

**The Hepatorenal Syndrome and  
Extracorporeal Liver Support**

**AKI 2010**  
Acute Kidney Injury and Renal Support

Constantine Karvellas MD FRCPC  
Assistant Professor  
Divisions of Gastroenterology (Liver Unit) and Critical Care  
Medicine  
University of Alberta

---

---

---

---

---

---

---

---

**I have no actual or potential conflict of  
interest in relation to this program or  
presentation.**

**AKI 2010**  
Acute Kidney Injury and Renal Support

---

---

---

---

---

---

---

---

**Hepatorenal Syndrome (HRS)**

- circulatory dysfunction of cirrhosis
  - ↑ systemic vasodilators (NO)
  - splanchnic arterial hypoperfusion
  - activation of RAS
  - Intense renal vasoconstriction → ↓GFR
- may occur spontaneously or secondary to factors that induce renal hypoperfusion
  - bacterial infections (SBP)
  - GI bleeding

---

---

---

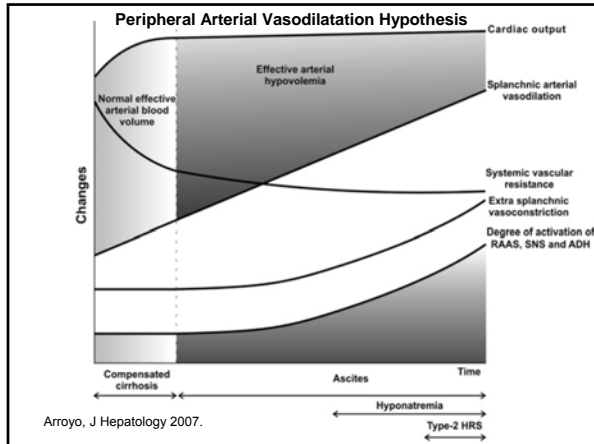
---

---

---

---

---




---

---

---

---

---

---

---

---

---

---

- ### HRS: Diagnostic Criteria
- Evidence of Portal Hypertension
  - Acute Kidney Injury
    - Cr > 150 or GFR < 40 ml/min
  - Absence of shock, recent treatment with nephrotoxic drugs and ongoing infection\*
    - Renal failure does not improve despite antibiotics
      - 1/3 of pts with SBP have transient renal dysfunction (not HRS)
  - No sustained improvement despite diuretic withdrawal or plasma expansion (albumin, NS)

---

---

---

---

---

---

---

---

---

---

- ### Clinical Types of HRS
- Type I
    - frequently associated with precipitating factor
      - Infection
      - Decompensation in hepatic function
    - rapidly progressive renal failure
    - doubling of Cr to > 250 in < 2 weeks
  - Type II
    - slowly progressive renal failure
      - Cr < 250
    - usually in the setting of ascites refractory to diuretic therapy

---

---

---

---

---

---

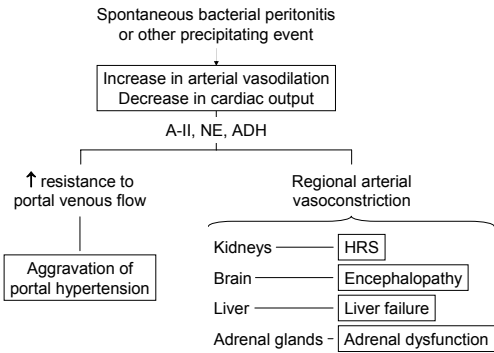
---

---

---

---

### TYPE-I HRS AS A PART OF A MULTIORGAN FAILURE




---

---

---

---

---

---

---

---

---

---

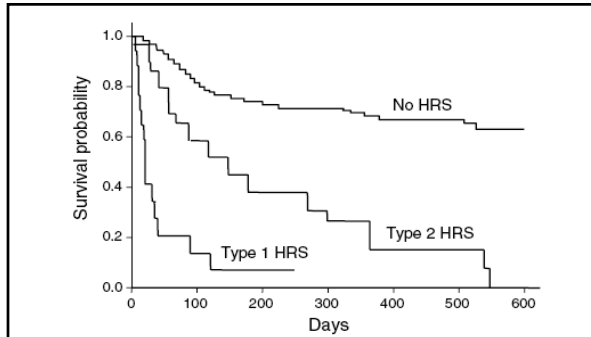


Fig. 2. Survival of patients with cirrhosis and ascites without HRS (data obtained from Llach et al. [22]) and with type-1 and type-2 HRS (data obtained from Ginès P et al. [6]).

Arroyo, J Hepatology 2007.

