resistance.

Hepatorenal Syndrome (HRS)

- First described in 1932 for post-op biliary tract Sx resulting in ATN
- Found to be a cascade of events
- Kidneys histologically normal
- Acute renal dysfunction occurs in 15% to 25% of hospitalized pts w/ cirrhosis
- HRS an extension of prerenal therefore potentially reversible
- Annual frequency of HRS 8% to 40%
 - SBP or other infection 30%
 - Severe alcoholic hepatitis 25%

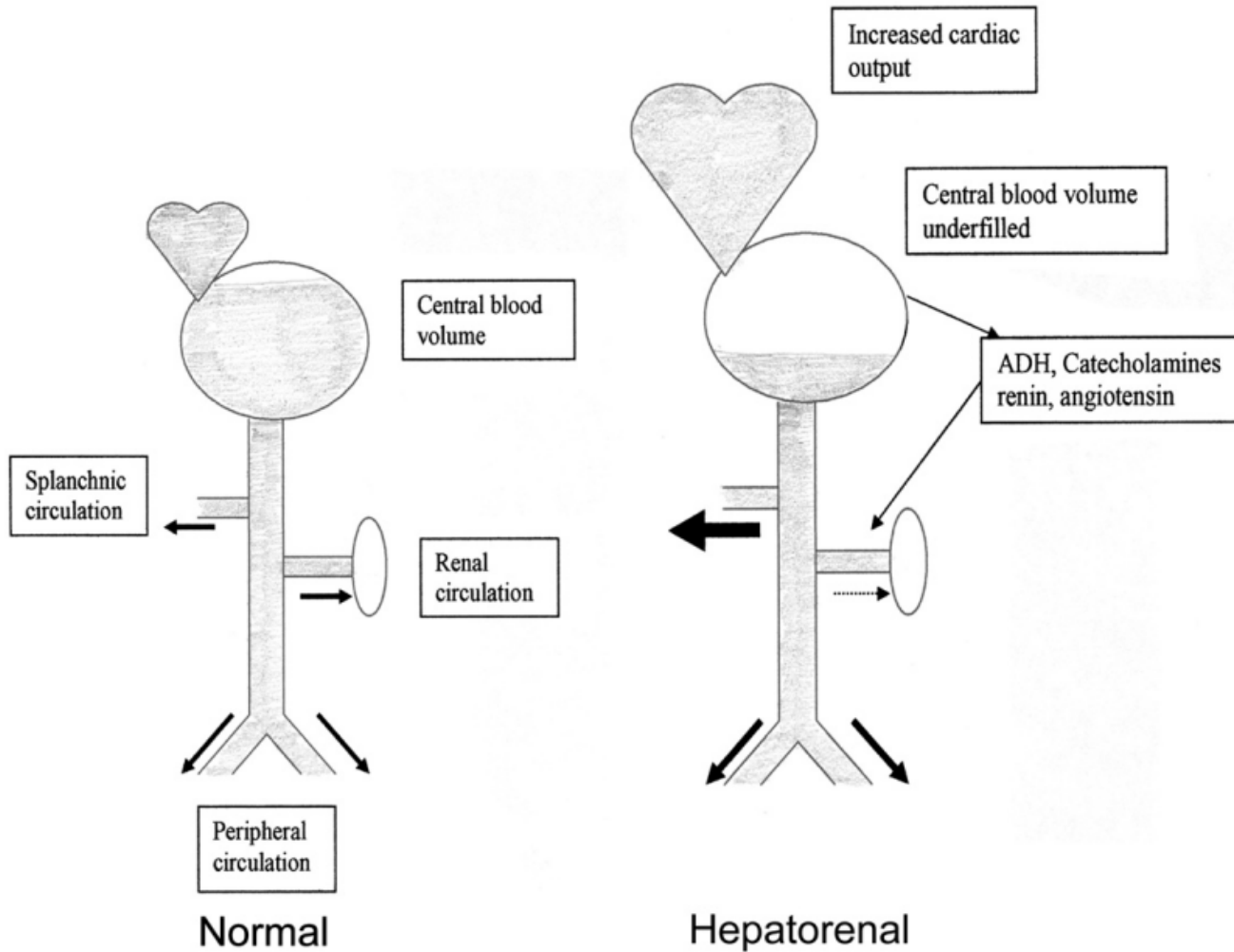
Pathophysiology

- Splanchnic & Systemic Arterial Vasodilatation
 - Hallmarks of progression of portal HTN in cirrhosis
 - Mediated by numerous endogenous substances
 - Early compensation includes increase in HR & CO
- Cardiac dysfunction
 - HRS developed in cirrhotic pt w/ more severe arterial vasodilation and lower CO

