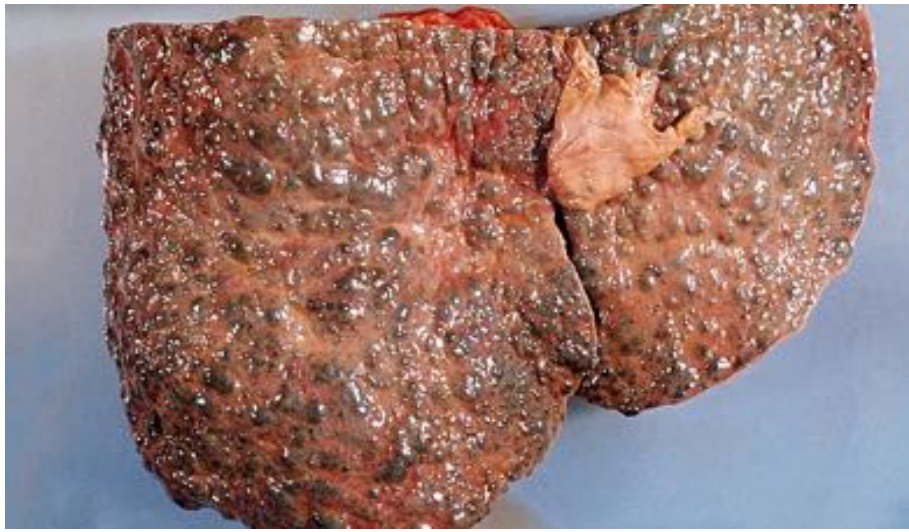
Organ support in ACLF – non PLEX systems



Lee Kang Hoe

Associate Professor, NUS Yong Loo Lin School of Medicine

The Liver Transplant Symposium 2023

NUS National University of Singapore

Yong Loo Lin School of Medicine

Definitions of ACLF

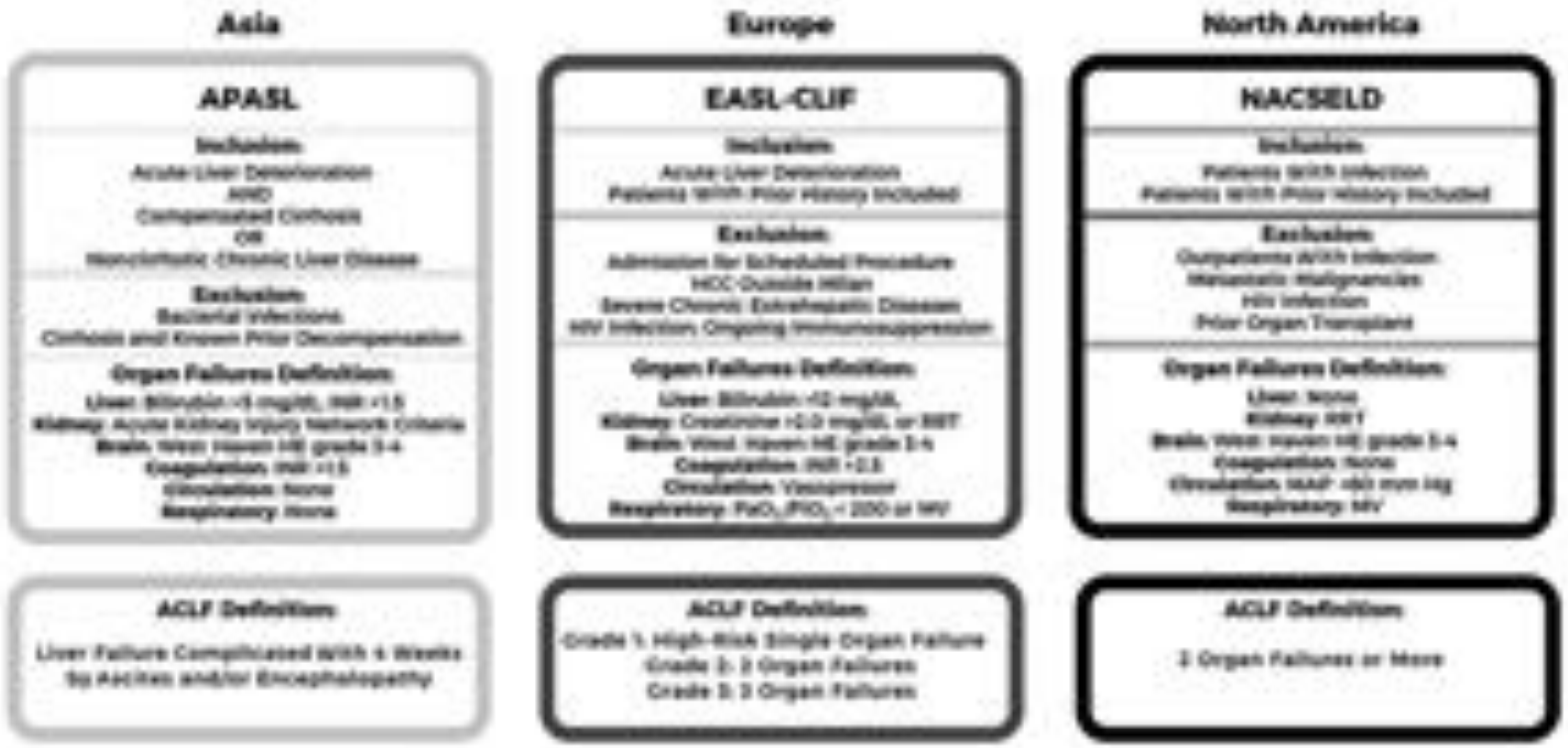


FIG. 2. Characteristics of major definitions of ACLF.[1–6] High-risk organ failure includes renal failure or other organ failure with either renal or cerebral dysfunction.

Extrahepatic and intrahepatic insults

TABLE 1. Precipitants of ACLF with Percentages Reported in Large Databases

	Europe	North America	Asia
Precipitating factors			
Extrahepatic			
Infection	33	—	28
GI hemorrhage	13	—	10
Procedures (TIPS, LVP, ERCP)	9-11	—	2
Intrahepatic			
Viral hepatitis	<5	—	36
Alcohol	25	—	6
DILI	—	—	11
Autoimmune disease	—	—	3
Not identifiable	44	—	20
More than 1 factor	14	—	9
Underlying etiology of cirrhosis			
Viral	18	50	63
Alcohol	67	42	30
Cryptogenic	3	15	7
Miscellaneous	8	18	4

NOTE: Data are given as percentages and are from Moreau et al.,[2] Bajaj et al.,[20] Cholongitas et al.,[11] Wehler et al.,[14] Xia et al.,[15] and Shi et al.[16]

ACLF – organ failure (s) (usually kidney) plus systemic inflammation, associated with increasing mortality coupled to the number of organ failures

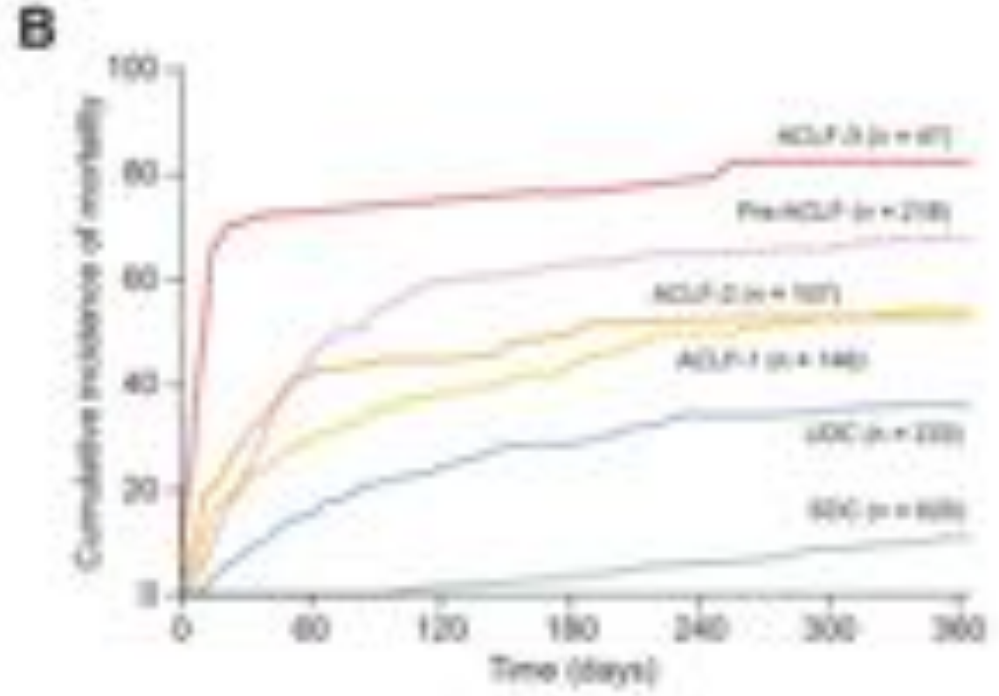


Fig. 1. Clinical trajectory of patients with cirrhosis. (A) Shows that patients can suffer either from acute decompensation, which implies need for hospitalisation with an acute liver-related complication or a less well-defined entity, called non-acute decompensation, which refers to the occurrence of a progressive liver-related complication that does not lead to hospitalisation. Patients with acutely decompensated cirrhosis without ACLF at presentation can be retrospectively classified into three distinct groups according to the three distinct disease trajectories during the 3 months after admission. Patients can be categorised as having SDC (patients in this group were discharged and not readmitted during the 3-month follow-up), UDC (patients in this group developed liver-related complications, but not ACLF, and were readmitted during the 3-month follow-up), or pre-ACLF (because patients in this group developed ACLF during the 3-month follow-up). Patients who present with ACLF meet criteria for one of three grades of ACLF. Overall, patients with acutely decompensated cirrhosis may therefore be divided into six distinct groups. Modified from Jalan et al.[1,2] and D'Amico et al.[3] (B) shows the outcomes of the six groups (Reproduced from[1,2]). ACLF, acute-on-chronic liver failure; SDC, stable decompensated cirrhosis; UDC, unstable decompensated cirrhosis.

