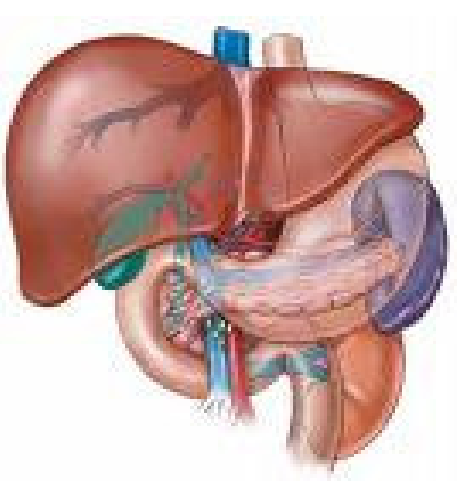

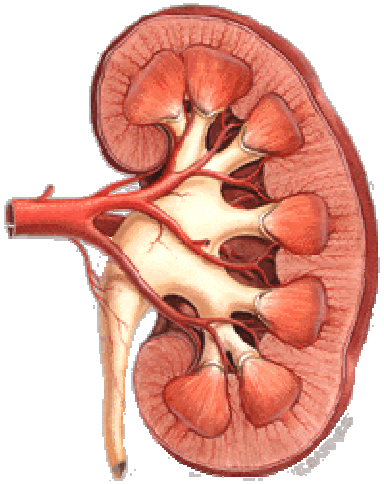

Liver and Kidney Interactions in Health and Critical Illness

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Emory University School of Medicine
Director, Critical Care Medicine and ECMO
Children's Healthcare of Atlanta at Egleston

The Liver and Kidney in Health

- Short list
- Vitamin D metabolism: 25,1-hydroxylation
- Hepatic regulation of renal function
  - Uncertain normal state
  - Hepatic osmoreceptors?
  - Enteral ingestion of protein: increased GFR
    - Liver-borne diuretic factor?

- Lang, Tschernko, Haussinger Exp Physiol 1992:77,663

The Liver and Kidney in Critical Illness

- Renal failure in the setting of liver failure
- Hepatorenal syndrome
- Liver transplant-associated interactions

Causes of Renal Failure in Patients with Liver Disease

- Prerenal
  - Volume depletion
- Congestive heart failure
- Nephrotic syndrome
- Anaphylaxis
- Anesthesia
- Renal
  - ATN
  - Toxic-drugs, solvents, heavy metals, heme
- Postrenal
  - Ureteral, bladder-outlet obstruction
- No specific cause: Hepatorenal Syndrome (HRS)

Hepatorenal Syndrome (HRS)

- Frerichs (1861) and Flint (1863): first noted association of liver disease and oliguria without renal histologic changes
- Hecker and Sherlock (Lancet 1956) describe HRS
- Still no definitive treatment

-Wadei et al. Clin J Am Soc Nephrol 2006
-Bunn, Symons, www.emedicine.com 2006

Hepatorenal Syndrome (HRS): Diagnostic Criteria

- 6 Major Criteria (Adult-no pediatric)
  - Low GFR (SCr > 1.5 mg/dl or CrCl < 40 ml/min)
  - Absence of shock, ongoing bacterial infection, fluid losses, nephrotoxic drugs
  - No sustained improvement in renal function
  - Proteinuria < 500 mg/dl
  - No U/S evidence of obstructive uropathy or parenchymal renal disease

- Additional Criteria
  - Urine volume < 500 ml/day
  - Urine sodium < 10 mEq/L, serum Na < 130 mEq/L
  - Urine osmo > plasma osmo

Hepatorenal Syndrome (HRS): Types

- Type 1
  - Rapidly progressive renal failure
  - Doubling of creatinine
  - Precipitating factor frequently identified
- Type 2
  - Moderate, steady renal failure
  - Milder elevation of creatinine
  - May arise spontaneously

Hepatorenal Syndrome (HRS): Does It Exist in Children?

- Little data-short answer: yes
- HRS most often occurs with advanced liver disease
- Can occur with acute hepatic failure/FHF
- No specific criteria for HRS in children
- Estimated 5% incidence of HRS in children with chronic liver disease (vs. 10-15% in adults)

HRS: Mechanism

- Hallmark: **Intense renal vasoconstriction**
- Starts at an early time point and progresses with worsening liver disease
- Not well studied in humans

HRS: Pathophysiologic Mechanisms

1. Peripheral (splanchnic) arterial vasodilation → subsequent renal vasoconstriction
2. Stimulation of renal sympathetic nervous system
3. Cardiac dysfunction → circulatory derangements and renal hypoperfusion
4. Cytokine/mediator action on renal circulation

HRS: Pathophysiologic Mechanisms

Peripheral arterial vasodilation → subsequent renal vasoconstriction:

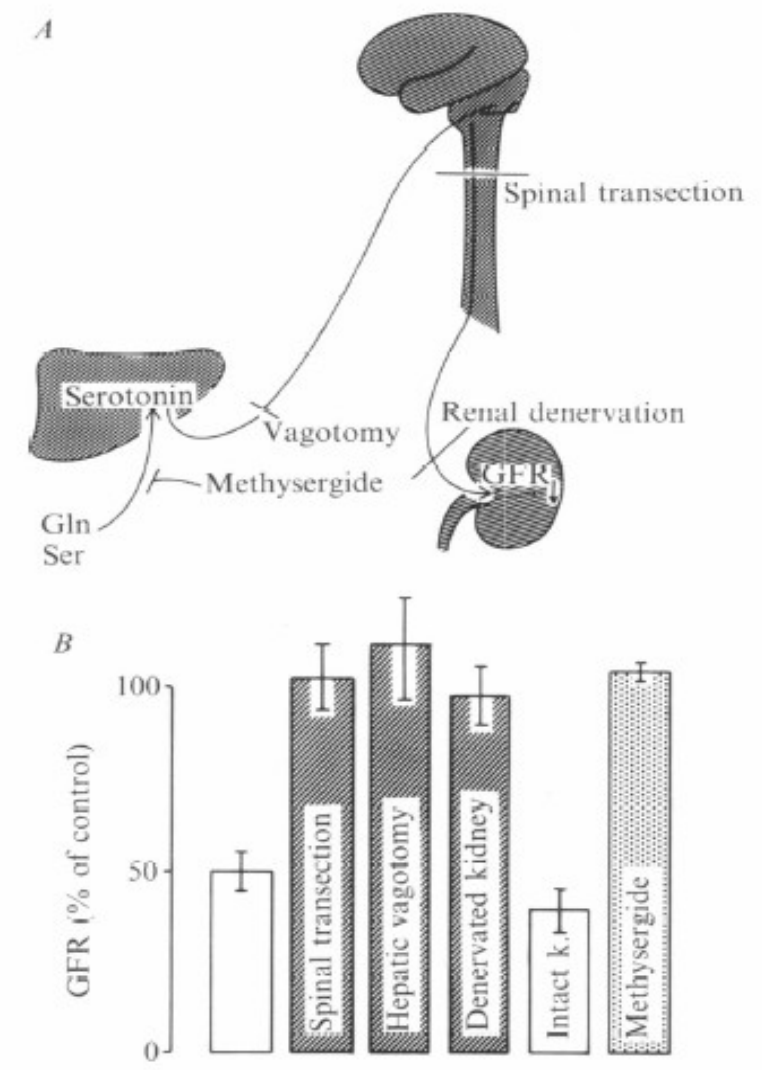
- ECV ↓ 2° to increased resistance through cirrhotic liver→increased splanchnic pooling
- Vasodilation of systemic and splanchnic circulation (cytokines)
- Activation of SNS, renin-angiotensin→ hyperdynamic circulation with ↓ SVR, ↑ CO, ↓ MAP
- Hyperdynamic circulation→renal vasoconstriction

HRS: Pathophysiologic Mechanisms

Stimulation of renal sympathetic nervous system:

- SNS tone increased with cirrhosis
- Increased intrahepatic pressure increases SNS = hepatorenal reflex?
- Increased arginine vasopressin, renin-angiotensin system response
- May play a selective role in vasoconstriction

Hepatorenal Reflex-Putative



- Amino acid infusion: hepatocyte swelling →reduction in GFR
- Response abolished by severing renal, hepatic, spinal nerves
- Activation by increased portal venous pressure, decreased sinusoidal flow

- Lang, Tschernko, Haussinger Exp Physiol 1992:77,663

HRS: Pathophysiologic Mechanisms

Cardiac dysfunction → circulatory derangements and renal hypoperfusion:

- Impaired myocardial function observed
- ↓Myocardial beta receptor transduction
- NOx and cytokine inhibition of function
- Diastolic dysfunction
- Impaired contractility

HRS: Pathophysiologic Mechanisms

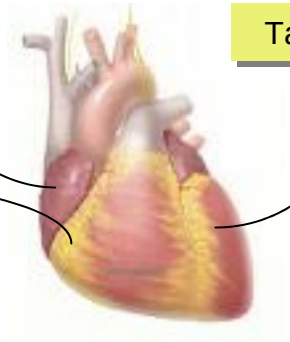
Cytokine/mediator action on renal circulation:

- NOx greatest attention
- Splanchnic shear stress→ increased eNOS→ increased NOx
- Lots of evidence for increased NOx
- Shouldn’t it counteract renal vasoconstriction?

1. ↑ Renal sodium retention
2. ↓ Capacity to secrete solute free water
3. Hyponatremia
4. ↓ GFR