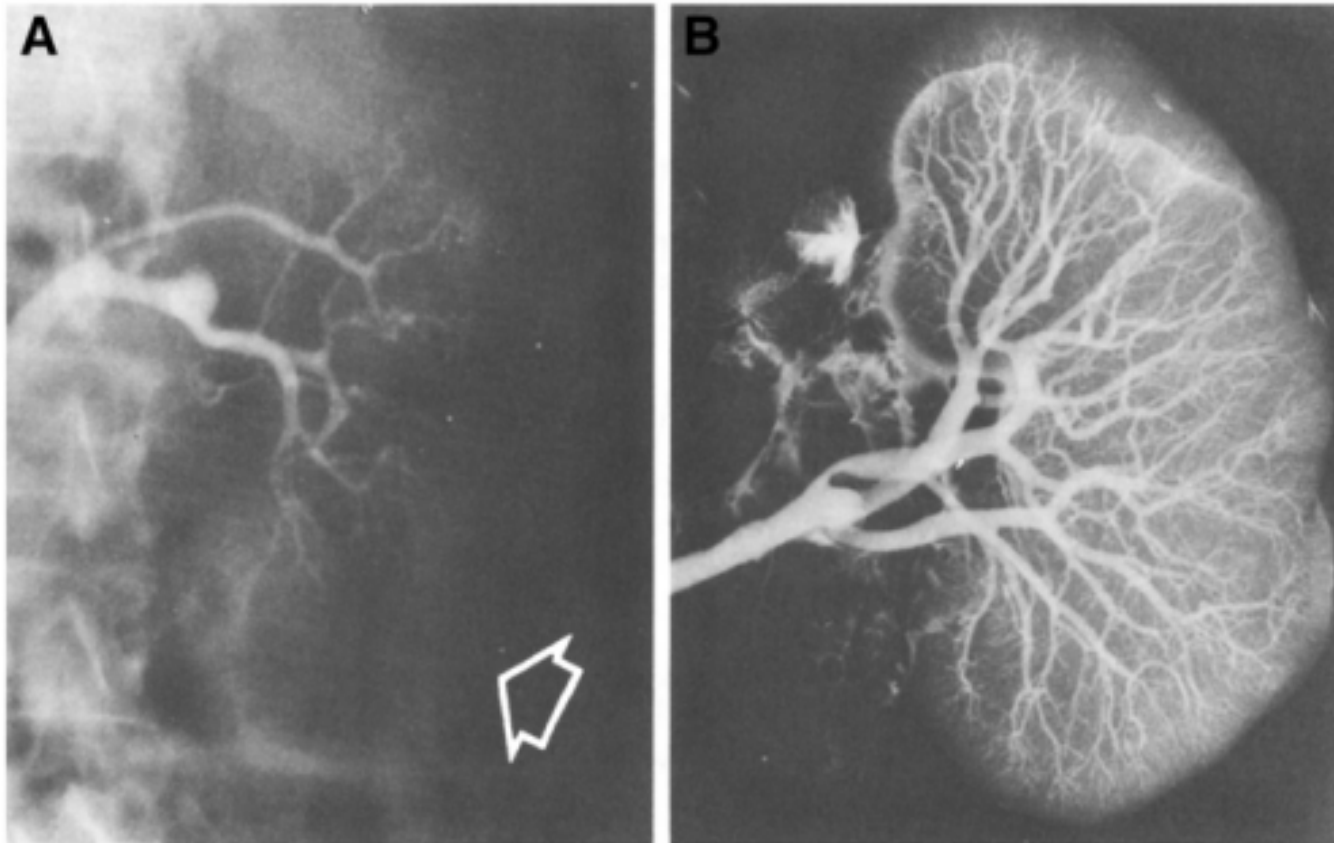
Pathophysiology

- Renal Arterial Vasoconstriction
 - Mediated by stimulation of SNS, activation of RAAS, nonosmotic release and activity of vasopressin(ADH)
 - Precise intrarenal mechanisms are speculative
 - Balance between vasoconstrictive responses in kidney and splanchnic vasodilation is lost

Pathophysiology



Pathophysiology of HRS



A: intense renal vasoconstriction B: normal renal blood flow.