---

---

---

---

---

---

---

---

---

---

### Therapies: Non-RRT

- Vasoconstrictors
  - Vasopressin analogues
    - Vasopressin, Terlipressin
  - Alpha-adrenergic agonists
    - Norepinephrine, Midodrine
- Mechanism
  - reverse arteriodilatation
  - usually in combination with albumin/plasma expansion
  - most studies report modest mortality improvement
    - 41% at one month in HRS Type 1.

---

---

---

---

---

---

---

---

---

---

## Toxin Hypothesis: Albumin

- most toxins in liver failure are water insoluble
- albumin binds toxins in liver failure<sup>1</sup>
  - Conjugated bilirubin, bile acids, inflammatory cytokines, aromatic amino acids, endogenous benzodiazepine ligands
- benefits exceed what would be expected with simple volume expansion<sup>2</sup>
- basis of albumin dialysis
  - blood is dialyzed against an albumin containing solution across a suitable membrane

1. Evans, Aliment Pharmacol Ther, 2002.  
2. Gines et al, Gastroenterology, 1996.

---

---

---

---

---

---

---

---

### RESULTS OF TWO RANDOMIZED CONTROLLED TRIALS COMPARING TERLIPRESSIN AND ALBUMIN (T+A) vs ALBUMIN ALONE (A) IN PATIENTS WITH HRS

	Martín-Llahí et al.		Sanyal A et al.	
	T+A	A	T+A	A
Patients	23	22	56	56
Reversal of HRS	8 (34.7%)	1 (4.6%)	19 (34%)	7 (13%)
3 months survival	26%	18%	48%*	48%*

\* 2 months survival

Gastroenterology 2008

---

---

---

---

---

---

---

---

## Albumin-based dialysis systems

### MARS

Molecular adsorbent recirculation system

### Prometheus (FPSA)

Fractionated plasma separation and adsorption

### SPAD

Single-pass albumin dialysis

---

---

---

---

---

---

---

---

# MARS

Molecular  
Adsorbent  
Recirculation  
System

---

---

---

---

---

---

---

---

## MARS™: 3 compartments

### Blood circuit

- blood dialyzed across albumin impregnated high-flux polysulfone dialysis membrane
- substances with MW > 50 kDa too large for pore size
  - Hormones, growth factors ...

### Albumin circuit (dialysate)

- 600 cc of 20% human albumin acts as the dialysate
- charcoal/anion exchange columns
- dialysate is regenerated

### Renal Circuit

- hemodialysis or hemofiltration (CRRT)
- can run on top of pre-existing machines

Strange and Mitzner, Artif Org, 1993.

---

---

---

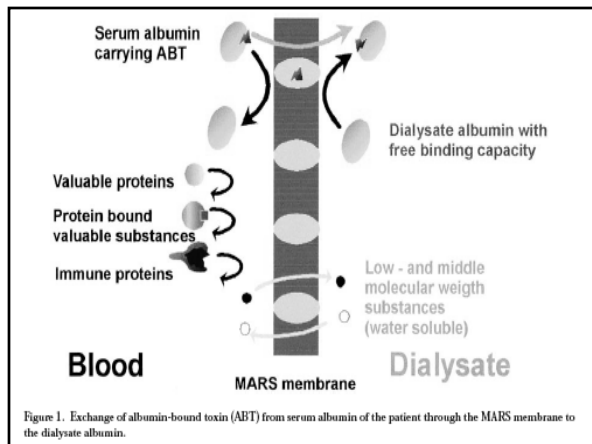
---

---

---

---

---



---

---

---

---

---

---

---

---

## MARS: Schematic Drawing

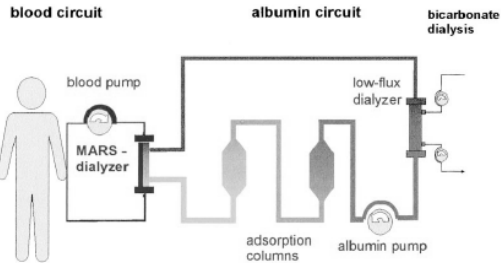


Figure 2. Schematic drawing of the MARS.