Table 3. Prognostic scoring systems[3,4,5]

(A) CLIF-SOFA Score

Organ/system	0	1	2	3	4
Liver (bilirubin, mg/dL)	<1.2	≥1.2 to ≤2.0	≥2.0 to <6.0	≥6.0 to <12.0	≥12.0
Kidney (creatinine, mg/dL)	<1.2	≥1.2 to <2.0	≥2.0 to <3.5	≥3.5 to <5.0	≥5.0
				or use of renal replacement therapy	
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (international normalized ratio)	<1.1	≥1.1 to <1.25	≥1.25 to <1.5	≥1.5 to <2.5	≥2.5 or platelet count ≤20×10^9/L
Circulation (mean arterial pressure, mm Hg)	≥70	<70	Dopamine ≤5 or dobutamine or terlipressin	Dopamine >5 or E ≤0.1 or NE ≤0.1	Dopamine >15 or E >0.1 or NE >0.1
Lungs					
PaO_2/FiO_2 or	>400	>300 to ≤400	>200 to ≤300	>100 to ≤200	≤100
SpO_2/FiO_2	>512	>357 to ≤512	>214 to ≤357	>89 to ≤214	≤89

CLIF C-ACLF score 10×[0.033×Clif OFs+0.04×Age+0.63×Ln(WBC)−2].

CLIF C-ACLF, chronic liver failure consortium acute-on-chronic liver failure; HE, hepatic encephalopathy; NE, nor epinephrine; WBC, white blood cell count.

(B) AARC Score

Points	Total bilirubin (mg/dL)	HE grades	INR	Lactate (mmol/L)	Serum creatinine (mg/dL)
1	<15	0	<1.8	<1.5	<0.7
2	15–25	I–II	1.8–2.5	1.5–2.5	0.7–1.5
3	>25	III–IV	>2.5	>2.5	>1.5

AARC score in ACLF grade 1=5–7, grade 2=8–10, grade 3=11–15.

INR, international normalised ratio; HE, hepatic encephalopathy; ACLF, acute-on-chronic liver failure; APASL, Asian Pacific Association for Study of Liver; AARC, APASL ACLF research consortium.

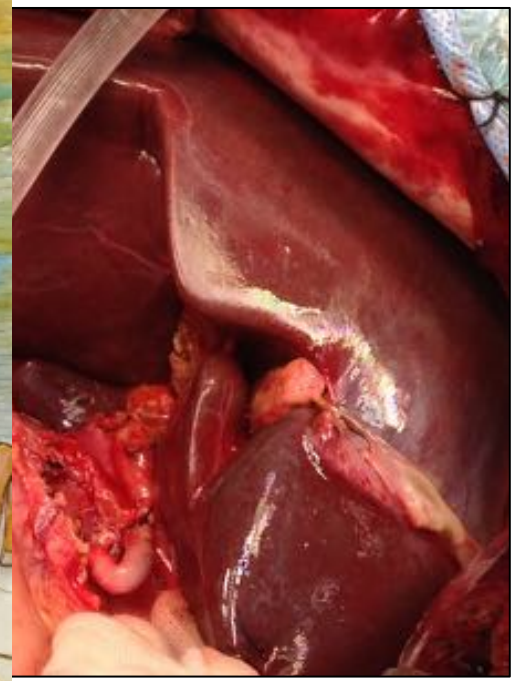
Role of ammonia in predicting the outcome of patients with acute-on-chronic liver failure

Chiriac et al. World J Clin Cases. 2021 Jan 26; 9(3): 552–564

- 456 pts with ACLF
- Receiver operating characteristic analysis showed good accuracy for the prediction of in-hospital mortality for the AARC score [Area under the curve (AUC) = 0.886], MELD score (AUC = 0.816), VA (venous ammonia) (AUC = 0.812) and a fair accuracy for the Child-Pugh score (AUC = 0.799).
- Subsequently, a cut-off value for the prediction of mortality was identified for **VA (152.5 µmol/L,** sensitivity = 0.706, 1-specificity = 0.190).
- Univariate analysis found acute kidney injury, severe HE (grade III or IV), VA ≥ 152.5 µmol/L, MELD score ≥ 22.5, Child-Pugh score ≥ 12.5, and AARC score ≥ 8.5 to be associated with in-hospital mortality.
- Multivariate analysis identified AARC score ≥ 8.5 and venous ammonia ≥ 152 µmol/L to be independent predictors of in-hospital mortality.

Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3

Artu et al. J Hepatology 2017



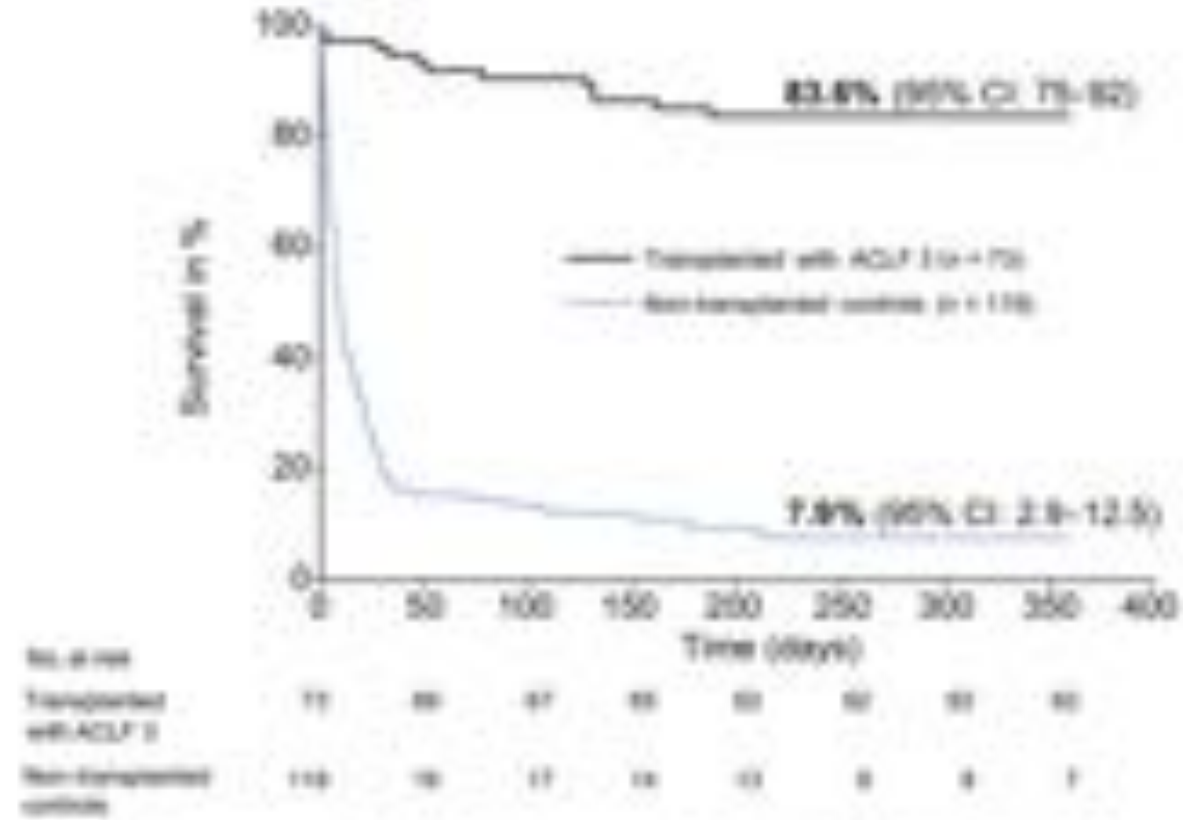


Fig. 2. One-year survival of patients transplanted with ACLF-3 and of non-transplanted matched controls with cirrhosis and multiple organ dysfunction. The 1-year survival rate was much higher in the transplanted patients than in controls: 83.6% (95% CI: 75–92) vs. 7.9% (95% CI: 2.9–12.5) with an HR for mortality of 0.07 (95% CI: 0.01–0.12; $p < 0.0001$). The 1-year survival of ACLF-3 case was compared with the control group by Cox regression models using a robust sandwich covariance matrix to account for the matched set.

Questions for organ support in ACLF ?