Diagnosis of HRS

- International Club of Ascites
Consensus Workshop 2017 (ICA)
- Recent consensus guidelines have been published by the International Club of Ascites (ICA) updating the recommended threshold for diagnosing AKI in patients with cirrhosis, which now align with the Kidney Disease Improving Global Outcomes (KDIGO) AKI classification. HRS is a diagnosis of exclusion and should be suspected in patients presenting with new renal impairment in the setting of cirrhosis with ascites

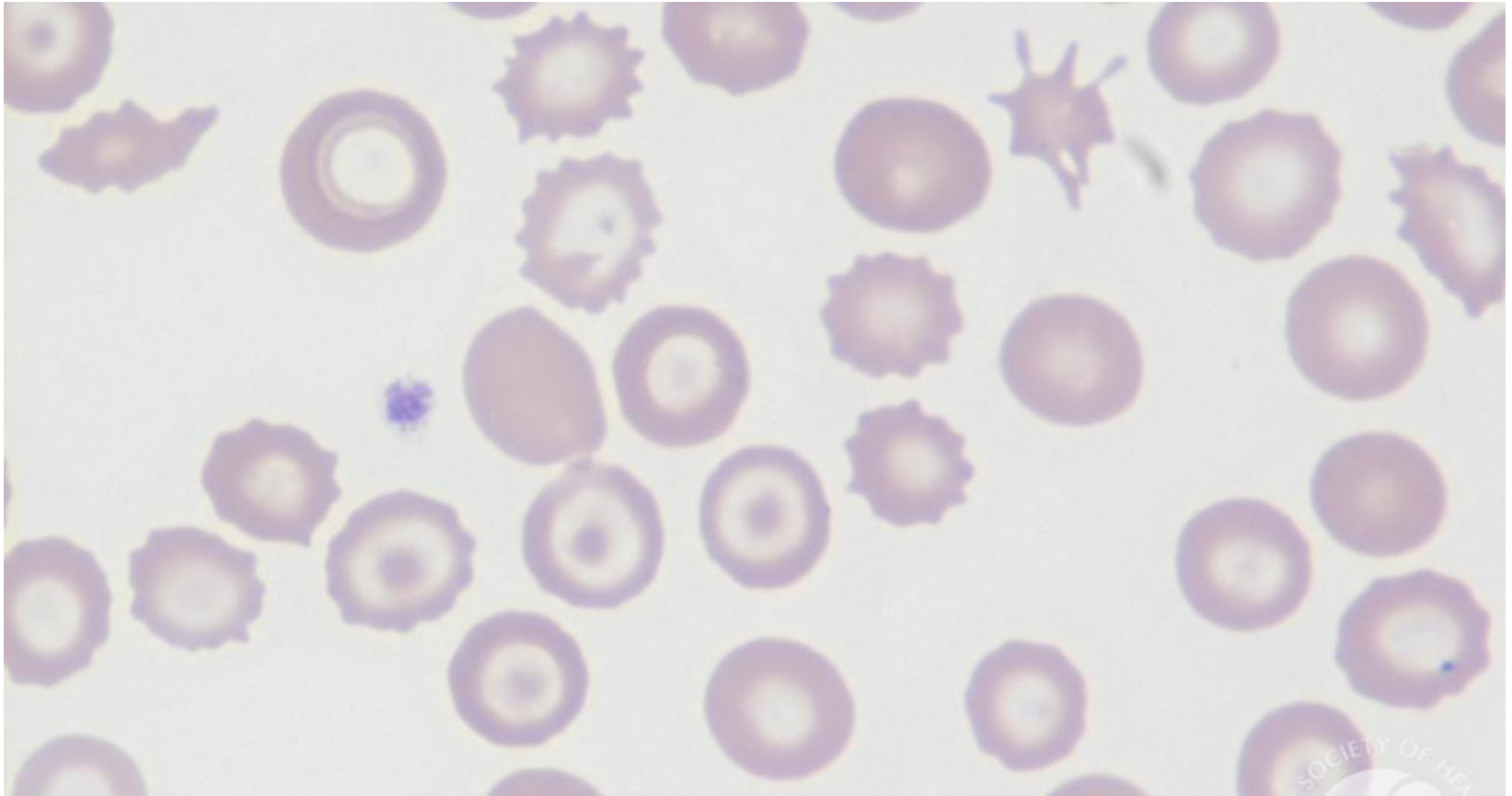
Diagnostic Criteria for HRS

- Diagnosis of cirrhosis and ascites
- Diagnosis of AKI according to ICA-AKI criteria
- No response after two consecutive days of diuretic withdrawal and plasma volume expansion with albumin 1 g per kg of body weight
- Absence of shock
- No current or recent use of nephrotoxic drugs (NSAIDs, aminoglycosides, iodinated contrast media, etc.)
- No macroscopic signs of structural kidney injury^{*}, defined as:
 - Absence of proteinuria (>500 mg/day)
 - Absence of microhaematuria (>50 RBCs per high power field)
 - Normal findings on renal ultrasonography
- Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. *J Hepatol.* 2015;62(4):968–74. <http://dx.doi.org/10.1016/j.jhep.2014.12.029>

Diagnosis of HRS

- No prior evidence or history of renal impairment
- Subset of pt w/ cirrhosis and ESLD have profound decrease in muscle mass and urea synthesis
 - Results in lower BUN and creat levels.
 - Complicates recognition of ARF in cirrhotic patients
- Many medications may influence intravascular volume status and renal perfusion
 - Diuretics, lactulose, ACE, ARBs, NSAIDs