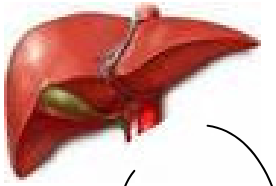
Atrial natriuretic peptide

Cardiac dysfunction



Tachycardia

↓ Renal VD
↑ Renal VC



Portal hypertension

↑ NO

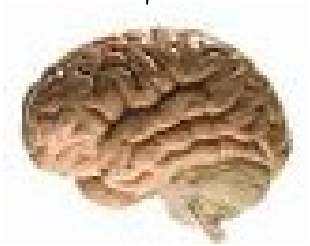
↑ RAAS

Renal vessels

Vasopressin release

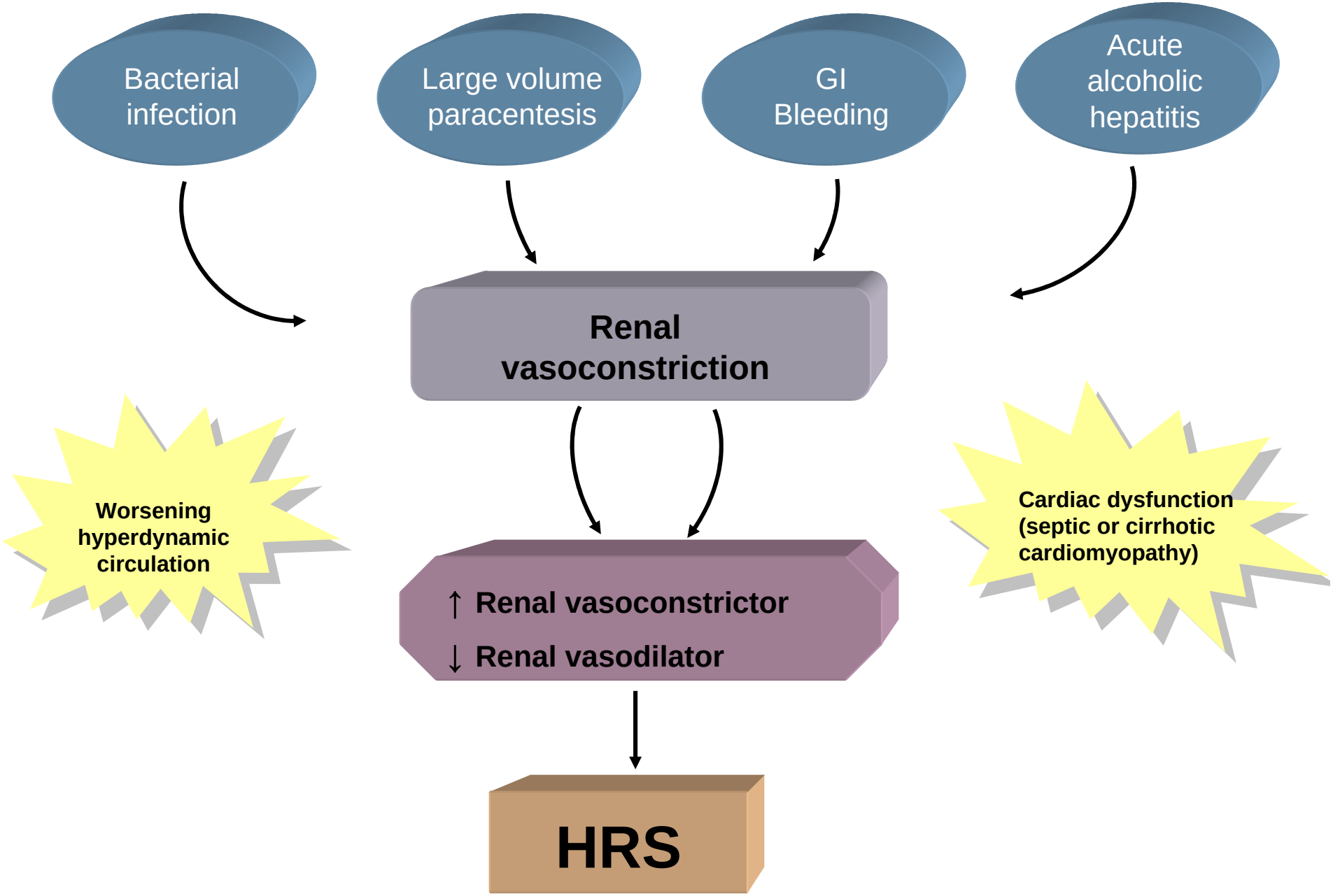
↑ SNS

Splanchnic vasodilation



Baroreceptor activation

↓ Effective circulating volume



Aggravating/Precipitating Factors

HRS: Prognosis

- Adult data
- Type 1: 80% 2 week mortality, 90% 3 month
- Type 2: 6 month median survival
- Prognosis worse if precipitating factor exists
- Severity of liver disease a determinant of survival

HRS: Treatment

- General measures:
  - Central venous access
  - Monitor fluid status
  - Volume: albumin/furosemide to titrate CVP
  - Nutrition critical: avoid high protein; low salt, free water restriction

HRS: Specific Treatments

- Renal vasodilators
- Systemic vasoconstrictors
- TIPS
- Renal replacement therapy
- Liver/renal replacement therapy
- Liver transplantation

HRS Treatment: Vasodilators

- Dopamine
- Fenoldopam
- Low-dose dopamine: no benefit for HRS GFR or urine flow

HRS Treatment: Systemic Vasoconstrictors

- Most promising pharmacologic agents
- Effort to decrease splanchnic vasodilation
  - Vasopressin analogues (terlipressin, vasopressin)
  - Somatostatin analogues (octreotide): not effective
  - Alpha-adrenergic agonists (norepinephrine)