---

---

---

---

---

---

---

---

---

---

## MARS and HRS

Stange et al Liver Tx 2000

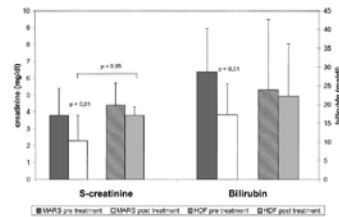
- N =13 pts (CTP C, Bili > 400)
  - No transplants, TIPS, vasopressin analogues
- Type 1 HRS (Cr > 150, U/O < 500 ml/day)
- MARS (n=8) vs CVVHDF (n=5), mean 5 treatments (1-10)

Mortality: 100% (controls)

62.5% MARS

↓ Creatinine: MARS > CVVHDF (p < 0.05)

↓ Bilirubin (p < 0.05)




---

---

---

---

---

---

---

---

---

---

## MARS and ACLF

- Mitzner, Strange et al Hepatology 2002
  - 23 patients with AoCLF (19 EtOH cirrhotics)
    - Bili > 340, Child-Pugh ~ 11.5
    - MARS vs control (some pts were on CRRT)
- **Results**
  - Improved 30 day survival in MARS group
    - 11/12 in MARS, 6/11 in control
  - Decrease in bilirubin (43%) and bile acids(29%) in MARS group
    - No change in control group
  - Improvement in hepatic encephalopathy and AKI (P < 0.05)
    - Some control pts were on CRRT

---

---

---

---

---

---

---

---

---

---

## MARS and HE: Blei Hepatology 2007

- 70 pts (CTP C, MELD 32)
  - 39 MARS + SMT
  - 31 SMT alone
- Daily 6 hour MARS x 5 days or 2 grade HE improvement
- 2-grade improvement in HE
  - 34% in MARS group
  - 19% in SMT group (p=0.044)
- Improvement in bile acids and ammonia from baseline (not compared to control)
- Study not intended to look at HRS or mortality

---

---

---

---

---

---

---

---

---

---

**Table 1**  
Molecular Adsorbent Recirculation System in acute on chronic liver failure

Study	Number	Controlled	Improvements			Survival (30 days) <sup>a</sup>
			Biochemical	CVS	CNS	
Stange et al. [7]	13	No	Yes	N/A	Yes	69%
Schmidt et al. [10]	8	No	Yes	Yes	No	50%
Jalan et al. [37]	8	No	Yes	Yes	Yes	50%
Di Campi et al. [38]	13	No	Yes	N/A	Yes	38%
Mitner et al. [8]	13	Yes	Yes	Yes	No	Yes (37.5% versus 0% at 7 days)
Hoemann et al. [9]	23	Yes	Yes	Yes	Yes	Yes (90% versus 55%)
Sen et al. [11]	18	Yes	Yes <sup>b</sup>	No	Yes	No (45% in both)
Blei [16]	70	Yes	N/A	N/A	Yes	N/A
Laleman et al. [12]	18	Yes	Yes <sup>c</sup>	Yes	N/A	N/A

Biochemical improvements: statistically significant reduction in bilirubin, bile acids, creatinine, and ammonia. <sup>a</sup>Percentages indicate uncontrolled survival data; <sup>b</sup>trend did not reach statistical significance; <sup>c</sup>bilirubin and bile acids only. CNS, improvement in hemodynamic parameters (mean arterial pressure, heart rate, vasopressor requirements); CVS, decrease in hepatic encephalopathy grade (neurological improvement); N/A, not assessed.

**Karvellas et al., Critical Care 11(3) 2007.**

---

---

---

---

---

---

---

---

---

---

## MARS: Pros and Cons

- Pros
  - Most evidence to date
  - Can run with hemodialysis or CRRT
  - Can run on pre-existing IHD/CRRT machines
- Cons
  - Lack of large robust randomized studies
  - Expensive
    - Need extra equipment (circuit, filters)
  - Concerns raised over risks of bleeding
    - In pts with ↑INR, thrombocytopenia (plt < 30)

Faybik et al, Crit Care 2006.  
Doria et al. Clin Tranp 2004.

---

---

---

---

---

---

---

---

---

---

## II: Prometheus



---

---

---

---

---

---

---

---

### Prometheus: FPSA

- detoxification of *the patient's* albumin by fractionated separation and adsorption
- uses albumin permeable membrane with cutoff of 250 kDa
- patient's (albumin) crosses albuflow membrane and then across adsorbers
  - Neutral exchange resin adsorber, anion exchanger
- cleaned albumin returned to plasma and then undergoes **hemodialysis**
  - Not compatible with CVVH

Sen et al, Am J Gastro, 2005.