Burr cells and target cells in liver disease



Classification

- Type 1 HRS: rapidly progressive form of renal dysfunction
 - Serum creat doubles to > 2.5 w/in 2 weeks
 - Rapid decline in hemodynamic parameters
 - Bacterial infxn, GIB, Surgery, acute liver injury
- Type 2 HRS: more slowly progressing entity
 - Severe ascites (diuretic resistant)
 - Serum creat < 2.5
- Type 3 HRS?
 - Many pts w/ cirrhosis and portal hypertension also have underlying CKD

Prevention- Try to Avoid insults

- Intravascular volume depletion,
 - Overdiuresis, diarrhea caused by lactulose, GIB (varices), large-volume paracentesis w/o colloid administration
- Nephrotoxins - CONTRAST
- Infection
 - Consider Prophylactic administration of Abx to pts at high risk of SBP (Neomycin 1 gm q6h)
 - Norfloxacin trial (Fernandez, 2007)

Treatment

- IV Albumin: Bolus 1g/kg/d on presentation (max 100 g/d)
 - Continue at 20 – 60 g/d to keep CVP @ 10-15
- Terlipressin: 1 mg IV Q4hr & up to 2 mg if baseline serum creat does not improve by 25% at day 3 (not available in US)
- Midodrine & Octreotide
 - M: 2.5 – 5 mg PO TID up to 15 mg TID
 - O: 100 mcg SQ TID to 200 mcg TID or 25 mcg IV bolus + 25 mcg/hr
- Norepinephrine: 0.1 – 0.7 mcg/kg/min and inc by 0.05 Q4hr
- Duration of vasopressor treatment is generally a max of 2 weeks until reversal of HRS or Liver Transplant.

Treatment

- Terlipressin vs Midodrine
 - Unblinded study from 2015
 - Terlipressin improved renal function better than Midodrine/Octreotide
 - 70% vs 29%
 - However, no significant difference in 3 month survival.
 - Cavallin, Hepatology. 2015 see ref.