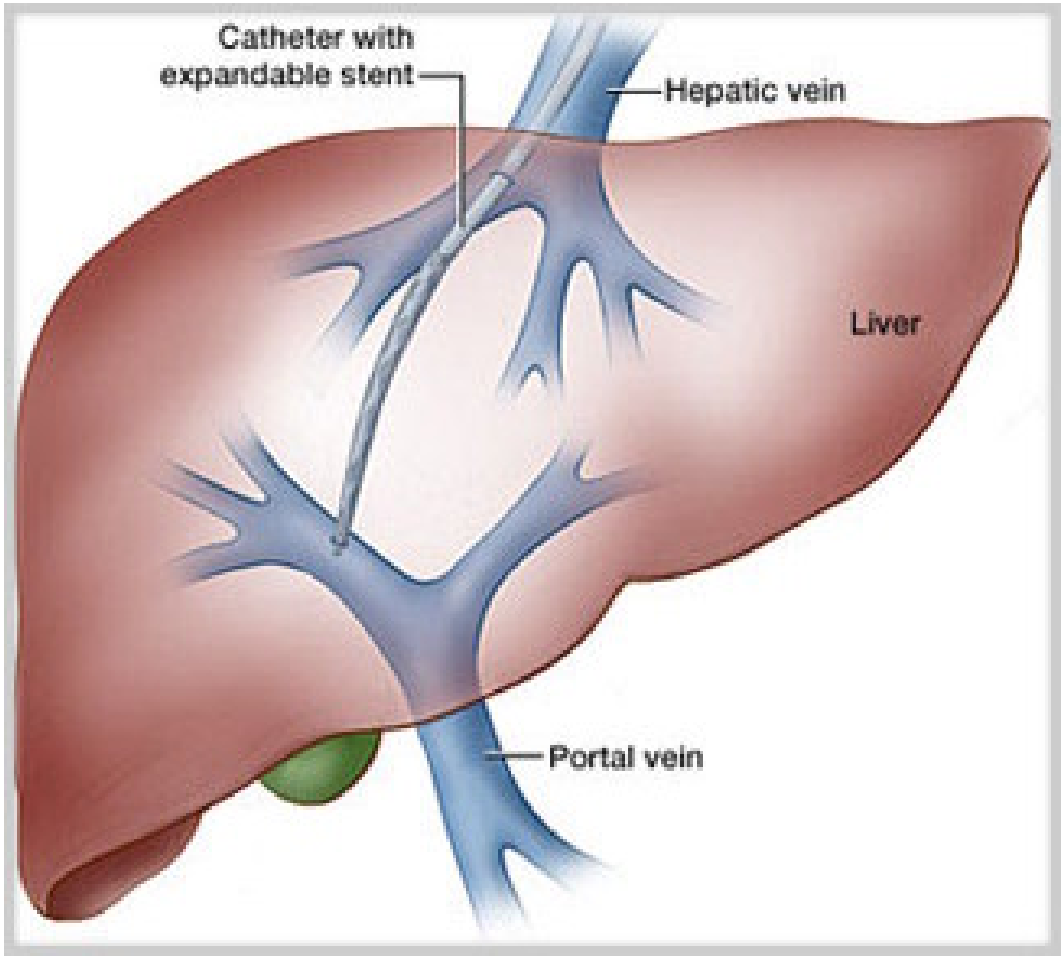
HRS Treatment: Vasopressin Analogues

- V1 receptor agonist-arterial smooth muscle
- Terlipressin best studied
  - Improved GFR, reduction of creatinine in 42-77% in several studies
  - In combination with albumin
  - Palliative only
- Vasopressin used in US due to availability
- What is renal effect?

HRS Treatment: TIPS

- Transjugular intrahepatic portosystemic shunt
- Reduction of portal venous pressure→ possible suppression of hepatorenal reflex, improved function
- 10 week HRS survival 53-81% with TIPS in adults

TIPS


Catheter with
expandable stent
Hepatic vein
Liver
Portal vein

HRS Treatment: TIPS

- Response: ability to d/c dialysis
- Decreased vasoconstrictor substances
- Hepatic encephalopathy and cardiac function may worsen
- Experience with children has been primarily for portal hypertension (> 5 years)

HRS Treatment: Renal Replacement Therapy

- May be reasonable option as bridge to transplant
- CRRT better tolerated than HD (Davenport, Detry)
- Cytokine removal produced: but is it an advantage?
- Prospective study: no benefit of CRRT over HD- BUT all ventilated pts. got CRRT (Witzke, 2004)
- Benefit of high ultrafiltrate flow CVVH?

Is Plasmapheresis Alone Helpful for Hepatic Failure in Children?

- 49 children with FHF
- Daily pheresis until death or transplantation
- Improved coagulopathy
- No sustained CNS improvement
- No impact on recovery

- Singer et al., Annals of Surgery 2001

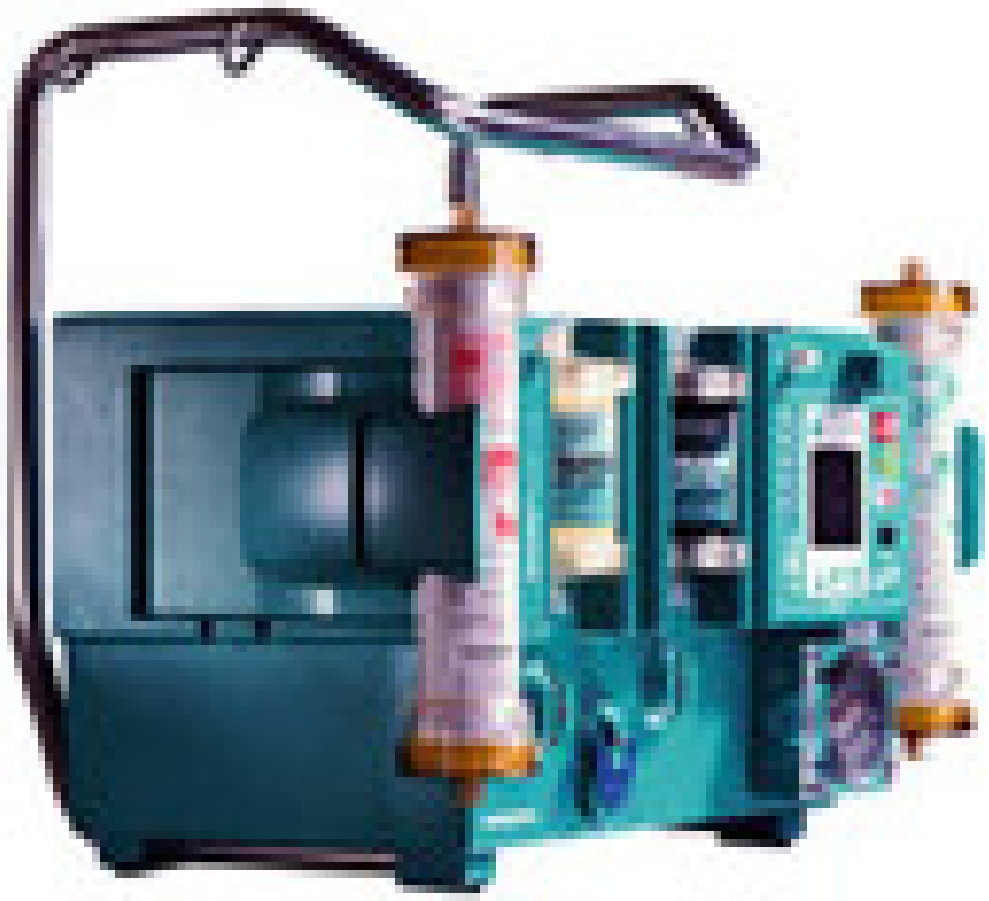
HRS Treatment: Extracorporeal Liver Support Devices