- Removal of cytokines (DAMPS) / endotoxin???
- Improves renal function ?
- Improves hepatic encephalopathy
- Removes ammonia ?
- Removes bilirubin ?
- Improves hemodynamics ?
- Lung function ?
- Coagulation ?
- Outcome / Better survival ?

We believe that:

1. **High ammonia is BAD**
2. **Reducing HE grade is desirable**
3. **Supporting renal function**
4. **Removing cytokines is probably good**
5. **We would like to have better outcomes by transiting pt to liver transplant in the best condition**

EASL Clinical Practice Guidelines on acute-on-chronic liver failure.

J Hepatology Aug 2023

Extracorporeal liver support

Do artificial or bioartificial extracorporeal liver support systems impact the outcome of ACLF?

Recommendations

- The routine use of artificial or bioartificial extracorporeal liver support or plasma exchange in ACLF is not recommended outside investigative trials **(LoE 2, strong recommendation, strong consensus).**

Statement

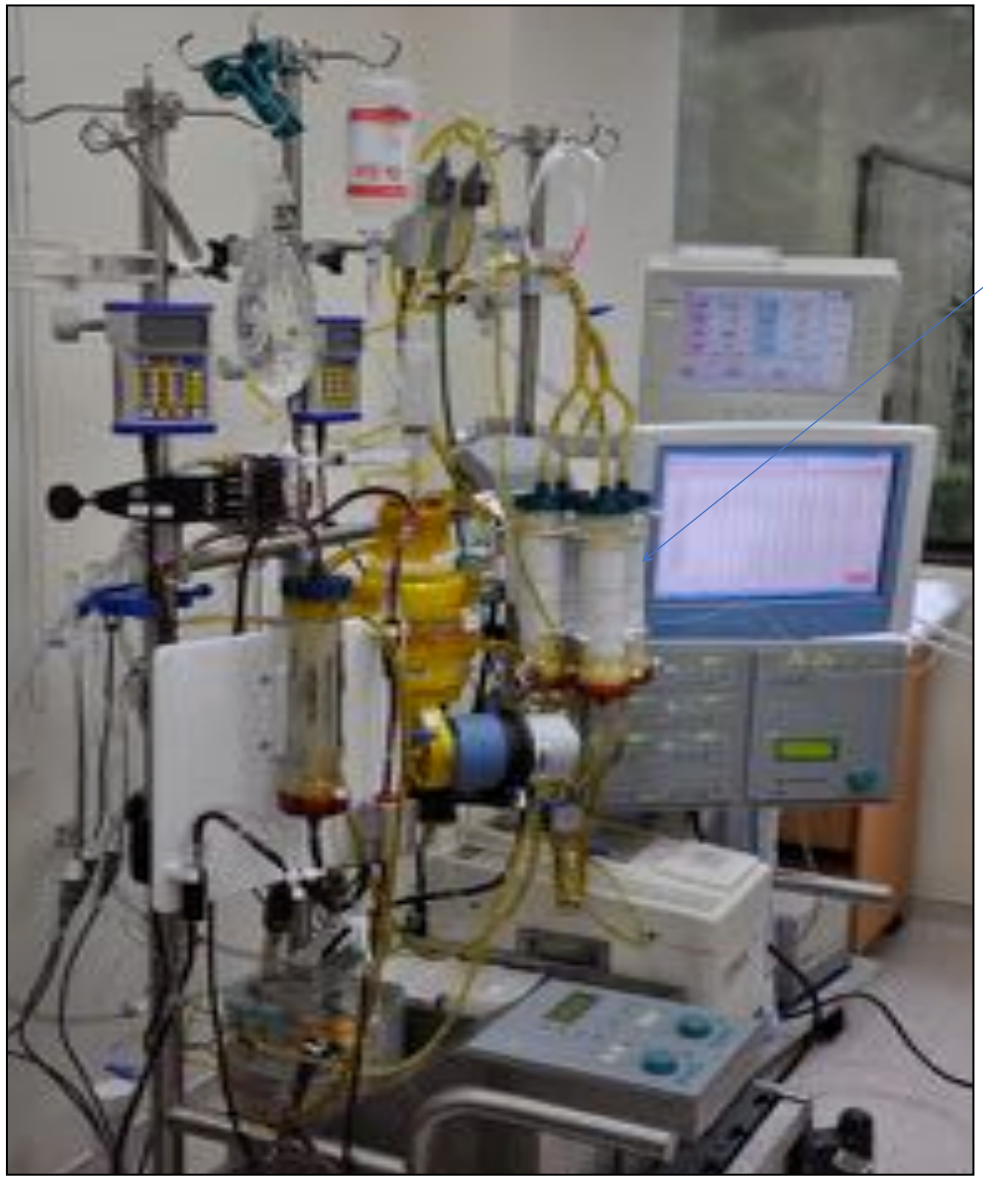
- Although albumin dialysis can improve the severity of hepatic encephalopathy, there is no evidence it improves the survival of patients with ACLF **(LoE 2, consensus)**

Extracorporeal liver support systems

- Biological – contains liver cells (human or animal)
  - Circe (porcine)
  - ELAD (hepatoblastoma cell line)

- Non biological systems
  - Plasmapheresis
  - Albumin dialysis (MARS)
  - Prometheus - a combination of direct adsorption of albumin bound toxins to an adsorber and the removal of water-soluble toxins by high-flux dialysis
  - CRRT with various filters (Hemodiafiltration versus hemodialysis)
  - Adsorption devices (Charcoal, Cytosorb, Jafron, Oxiris, Dialive)
  - ADVOS (Advanced organ support) – multiple combined function

Extracorporeal Liver Assist Device (ELAD)



Cartridges with the liver cells (C3A)

ELAD treatment consisted of drawing blood from the subject via a dual-lumen catheter using an extracorporeal pumping unit and then separating the plasma fluid (ultrafiltrate [UF]) from the cellular components using a specifically designed UF generator cartridge. While the cellular components are returned to the subject via the venous access, the UF is circulated at a high flowrate through 4 metabolically active hollow-fiber ELAD cartridges containing approximately 440 g of C3A cells. After circulation through the cartridges, the UF passes through a 0.2-mm pore-size filter, is recombined with the cellular components of the subject's blood, and is returned to the subject through the dual-lumen catheter

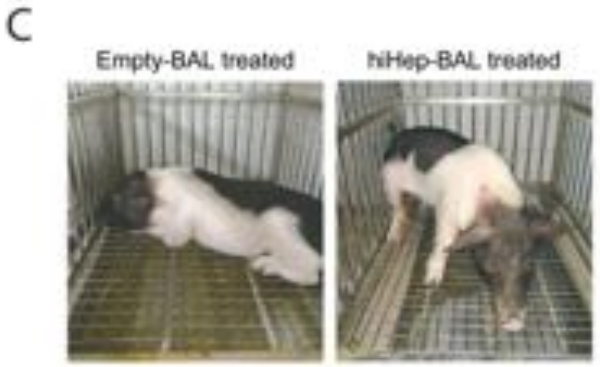
Extracorporeal Cellular Therapy(ELAD) in Severe Alcoholic Hepatitis: A Multinational, Prospective, Controlled, Randomized Trial

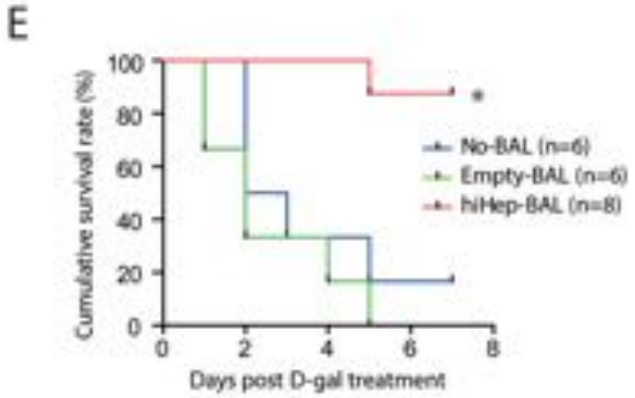
Liver Transplantation 24 380–393 2018

Improved survival of porcine acute liver failure by a bioartificial liver device implanted with induced human functional hepatocytes.

Cell Research (2016) 26:206-216.

- We previously generated human functional hepatocytes by lineage conversion (hiHeps).
- Here, by improving functional maturity of hiHeps and producing hiHeps at clinical scales (3 billion cells), we developed a hiHep-based BAL system (hiHep-BAL).
- In a porcine ALF model, hiHep-BAL treatment restored liver functions, corrected blood levels of ammonia and bilirubin, and prolonged survival.
- Importantly, human albumin and α-1-antitrypsin were detectable in hiHep-BAL-treated ALF pigs.
- Moreover, hiHep-BAL treatment led to attenuated liver damage, resolved inflammation and enhanced liver regeneration.





What are we trying to remove in our ACLF pt?

- 55 year female with MELD 18 chronic hep B presents with fever and hypotension and abdominal pain
- Bilirubin was 300 umol/L. INR was 3, ammonia was 200 umol/L and creatinine was 250 umol/L
- Blood culture was positive for gram negative rods, and ascites on examination with HE grade 3.
- Diagnosis was SBP with septic shock and ACLF.