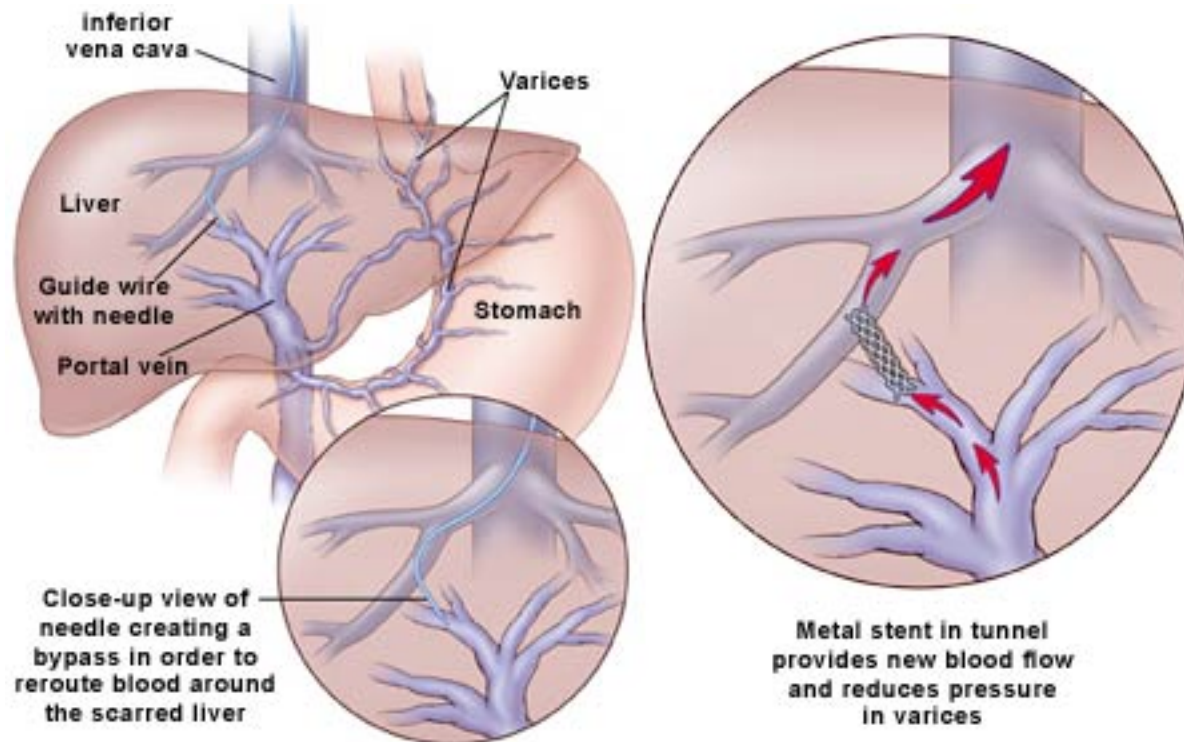
Treatment of HRS

- Midodrine: 5-10 mg up to TID
 - Side effects: tachycardia, angina
- Octreotide: 50 Microgram SQ or IV BID or TID. Max dose 1500 mcg/day.
 - Side effects: diarrhea, N/V, syncope, bradycardia.

Treatment

- Transjugular Intrahepatic Portosystemic Shunt - TIPS
 - Effective for treatment of diuretic-resistant ascites
 - 4 pilot studies have evaluated the use of TIPS in nontransplant candidates with type 1 & 2
 - Limited by potential to accelerate liver dysfunction and worsen encephalopathy

TIPS



Treatment

- Orthotopic Liver Transplantation (OTL)
 - ONLY therapy that has the potential to reverse
 - Should be considered in any pt found to have HRS
 - 35% of pts w/ HRS require long-term renal replacement
 - 3 yr survival is approximately 60%
 - Degree of renal dysfunction preoperatively may be independent predictors of survival
 - Pts who responded to a vasopressin analog prior to OTL had outcomes similar to those of pts who had OTL w/o HRS

HRS Treatments under going study

- Pentoxifylline 400 mg TID with meals
 - Trental
- Vaptans : Samsca 15-30 mg daily,
 - Tolvaptan = samsca
 - Conivaptan - Vaprisol (IV version)