---

---

---

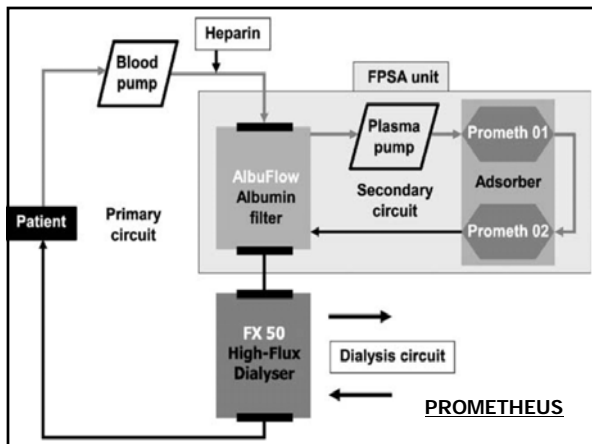
---

---

---

---

---



---

---

---

---

---

---

---

---

## **Prometheus and HRS**

Rifai et al. Hepatology 2003

- 11 patients with AOCLF, HRS Type 1
- 2 prometheus treatments on consecutive days for > 4 hours
- All pts CTP B/C in ICU setting
- **Uncontrolled**

### • **Results**

- Significant improvement in total/conjugated bilirubin, bile acids
- Significant improvement in Cr, Urea and ammonia
- Non-significant improvement in CRP, IL-6 (not TNF)
- 8/11 patients died
- No treatment related complications

---

---

---

---

---

---

---

---

## **Prometheus vs. MARS: ACLF**

### • Evaluation of hemodynamics with MARS and Prometheus in pts ACLF

- 18 pts (CTP ~ 12.5, Maddrey score 63.1)
- EtOH cirrhosis and superimposed EtOH hepatitis
- MARS (n = 6) or Prometheus (n = 6) or were treated with SMT alone (n = 6) on three consecutive days (6 hours/session).

### • Both MARS and Prometheus ↓ bilirubin levels

- P < 0.005 versus SMT,
  - Prometheus more effective than MARS (P = 0.002).

Laleman, Crit Care 2006.

---

---

---

---

---

---

---

---

## **Prometheus vs. MARS: AoCLF**

### • MARS group only

- significant improvement in hemodynamics
  - (MARS  $\Delta$  +9 +/- 2.4 vs Prometheus -0.3 +/- 2.4 vs -5.2 mmHg with SMT, P < 0.05)
  - SVRI (MARS +131.5 vs Prometheus -92.8 vs SMT -30.7 SMT; P < 0.05),
- decrease in
  - plasma renin activity (P < 0.05),
  - aldosterone (P < 0.03), norepinephrine (P < 0.05),
  - vasopressin (P = 0.005) and nitrate/nitrite levels (P < 0.02).

### • No comment on survival in any group

Laleman, Crit Care 2006.

---

---

---

---

---

---

---

---

## Prometheus: Evidence

Table 3

### Prometheus in liver failure

Study	Classification	Number	Controlled	Improvements				Survival
				Biochemical	CVS	CNS		
Ritai et al. [28]	Acute on chronic liver failure	11	No	Yes	No	No	28% at 30 days	
Skwarzek et al. [91]	Acute liver failure	13	No	Yes	N/A	N/A	23% at 6 months	
Laleman et al. [112]	Acute on chronic liver failure (ethanol)	18	Yes	Yes*	No	N/A	N/A	

Biochemical improvements: statistically significant reduction in bilirubin, bile acids, creatinine, and ammonia. \*Bilirubin and bile acids only; CNS, improvement in hemodynamic parameters (mean arterial pressure, heart rate, vasopressor requirements); CVS, decrease in hepatic encephalopathy grade (neurological improvement); N/A, not assessed.

Karvellas et al., *Critical Care* 11(3) 2007.

---

---

---

---

---

---

---

---

---

---

## Prometheus: Limitations

### Pros

- do not need to use albumin dialysate
- promising improvements in biochemical profile
  - Creatinine, Bile acids, conjugated bilirubin

### Cons

- very few studies
  - Currently large randomized multi-centred study ongoing
- need separate machine and filters (albuflow)
- can only run on **hemodialysis**
- not currently available in North America
- risk of bleeding
  - Company states not to run patients with INR > 3 or plt < 30

---

---

---

---

---

---

---

---

---

---

## III. Single Pass Albumin Dialysis (SPAD)

---

---

---

---

---

---

---

---

---

---

## SPAD: Mechanism of Action

- standard hemodialysis or CVVHDF machine
  - no additional perfusion pump system
  - Either IHD or CRRT
- blood/plasma dialyzed against a 4.4% albumin solution as well as standard dialysate solution
- blood pumped through a high-flux hollow fiber hemodiafilter
  - Same as for CVVHDF
- albumin dialysate is not regenerated as in MARS
  - No adsorbent columns employed
  - Albumin discarded
- need an albumin gradient for effective toxin removal
  - Will not work if patient has a normal albumin level

Sauer et al., Hepatology, 2004.