- We would like to improve:
  - Reduce **ammonia levels** and hopefully improve HE
  - Treat septic shock
  - Support renal failure
  - Maybe reduce **bilirubin** and support INR

Chemistry

- Ammonia:
  - Small molecule (smaller than water). Removal correlates with urea clearance.
  - 17 daltons
  - Water soluble
- Bilirubin, being insoluble in an aqueous solution, is carried in circulation bound to albumin which is a reversible and covalent type of bonding.

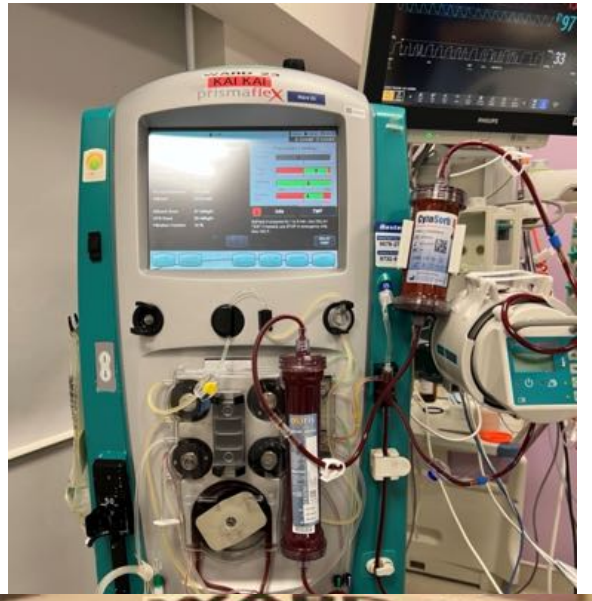
Basis for “dialysis” – setup is important

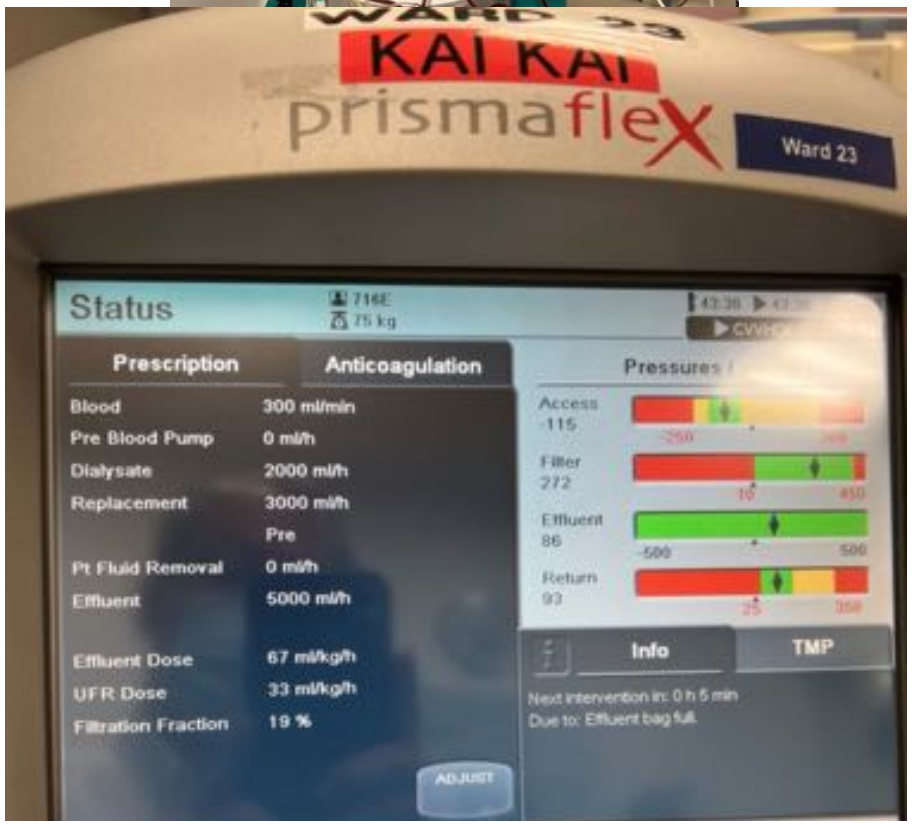
- “Wastes” (Solutes) and excess water are removed by using an external filter called a dialyzer, which contains a semipermeable membrane. The separation of wastes is done by creating a counter-current flow gradient, where blood flow is in one direction and the fluid of the dialyzer is in the opposite direction
- Diffusion
- Osmosis
- Ultrafiltration

- Net removal of solutes is influenced by: (1) the concentration gradient for diffusion, (2) the diffusivity of the solute, (3) permeability characteristics and surface area of the membrane, (4) blood and dialysate flow within the dialyzer, (5) the duration of dialysis, (6) the distribution volume of the solutes, and (7) amount of ultrafiltration (convective transfer).

Setup for CRRT

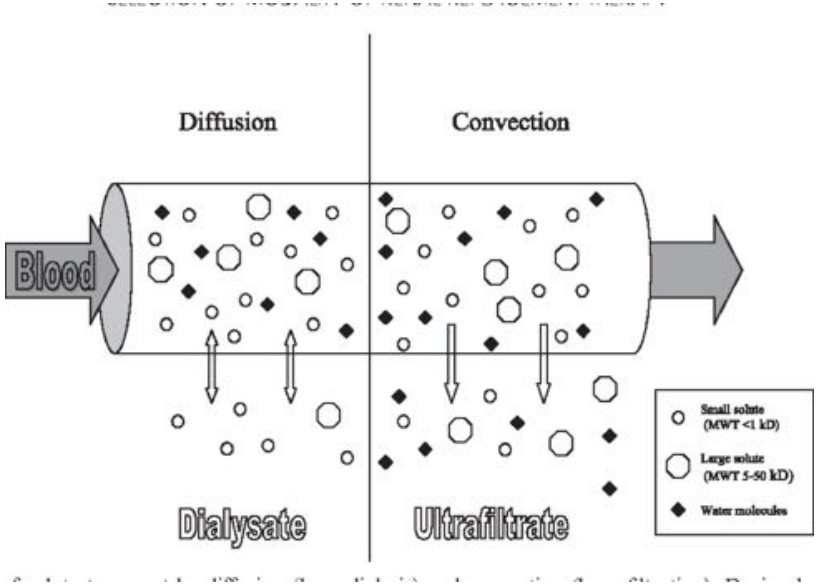
- Vascular access – may influence blood flow rates
- Orders require:
  - Modality (CVVH, CVVHD or CVVHDF (convective clearance))
  - Blood flow
  - Dialysate flow rate
  - Type of dialysate and type of replacement fluid
  - Replacement fluid (pre or post filter)
  - Ultrafiltration
  - Dialyzer (biocompatible membrane, high flux (pore size), high permeability ?)
  - Anticoagulation
  - Duration
  - Additional cartridge (e.g. Cytosorb)





Dialyzer

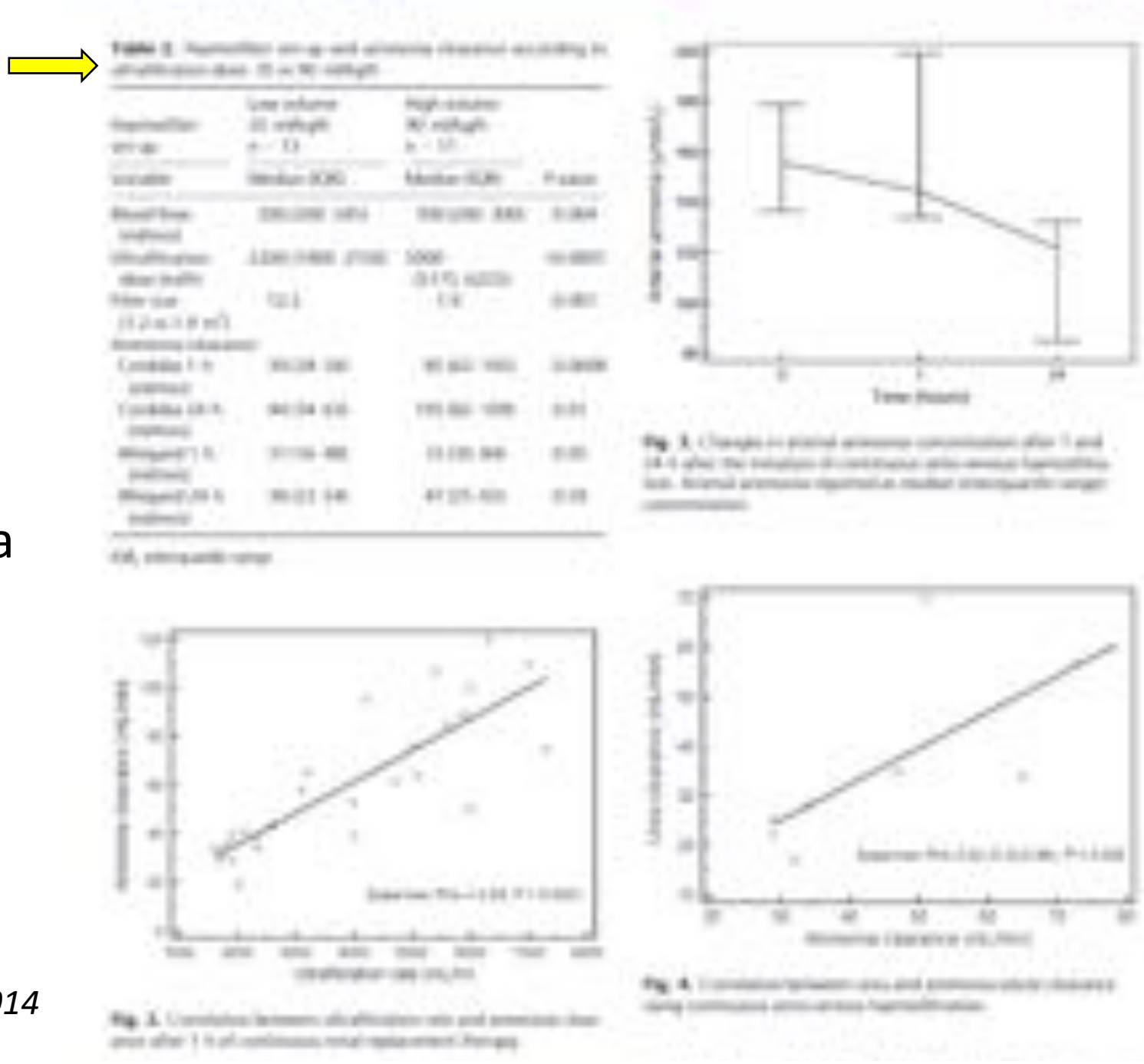
- The utilized membranes are classified into two main groups:
  - low-flux, which is based on using dialyzers with low permeability for water; and
  - high-flux, non-celluloses membrane with increased permeability, which is capable of removing moderate-sized molecules between 10000 to 15000 Dalton, including many of the inflammatory proteins, $ß_2$ microglobulin and lipoproteins
- High flux dialysers are 'leakier' dialysers .. and that holds true for bi-directional membrane transit. This means that not only can more and larger solutes be removed from the patient—but at least potentially, more water-borne contaminants, e.g. endotoxin, can get in!
- Also need bicarbonate dialysate