- Promising therapy
- = RRT + LRT
- 2 Basic Approaches
  - Artificial
    - MARS
    - Prometheus
    - Coupled plasma filtration/absorption and hemofiltration
  - Non-artificial
    - Hepatocyte supported

Disclosure

- I have no financial interest to disclose regarding these devices

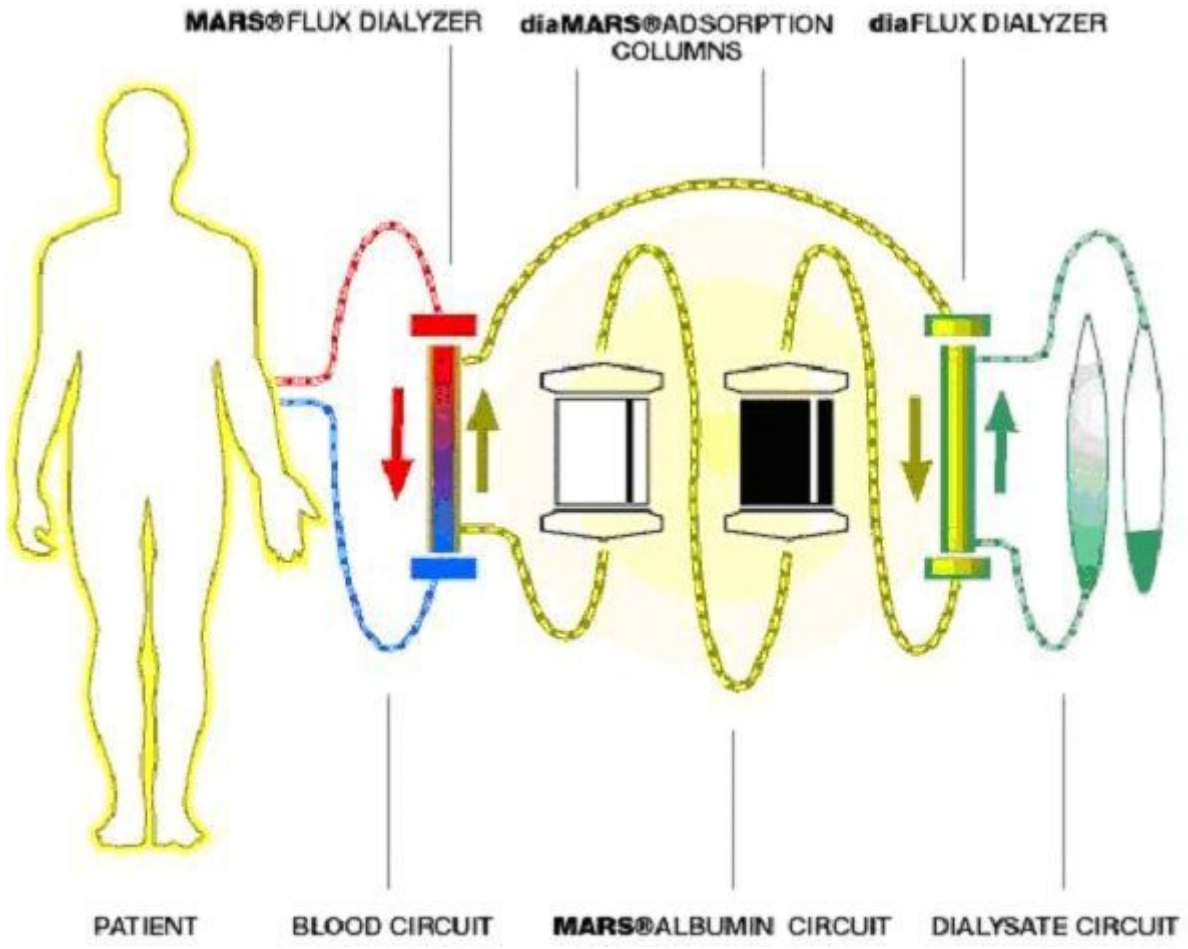
MARS System



HRS Treatment: MARS Experience

- MARS: Molecular Adsorbent Recycling System
- Polysulfone high permeability dialyzer (< 50K MW)
- 20% albumin dialysis for protein-bound (bilirubin, etc.) toxins
- Cleansing system to recycle dialysate
  - Hemofiltration
  - Charcoal adsorbent column
  - Anion exchanger
- Hemofiltration removes water-soluble toxins (NH_3, creatinine), and allows fluid balance