---

---

---

---

---

---

---

---

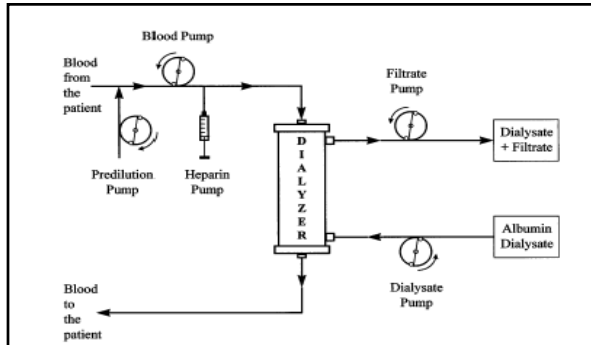


Fig 1. Modified albumin dialysis set-up. Blood pump, filtrate pump, and dialysate pump are already integrated into the bedside monitor. The filtrate pump rate = dialysate flow + predilution flow + desired ultrafiltration rate.

---

---

---

---

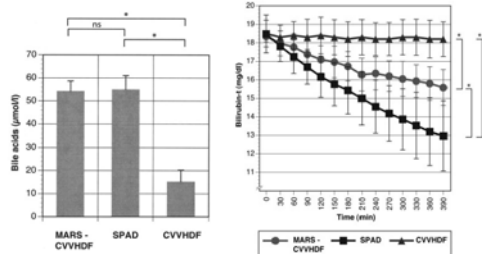
---

---

---

---

## Sauer et al 2004: SPAD In Vitro



In vitro samples: 6 pts with MARS, 6 SPAD, 6 CVVHDF  
 Ammonia → No difference between MARS, SPAD, CVVHDF  
 Bile Acids → MARS = SPAD  
 Total Bilirubin → SPAD > MARS

---

---

---

---

---

---

---

---

## SPAD in ALF/AKI

- Retrospective analysis of n=6 AALF patients receiving  $\geq 1$  SPAD session
- Admission: mean APACHE II 29, MELD 38
- Five pts met KCH criteria for LT
- 6 pts received 21 sessions of SPAD
  - total 147 hours, 24.5 hours or 3.5 runs/pt
  - Admission, median GCS 3
  - Mean INR 5.8, Bili 117 mmol/L, Cr 282  $\mu\text{mol/L}$ , NH3 135  $\mu\text{mol/L}$

Blood Purif. 2009

---

---

---

---

---

---

---

---

## SPAD for ALF/AKI

- Post-SPAD
  - INR, AST, pH and Cr improved
    - $p < 0.04$  for all from admission
  - No significant changes in clinical, physiological or biochemical parameters occurred during therapy.
  - Three died, two recovered and one patient was bridged to LT.
  - Compared with historical controls (n=7)
    - no statistically significant differences in physiological and biochemical profile as well as mortality.

Blood Purif. 2009

---

---

---

---

---

---

---

---

## Evidence for SPAD

- Keyman et al J Hepatology 1999
  - 18 yr old pt Hyper-acute Liver Failure (Wilson's disease)
  - treated with SPAD for 59 days (transplanted)
  - efficiently cleared bilirubin and copper
- Siege, Transplant Proc 1999
  - 3 patients with AOCLF, Grade III HE, Bili > 300
  - 2 successfully transplanted
- Other case reports
  - Cholestasis
  - SPAD/EDD

---

---

---

---

---

---

---

---

## **SPAD: Limitations**

### Pros

- equipment costs are cheaper than MARS or Prometheus
  - No extra machines/filters
- ease of setup
  - Nursing staff who can run with existing IHD/CRRT machines
  - add albumin to dialysate
- less concern of exacerbating bleeding in coagulopathic patients

### Cons

- very little human data (small case series)
- albumin not regenerated
  - > 1kg of albumin used for standard 6 hour SPAD run

---

---

---

---

---

---

---

---

## **Conclusions**

- HRS is a known consequence of decompensated cirrhosis carrying a poor prognosis (esp. Type I)
- Vasopressors and albumin are the mainstay of therapy at present
  - Reversal of arteriodilatation
  - Scavenging properties of albumin
- While albumin dialysis shows promise in the treatment of HRS, an evidence-based recommendation can not be made at this time
- Adequately powered trials are still required to show the benefit of albumin dialysis compared with standard medical therapy in HRS
  - RELIEF
  - HELIOS

---

---

---

---

---

---

---

---