Ammonia

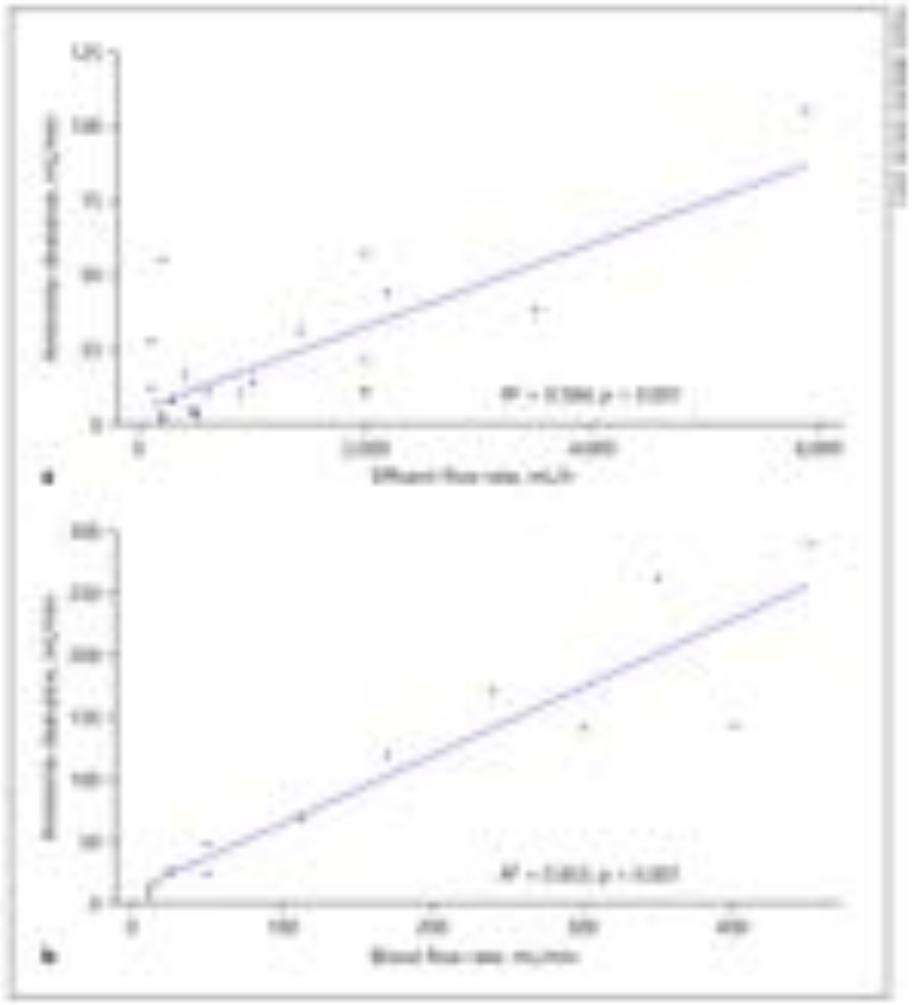
- Ammonia clearance was increased by either higher dialysate flow rate (DFR) or ultrafiltration rate (dialysis dose), a higher blood flow rate (BFR), and removal by a longer duration of treatment. There was a moderate correlation between ammonia clearance and EFR.

Liver International. Jan 2014



Extracorporeal Ammonia Clearance for Hyperammonemia in Critically Ill Patients: A Scoping Review

Blood Purif 2021;50:453–461



Ammonia clearance was increased by either higher dialysate flow rate (DFR) or ultrafiltration rate (dialysis dose), a higher blood flow rate (BFR), and removal by a longer duration of treatment

Correction and Control of Hyperammonemia in Acute Liver Failure: The Impact of Continuous Renal Replacement Timing, Intensity, and Duration.

Warillow et al. Crit Care Med Feb 2020

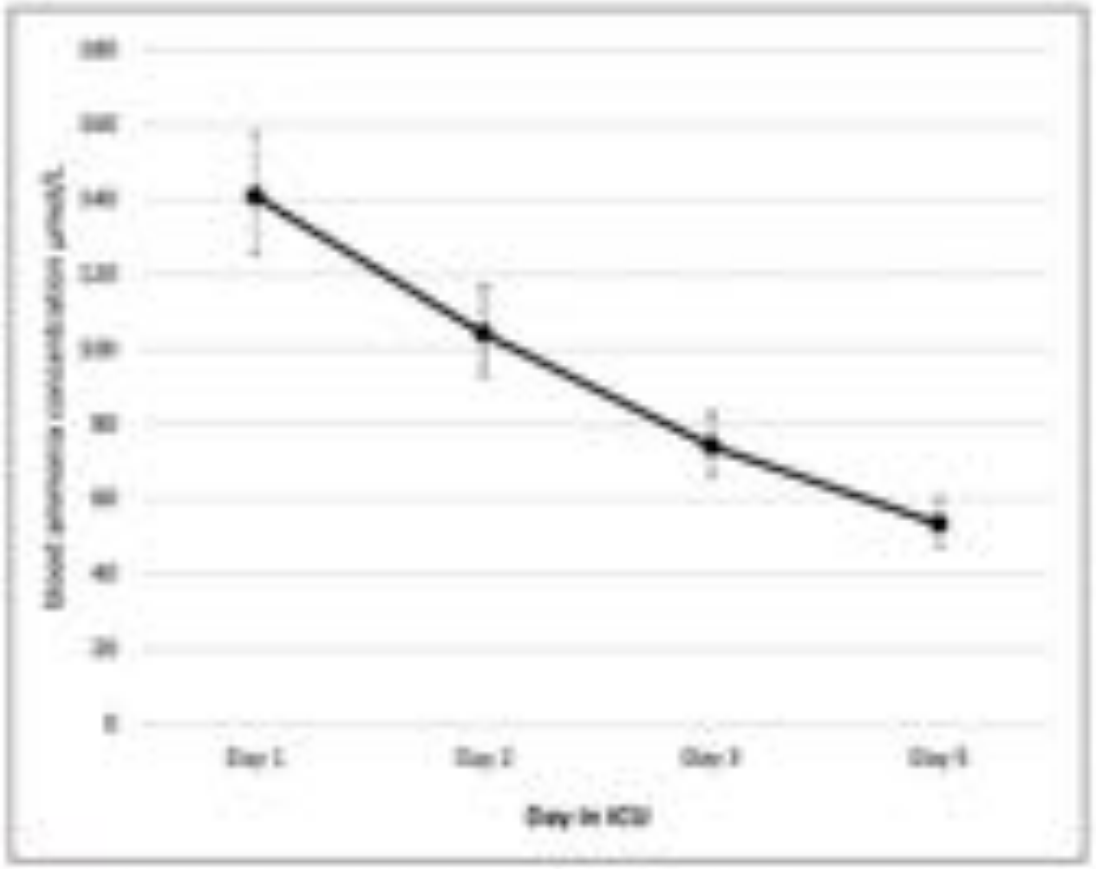
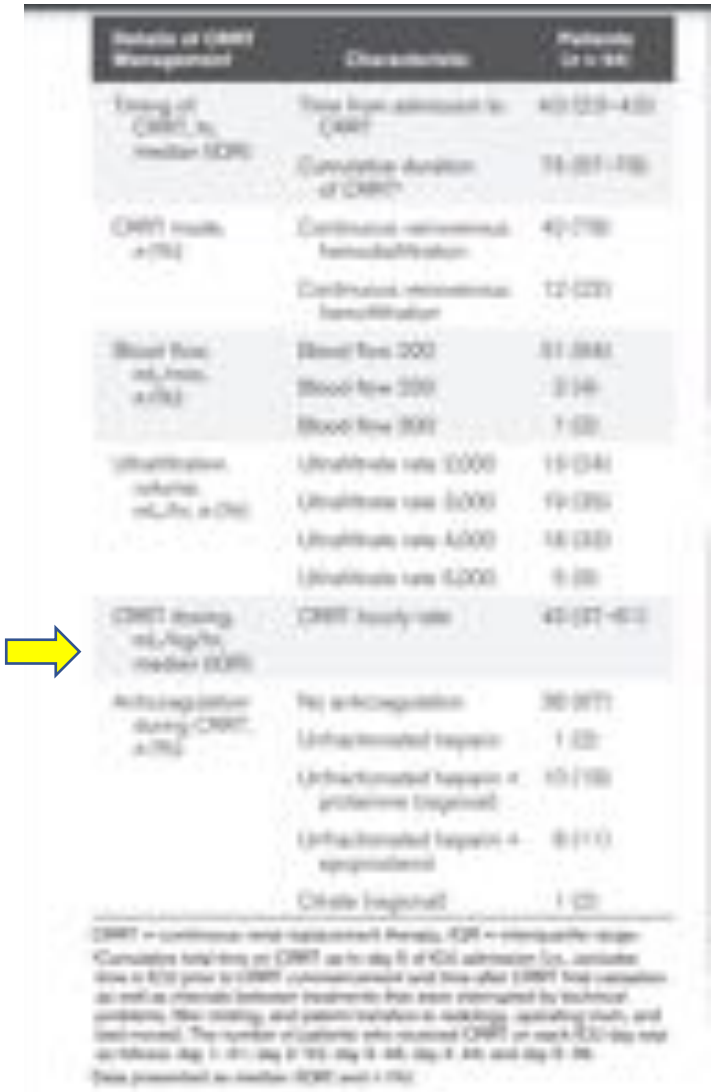