MARS System

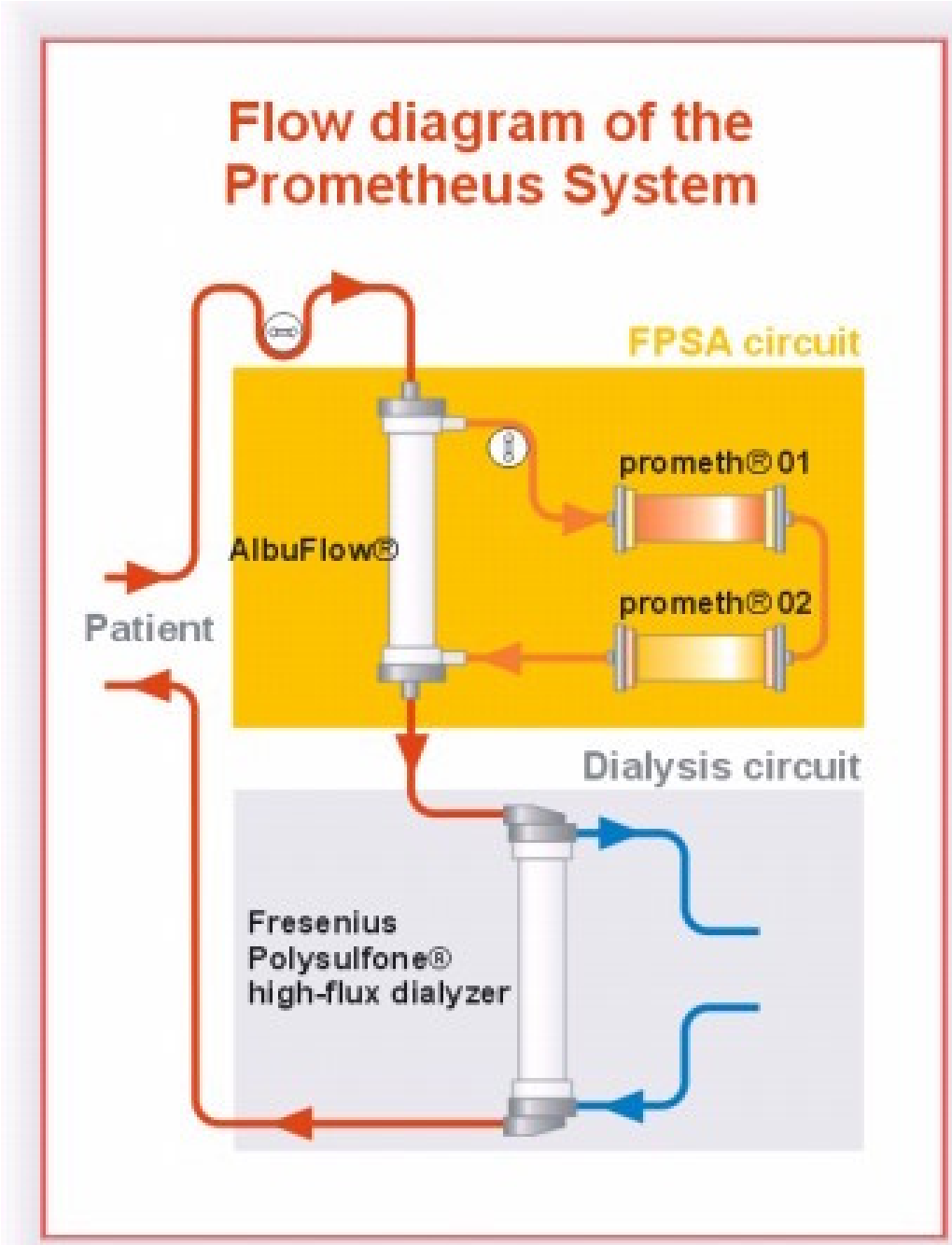

MARS® FLUX DIALYZER
diaMARS® ADSORPTION COLUMNS
diaFLUX DIALYZER
PATIENT
BLOOD CIRCUIT
MARS® ALBUMIN CIRCUIT
DIALYSATE CIRCUIT

HRS Treatment: MARS Experience

- International MARS registry (over 176 patients, some children)
- Anecdotal reports (4 in children)
- Industry data: 79 pts., improved encephalopathy
- Prospective Adult RCTs
  - Mittzner (2000)
    - 6/8 MARS vs. 5/5 control deaths
    - Mean survival 25d vs. 4.6 days
    - Buying time?
  - Heeman (2002)
    - 1/12 MARS vs. 6/12 control deaths

Prometheus System

- Mythological foundation
- Newer artificial liver/kidney support device
- Fractionated plasma separation and adsorption (Falkenhagen, 1999)
- Possible advantages over MARS


Flow diagram of the Prometheus System
FPSA circuit
prometh® 01
AlbuFlow®
prometh® 02
Patient
Dialysis circuit
Fresenius
Polysulfone®
high-flux dialyzer

ELKS System Differences

- MARS
  - 50 kDa filter
  - Dialyzed albumin passes through adsorbers
  - Hemodialysis of dialyzed fraction only
  - Plasma/HD circuits in series
- Prometheus
  - 250 kDa filter
  - All separated albumin passed through adsorbers
  - High flux hemodialysis of all blood: better renal effect?
  - Plasma/HD circuits in parallel: can perform one or both

Prometheus: Clinical Experience

- Case reports:
  - Young adult-cocaine ingestion, rhabdomolysis, liver failure
  - 2 year old in liver failure for retransplant
- Small case series (N = 9,11) with good clearance of ammonia, bilirubin, creatinine
- No clinical outcome data

-Rifai, Manns, Ther Apher Dial 2006

Prometheus vs. MARS

- Crossover trial: MARS vs. Prometheus:
  - Prometheus-higher clearance of ammonia, urea
  - Higher reduction ratios
- Crossover trial for cytokine clearance
  - Cytokines elevated baseline
  - Both produced clearance but no overall effect on serum levels

-Stadlbauer et al., Crit Care 2006

-Evenepoel et al., Artificial Organs 2006

Current Device Use

- MARS and Prometheus used in Europe
- MARS FDA approved in adults in US for certain conditions/not approved for use in children
- No pediatric trials to date/no plans for US pediatric study at present
- Small MARS filters/lines (60 ml and 0.6 m^2 area) now available for children