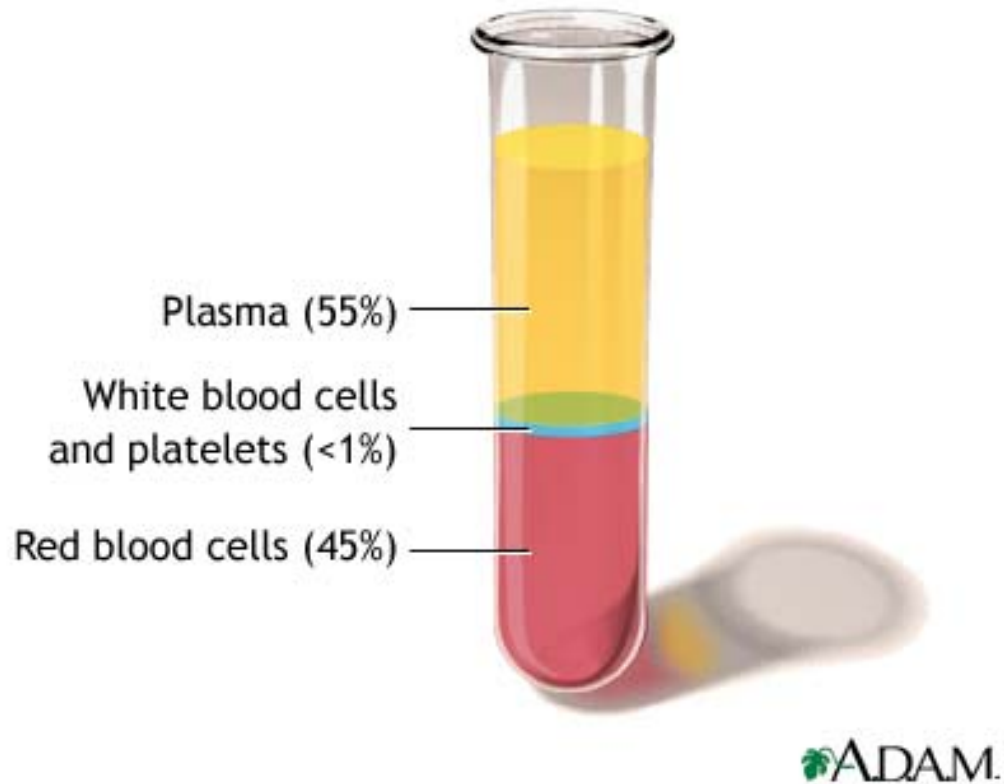
Renal Replacement Therapy in HRS

- Acute RRT has been controversial
 - May be contra-indicated in patients who are not candidates for liver transplant
 - But how do you know who is a candidate?
- Not All AKI is due to HRS
- Survival may be better in patients with ATN or Acute GN and it may take time to sort out which renal injury is involved
- May be a bridge to transplant, or
- May buy time to make a decision about hospice care, etc. *Medscape Presentation March 2018.*

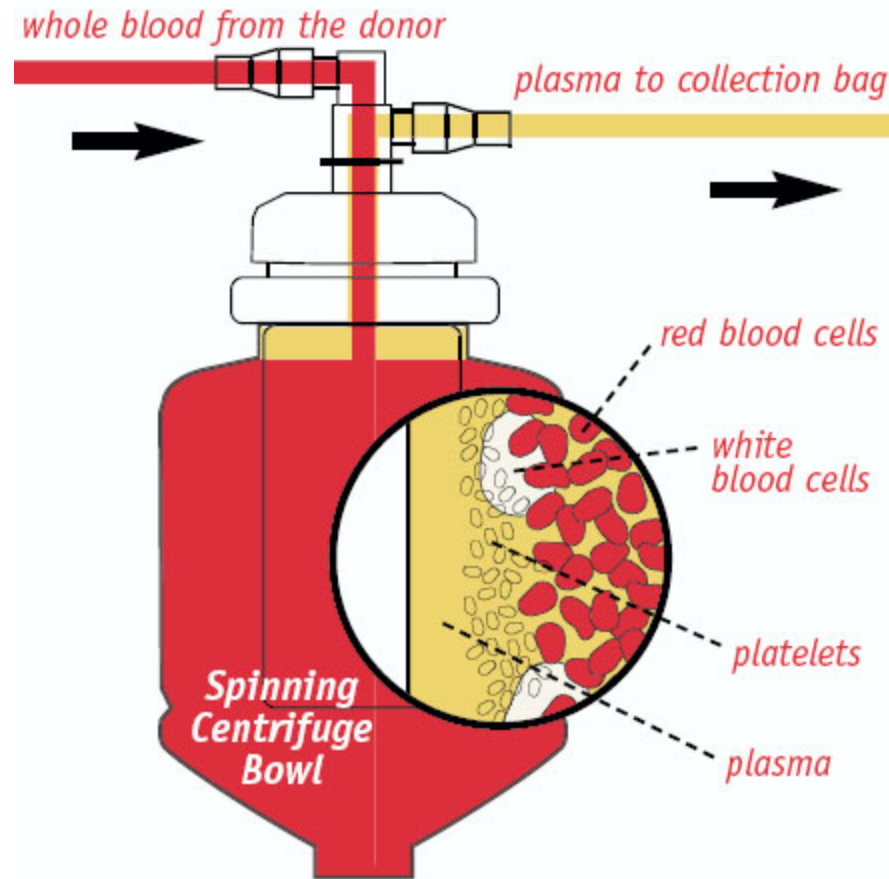
Liver Dialysis

- Hepatassist treatment
 - Dialysis-like treatment that clears plasma of nitrogenous wastes
 - Actually more like a combo of plasmapheresis and hemodialysis