Figure 1. Ammonia dynamics over 5 d of treatment with continuous renal replacement therapy in acute liver failure. $p < 0.0001$. Geometric means of log transformed data. Error bars indicate 95% CI.



85% acetaminopohen
83% Grade 3 or 4
9% liver Tx
74% hospital survival

Renal dose in CRRT

- Assume complete saturation of small solutes in the effluent (Lancet 356,26–30 (2000))
- Clearance is therefore equal to **<u>total effluent volume</u>**

Box 1 | Assessment of dialysis dose in CRRT

CVVH

- Prescribed dose = (Qr + Qnet)
- Delivered dose = (Qr + Qnet) × S

CVVHDF

- Prescribed dose = (Qr + Qd + Qnet)
- Delivered dose = (Qr + Qd + Qnet) × S

Abbreviations: BUN, blood urea nitrogen; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; CVVHDF, continuous venovenous hemodiafiltration; FUN, effluent fluid urea nitrogen; Qd, dialysate fluid rate; Qnet, net fluid removal rate; Qr, replacement fluid rate; S, FUN/BUN ratio.

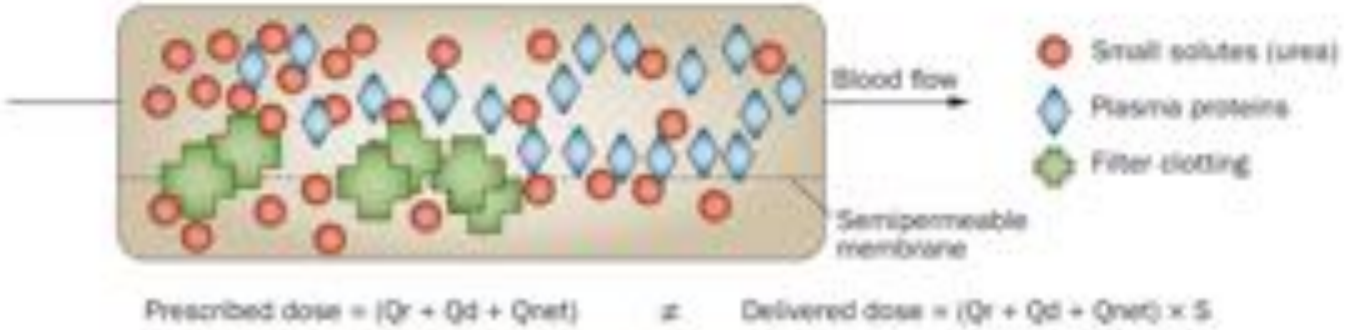


Figure 1 | The effect of concentration polarization and clotting on delivered dialysis dose. Filter efficacy declines over time; protein fouling and filter clotting occur on the membrane and decrease the surface available for diffusion or convection, which reduces the amount of dose being delivered. These important factors must be frequently monitored during continuous renal replacement therapies. Abbreviations: BUN, blood urea nitrogen; FUN, effluent fluid urea nitrogen; Qd, dialysate fluid rate; Qnet, net fluid removal rate; Qr, replacement fluid rate; S, FUN/BUN ratio.

Macedo, E. et al. Nat. Rev. Nephrol. 8, 57–60 (2012)

Renal dose for ammonia clearance

Dilution factor = plasma flow rate (ml/hr)/ (plasma flow rate + pre filter replacement fluid rate.

Plasma flow rate (ml/hr) = blood flow rate (ml/min) x 60 (min/hr) X (1-hematocrit)

Example shown: Hct was 0.26

Show dilution factor = 300 x 60 x 0.74 / ((300 x 60 x 0.74)+ 3000) = **0.727**

Actual dose = (Eflluent dose x dilution factor)/ weight = (5000 x 0.727) / 75 = **48.5 ml/kg/hr**

Assuming sieving coefficient of urea is 1

Adsorption options

- Charcoal hemoperfusion
- Oxiris
- Jafron
- Cytosorb

Hemoperfusion is the method by which blood is cleared of various compounds by directly perfusing it over a sorbent bed or column, which have a binding affinity for the substances to be removed. The sorbent used may be activated charcoal, non-ionic or ionic resins, or immunosorbents. Adsorption of the solute to the sorbent is based on chemical affinity, rather than molecular size.

Removal of Cytokines and Endotoxin and may benefit vasoplegic shock

Also utilized in septic shock and severe ARDS

Sieving coefficient

Bovine plasma, Cp 60 g/L, T = 37°C)
Q_b = 100 mL/min, Q_{ul} = 20 mL/min

Urea	1
Vitamin B_{12}	1
Inulin	0.96
(Human plasma, Cp 60 g/L, T=37°C)	
Myoglobin	0.70
Albumin	<0.0045

Cytokine adsorption

Cytokine adsorption removal rate (%) [1]
(human plasma, Cp 60 g/L, 37°C)
Q_b = 150 mL/min, Q_{ul} = 0 mL/min

IL-10 (≥ 10%)	96
IL-6 (≥ 10%)	84
HMGB-1 (≥ 10%)	94
TNF-α (≥ 30%)	82

[1]Removal Rate expressed at t=120 min with a theoretical initial IL-10, IL-6, HMGB-1 and TNF-α respective concentration of 500 pg/mL, 1500 pg/mL, 30 ng/mL and 250 pg/mL

Endotoxin adsorption

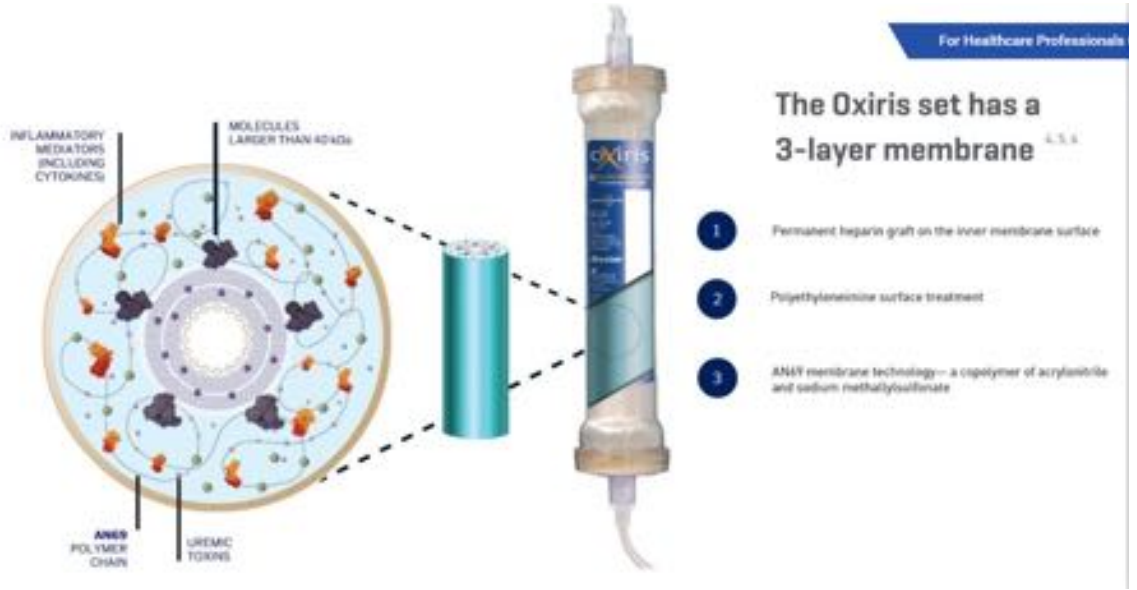
Lipopolysaccharide adsorption removal rate (%)[1]
(human plasma, Cp 60 g/L, 37°C)
Q_b = 150 mL/min, Q_{ul} = 0 mL/min