HRS Treatment: Extracorporeal Liver Support Devices

- Meta-analysis
  - Review of 12 trials
  - Overall support systems: no mortality effect BUT revised (-1973 trial) RR 0.78; 95% CI 0.61-1.00
  - Mortality
    - reduced in acute-on-chronic liver failure (RR 0.67; 95% CI 0.51-0.90)
    - not in acute liver failure

-Kjaergard et al., JAMA 2003

HRS Treatment: Liver Transplantation

- Still the most definitive treatment for HRS
- 2 year OLT patient and graft survival similar with and without HRS (Gomwa et al., 1991)
- More recent: HRS post-transplant ARF reversal in only 58% (Marik, NDT, 2005)
- BUT similar to non-HRS patients IF treated with vasopressin pre-op (Arroyo, Hepatology, 2005)

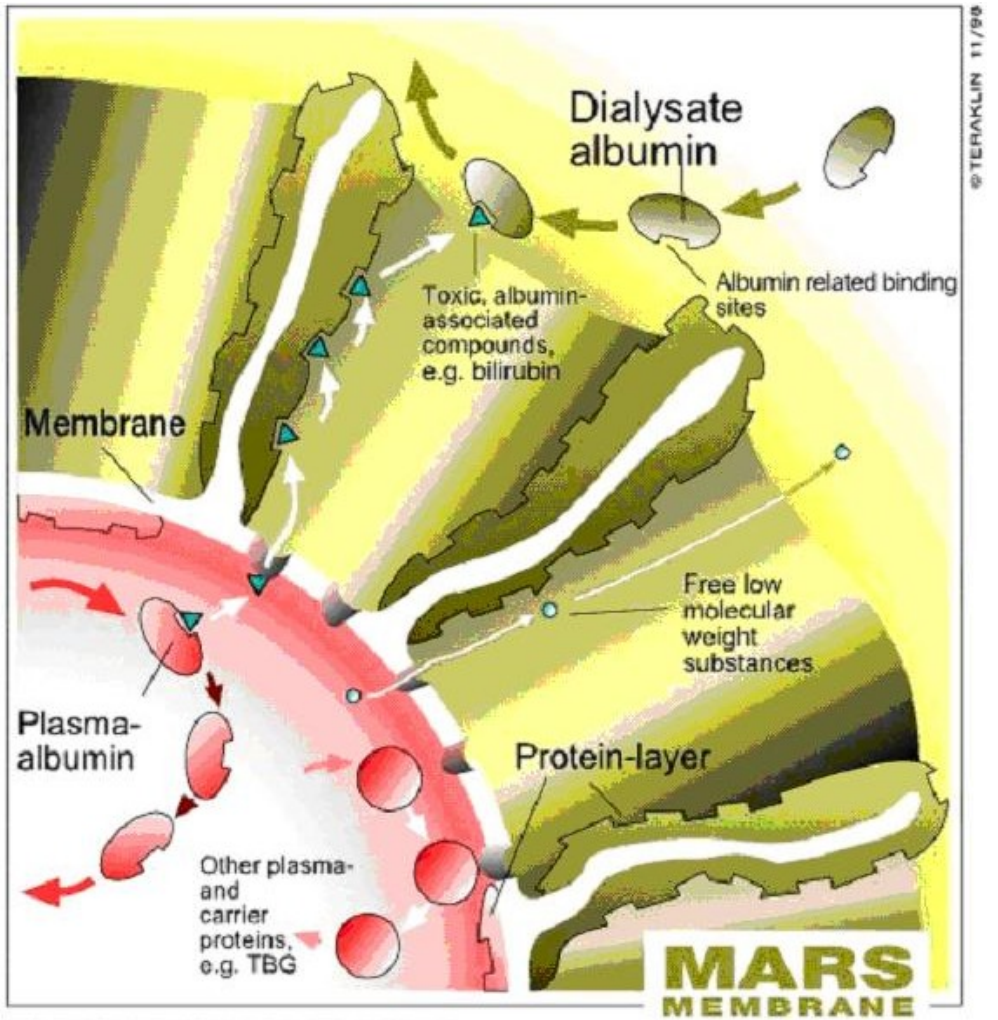
HRS Treatment: Liver Transplantation

- Post-tx renal recovery in HRS also more likely in younger adults, non-alcoholic liver dz
- In acute FHF, getting to transplant is the problem
- HRS NOT an exclusion in AASLD transplant guidelines (but think about it!)

Conclusions

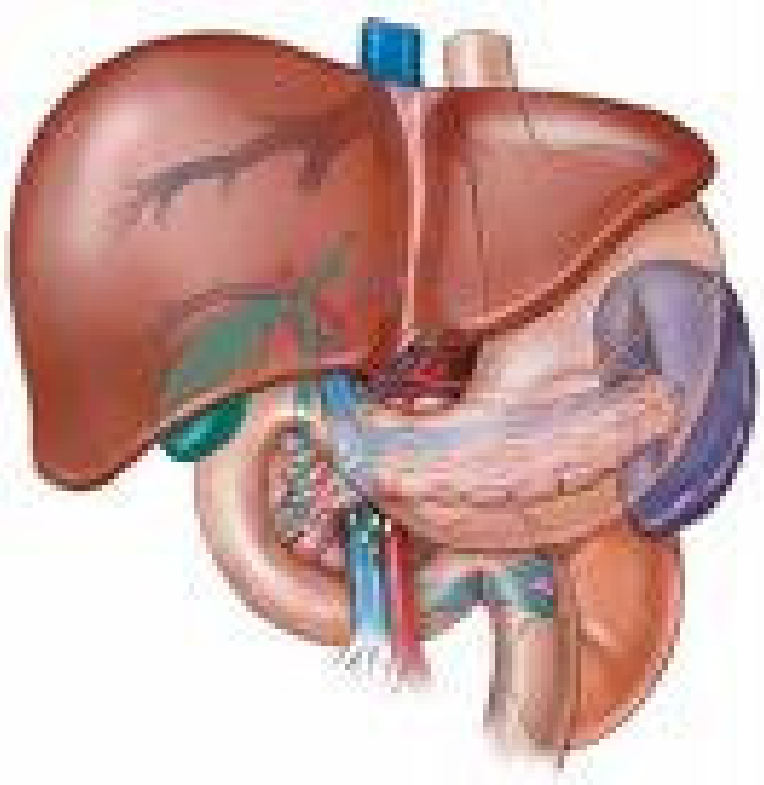
- Liver interactions potentially alter kidney function in critical illness
- Renal vasoconstriction drives HRS
- Hepatorenal syndrome is a potential risk for children with high mortality
- Multiple therapies for HRS-no magic bullet
- Potential for extracorporeal devices in adults and children