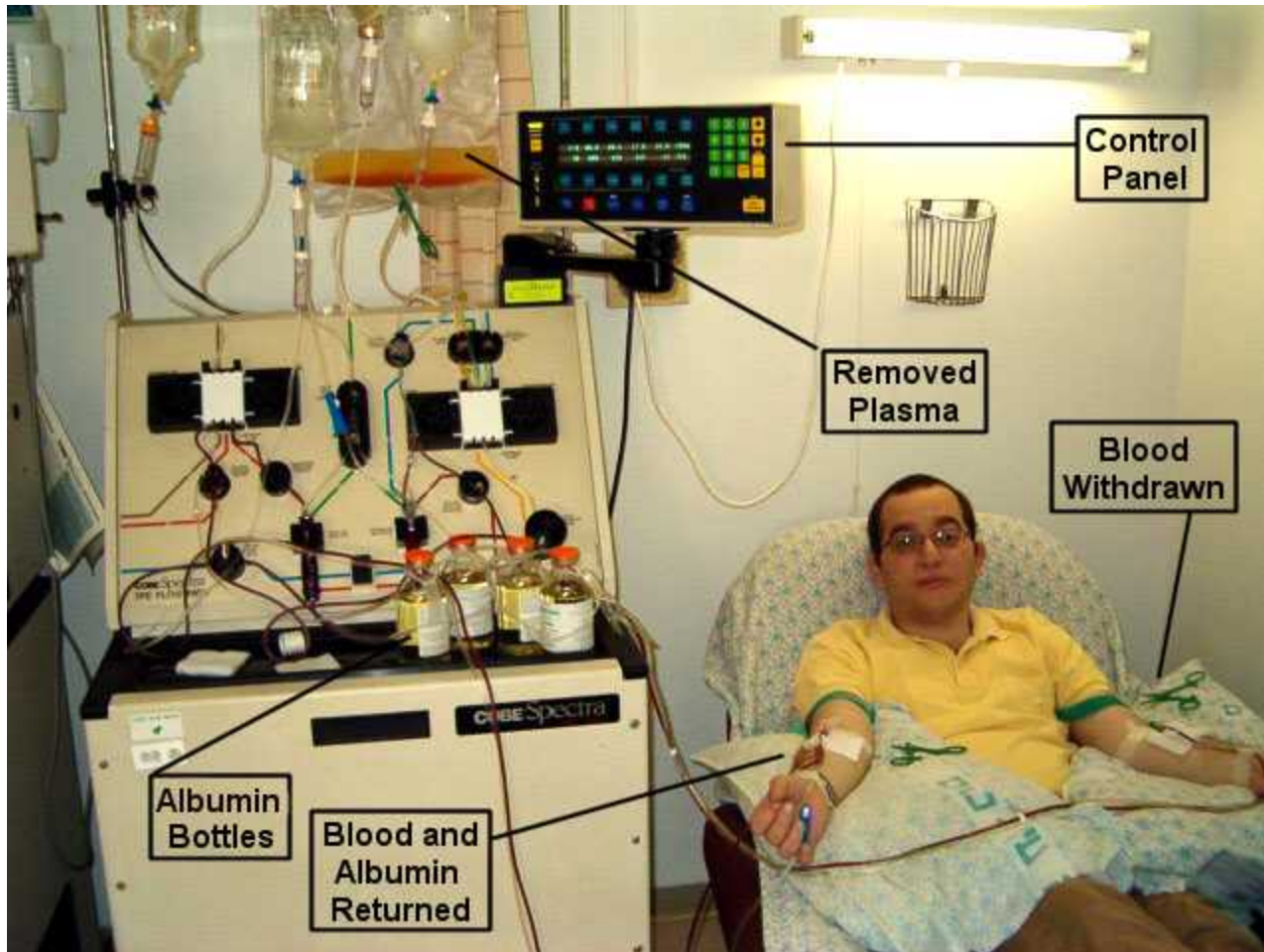
Whole blood fractions



Plasmapheresis Centrifuge

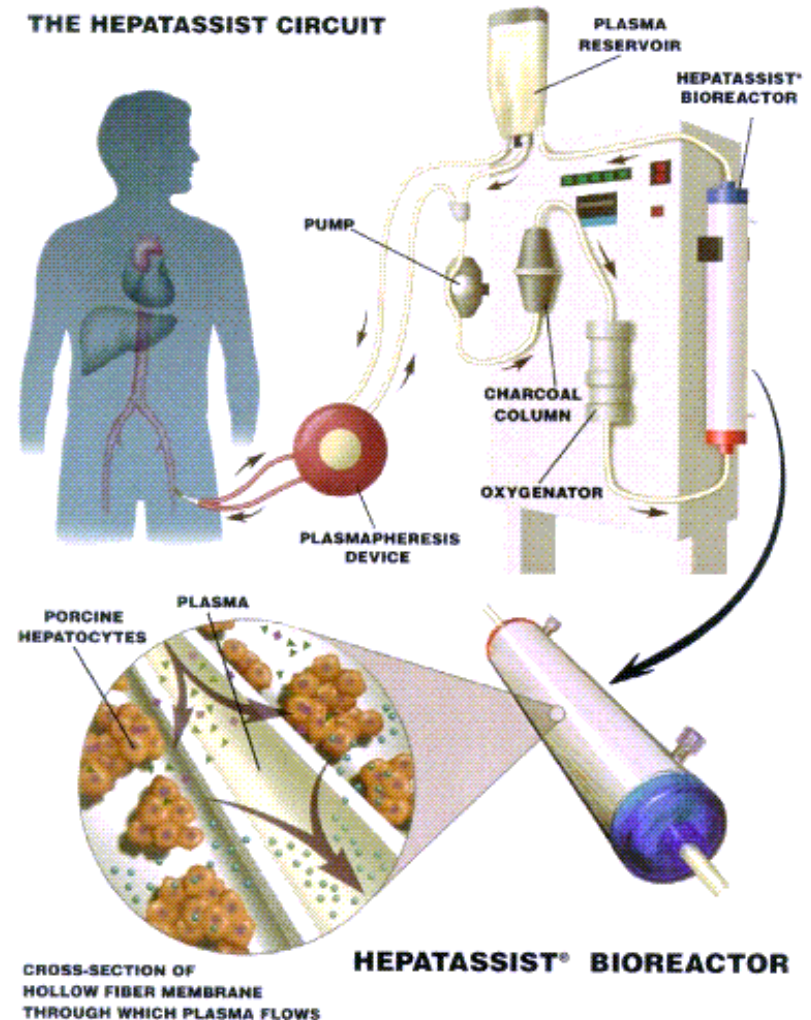


Plasmapheresis Patient



Hepatassist for liver failure

- Plasmapheresis
- Circuit for
 - Regeneration of
 - Perfusate and
 - Oxygenation
- Hollow fiber kidney
- Porcine Hepatocytes



Prognosis

- Prior to advent of newer therapies median survival for pts w/ type 1 HRS was 1.7 weeks and 90% dead w/in 10 wks
- Today treatments have allowed some increase in short-term prognosis

MELD Score and mortality

	Compensated Cirrhosis		Decompensated Cirrhosis	
Stage	Stage 1	Stage 2	Stage 3	Stage 4
Clinical	No Varices No Ascites	Varices No Ascites	Ascites +/- Varices	Bleeding +/- Ascites
Death (at 1 Year)	1%	3%	20%	57%

References

- Sleisenger & Fordtran's Gastrointestinal and Liver Disease Pathphysiology/Diagnosis/Management . 9th edition. Ch 92
- P.A. McCormick. Management of hepatorenal syndrome. Pharm & Therap. 119 (2008) 1-6.
- T Restuccia. et al. Effects of treatment of hepatorenal syndrome before transplantation on post transplantation outcome. A case-control study. Journ of Hepat. 40 (2004) 140-146.
- P Gines. Renal Failure in Cirrhosis. N Engl J Med. 2009;361:1279-90
- <https://cdn.hepatitisc.uw.edu/> Prognosis in Cirrhosis.
- Angeli P, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. J Hepatol. 2015;62(4):968–74.
<http://dx.doi.org/10.1016/j.jhep.2014.12.029>

References

- Diabetes and Hep C: a two way Association. Hammerstad et al. Front Endocrinol 2015; 6: 134 Published online
- Cavallin M, et al. Terlipressin plus Albumin versus Midodrine and Octreotide plus albumin in the treatment of hepatorenal syndrome. Hepatology. 2015;62(2). 567-574
- Boyer TD, et al. Terlipressin plus albumin is more effective than albumin alone in improving renal function in patients with Cirrhosis and HRS Type 1. Gastroenterology. 2016;150(7) : 1579-1589
- O'Brien Z et al. Higher vs Lower CRRT intensity in Critically Ill patients with Liver Dysfunction. Blood Purification. 2018;45:36-43