LPS (≥ 20%)	75

[1]Removal Rate expressed at t=120 min with an initial LPS concentration after stabilization of 50±10 EU/mL

Cp: Protein concentration
RR: removal rate
IL-10: Interleukin-10
IL-6: Interleukin-6
HMGB-1: High mobility group box 1
TNF-α: Tumor necrosis factor – α
LPS: Lipopolysaccharide

ORDERING INFORMATION



The oXiris set has a unique, proprietary three-layer membrane structure:
The base AN69 membrane enables absorption of cytokines and toxins while providing efficient renal support by diffusion and convection.
The PEI (polyethyleneimine) surface treatment allows for the adsorption of endotoxins while the removal of fluid and toxins (CRRT) occurs throughout the entire membrane.
The heparin graft on the membrane reduces membrane thrombogenicity and is designed to minimize treatment interruptions while supporting adequate dialysis dose delivery

Surface Area for Oxiris 1.5 m² vs m100 0.9 m²

It is a 300 mL container filled with biocompatible, highly porous polystyrene divinylbenzene beads that form a large surface of about 45,000 m^2 , adsorbing hydrophobic molecules up to approximately 55 kDa. As most cytokines fall within this range, the device is potentially capable of eliminating toxic substances rapidly from the blood.

IJAO The International Journal of Artificial Organs

Short communication

Haemoadsorption by CytoSorb® in patients with acute liver failure: A case series

The International Journal of Artificial Organs
2021, Vol. 44(8) 565–569
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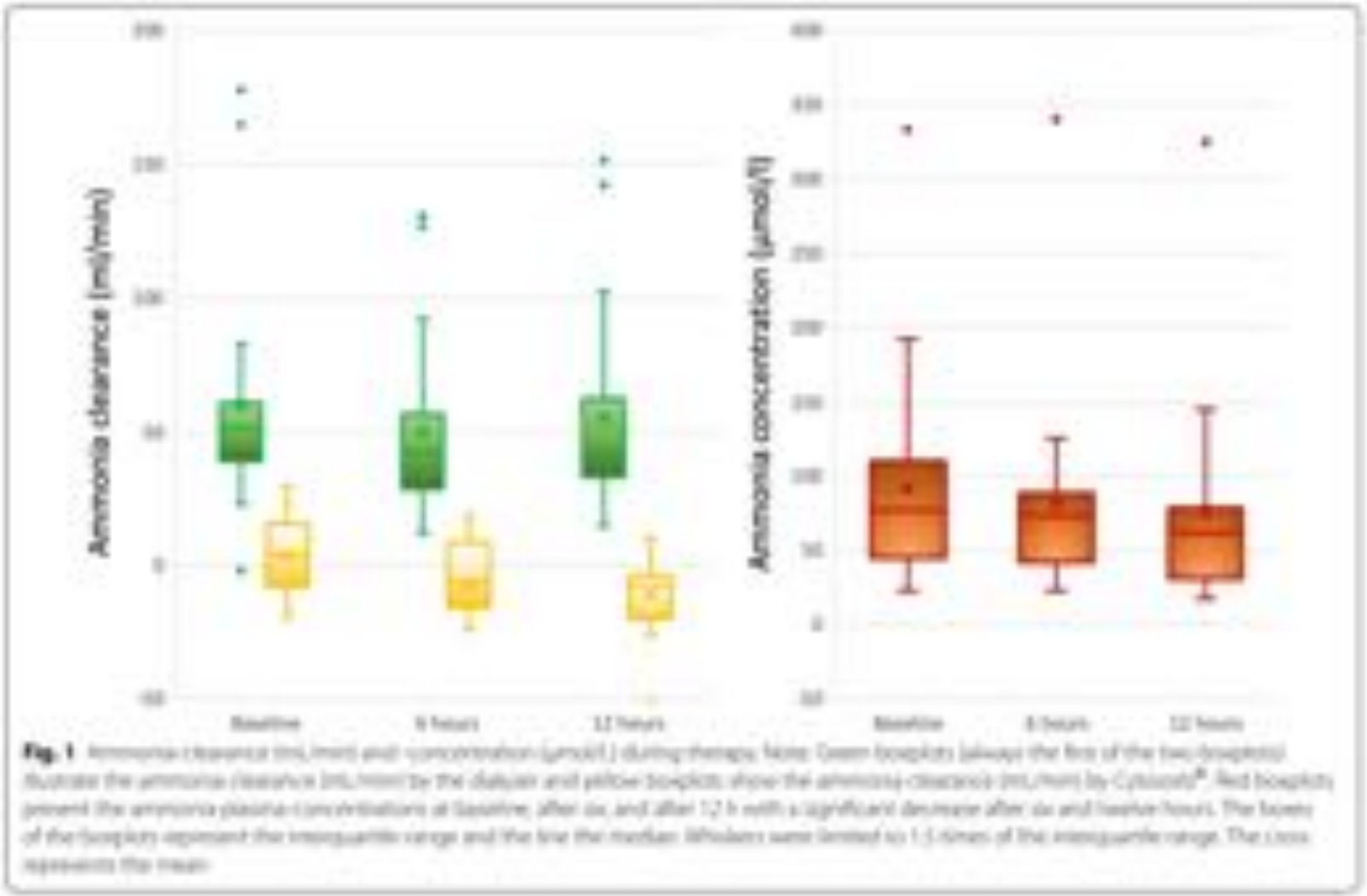
Dana Tomescu[1,2], Mihai Popescu[1,2], Corina David[2], Romina Sima[1] and Simona Dima[1]

Abstract

Acute liver failure (ALF) is a life-threatening disease associated with multi-organ failure and increased mortality. Severe inflammation is now considered the main pathophysiological mechanism for organ dysfunction, thus rebalancing pro- and anti- inflammatory cytokines may improve liver function and outcome. The aim of this study was to assess the clinical effects of a haemoadsorption column on biochemical parameters in patients with ALF. We prospectively included 28 patients with ALF who were treated with three consecutive sessions of continuous venovenous haemofiltration in combination with CytoSorb®. Our results show an improvement in liver functional tests and a decrease in C-reactive protein. Thrombocytopenia remains one of the most important side effects of this treatment and careful consideration should be made before initiation of treatment.

The cytokine adsorber Cytosorb® does not reduce ammonia concentrations in critically ill patients with liver failure.

Intensive Care Med 2023



Albumin based extracorporeal blood purification (SPAD, MARS, Prometheus, DIALIVE and ADVOS)

MARS™ Currently The Most Widely-used System

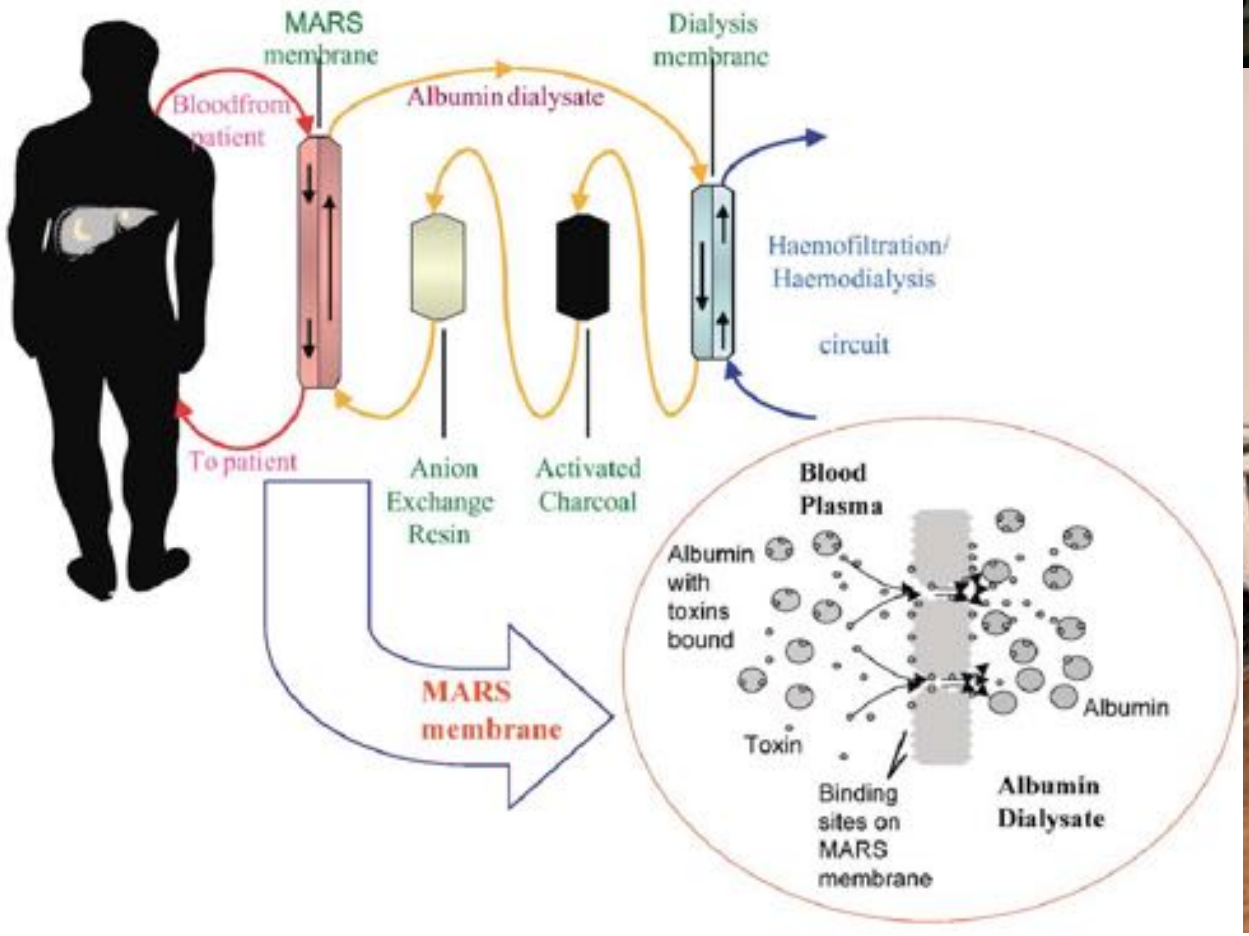
- Molecular Adsorbents Recirculating System
- Developed at the University of Rostock, Germany – currently owned by Gambro.
- Hollow fibred dialyzer with albumin impregnated polysulfone membrane with a pore size of 50 kD.
- Constant flow of albumin-rich (20%) dialysate (600mL) in the extracapillary compartment. Recirculation.
- **Removal of protein bound molecules (like bilirubin) and water soluble toxins**