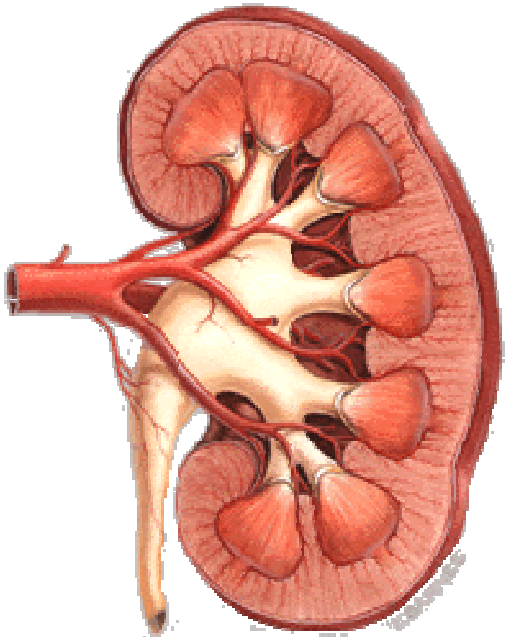
Liver and Kidney Go Well Together



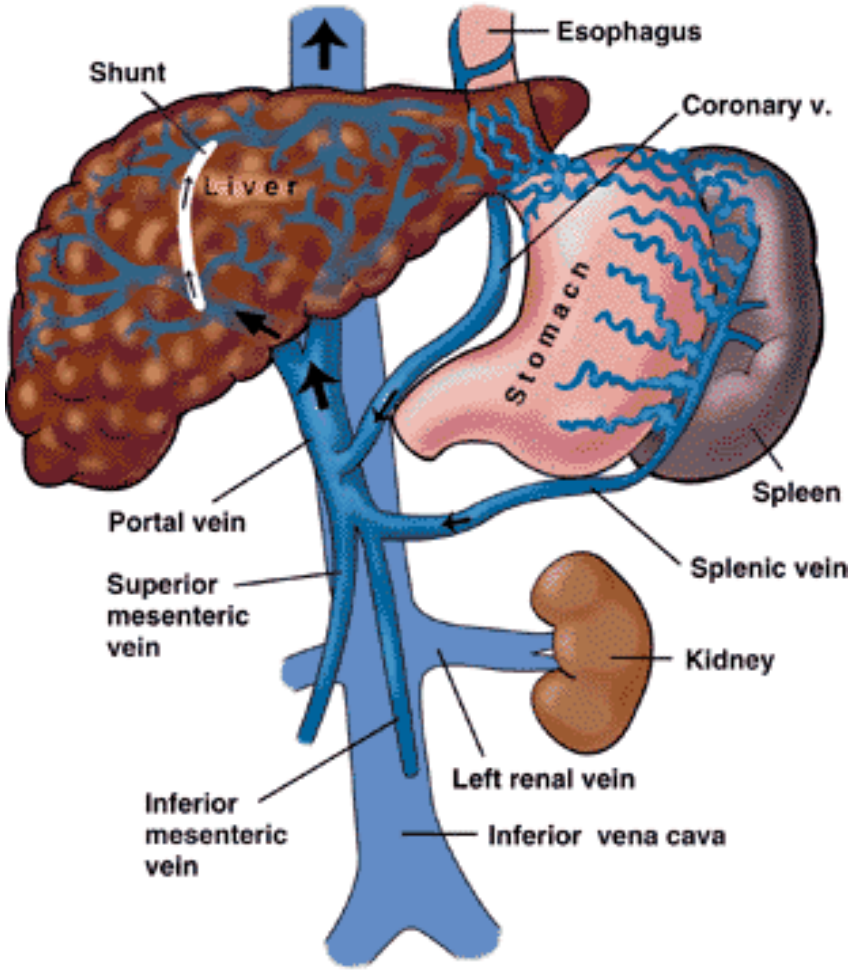
ELIMINATION OF TOXINS

Liver-Kidney Interactions





TIPS


Esophagus
Shunt
Coronary v.
Liver
Stomach
Spleen
Portal vein
Splenic vein
Superior mesenteric vein
Kidney
Left renal vein
Inferior mesenteric vein
Inferior vena cava

Liver Transplantation: Post-Op Impact on Renal Function

- Renal function in general worsens over time
  - Adults: 10% incidence
  - Children: post-transplant up to 32%

HRS: Diagnosis

- Clinical criteria: need major criteria to differentiate
- May be difficult to differentiate from other causes of ARF in liver failure
- Urine sodium may be helpful
- HRS may have high urine sodium if treated with diuretics