SPAD – Single Pass Albumin Dialysis.

Just add albumin to the dialysis and discard after single pass!

For instance, dialysate usage of 2 l/hr (to achieve ~ 25 ml/kg/hr effluent dose) using an albumin concentration of 3%, results in a consumption of 1440 g/24 hours. Costly!

MARS™ (Molecular Adsorbent Recirculating System)



Wagholikar GD, Lee KH, Pandey D, Leong SO, Singh R, Tan KC. Pre-transplant optimization by molecular adsorbent recirculating system in patients with severely decompensated chronic liver disease. Indian J Gastroenterol 2007;26:110-112

May 2007 · Indian Journal of Gastroenterology
26(3):110-2

Table: Clinical and biochemical characteristics at baseline and treatment details in 9 patients who underwent MARS before liver transplantation*

No.	Age / sex	Bilirubin#	Creatinine#	INR	Ammonia#	HE@	MELD score+	Child score+	MARS@	Duration	Post-LT follow up (mo)
1	61 M	563	226	5.2	142	4	47	13	3	5	8 mo
2	58 F	608	138	2.3	128	3	33	13	2	3	9 mo
3	43 M	559	319	3.9	181	4	47	12	6	10	Died
4	42 M	483	90	1.9	70	2	26	12	1	3	24 mo
5	50 M	509	84	2.6	109	2	30	12	2	7	59 mo
6	62 M	231	138	2.4	148	3	30	13	1	5	33 mo
7	58 M	549	160	1.9	102	2	32	12	1	5	34 mo
8	46 M	997	173	2.5	102	3	38	13	4	5	31 mo
9	51 M	1126	211	1.8	84	2	37	13	2	3	6 mo

*Case #2 had HCV-related disease, #8 and 9 had cryptogenic cirrhosis, the rest had HBV-related disease. HE: grade of hepatic encephalopathy; Duration: duration in days between start of 1st MARS dialysis and LT; INR: international normalized ratio; HBV: hepatitis B virus; HCV: hepatitis C virus; POD: post-operative day; #data in µmol/L (conversion of SI units: bilirubin - µmol/L x 0.0585 = mg/dL, creatinine - µmol/L x 0.0113 = mg/dL). @: data as number of sessions

The outcome of liver transplantation (LT) is influenced by the recipient's clinical condition. In a retrospective observational study, we evaluated the role of pre-LT Molecular Adsorbent Recirculating System (MARS) treatment in improving the clinical status and thereby the outcome of patients with chronic liver disease and severe hepatic decompensation. Between March 2002 and September 2006, 70 patients with end-stage chronic liver disease underwent living-donor LT (LDLT). Of these, 9 (13%) patients with severely decompensated liver function (serum bilirubin> 350 micromol/L [20 mg/dL] and/or hepatic encephalopathy > or = grade 2) received pre-LT MARS treatment. The median MELD score was 33 (range, 26-47). A median of 2 (range, 1-6) sessions (8 hour/session) of MARS dialysis was performed per patient. MARS treatment was associated with reduction in serum bilirubin, creatinine and ammonia levels and no procedure-related complications. Pre-LT MARS is well tolerated and results in reduction of jaundice and improvement in renal function and may be useful in the management of patients with severe hepatic decompensation.

Extracorporeal Albumin Dialysis With the Molecular Adsorbent Recirculating System in Acute-on-Chronic Liver Failure: The RELIEF Trial

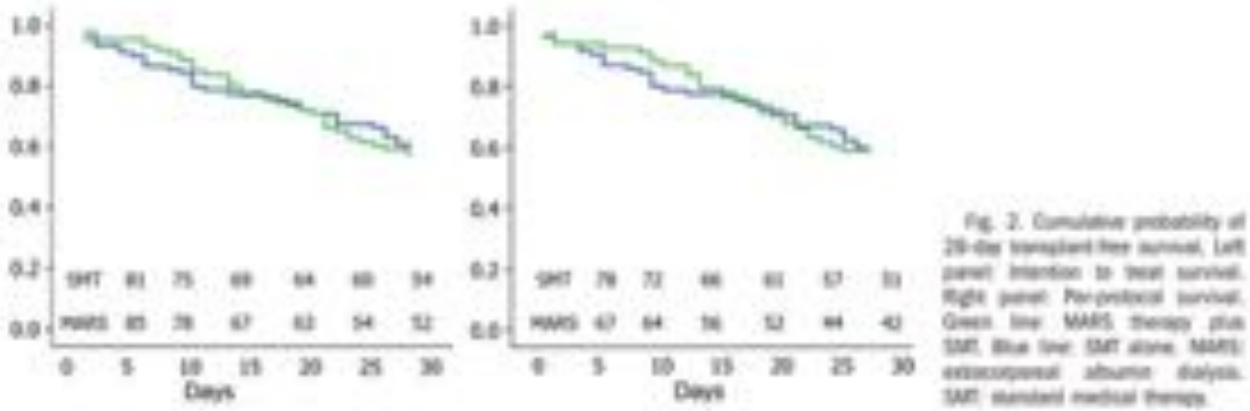


Fig. 2. Cumulative probability of 28-day transplant-free survival. Left panel: Intention to treat survival. Right panel: Per-protocol survival. Green line: MARS therapy plus SMT. Blue line: SMT alone. MARS: extracorporeal albumin dialysis. SMT: standard medical therapy.

At scheduled doses, a beneficial effect on survival of MARS therapy in patients with ACLF could not be demonstrated.

(HEPATOLOGY 2013;57:1153-1162)

In all, 189 patients with ACLF were randomized either to MARS (n = 95) or to standard therapy (SMT) (n = 94).

The 28-day survival was similar in the two groups in the ITT and PP populations (60.7% versus 58.9%; 60% versus 59.2% respectively).

MELD score and HE at admission and the increase in serum bilirubin at day 4 were independent predictors of death.

At day 4, a greater decrease in serum creatinine (P = 0.02) and bilirubin (P = 0.001) and a more frequent improvement in HE (from grade II-IV to grade 0-I; 62.5% versus 38.2%; P = 0.07) was observed in the MARS group.

Benefits From MARS™ Treatment

- Reduces bilirubin and ammonia levels
- Improves hepato-renal syndrome (HRS)
- Improves encephalopathy (reduces cerebral oedema)
- Improves hemodynamics (NO removal)
- **Improves outcome (7 day Type 1 HRS survival: 67% MARS and 0% in control; MARS-RELIEF trial – no survival benefit; French high urgency ALF pts – better transplant free 6 month survival).**

- BUT …???
  - Reduces antibiotic levels
  - Causes hypoglycemia when glucose-free dialysate utilized
  - Pro-inflammatory

Recent US/Europe Trial on Hepatic Encephalopathy

- Multi-center (6 US and 2 Europe)
- 70 pts recruited: mean MELD 31 ± 10; CTP 12.7 ± 1.3; Age 53 ± 11; 56% male; 56% HE grade 3; 44% HE grade 4
- 6 hrs of MARS for 5 consecutive days
- Significant improvement in hepatic encephalopathy (2 grades or more) with MARS treatment compared to controls and more rapid improvement
- Excluded pts with renal failure

Table 4. Percentage of Patients Showing a Response to Treatment During the Study

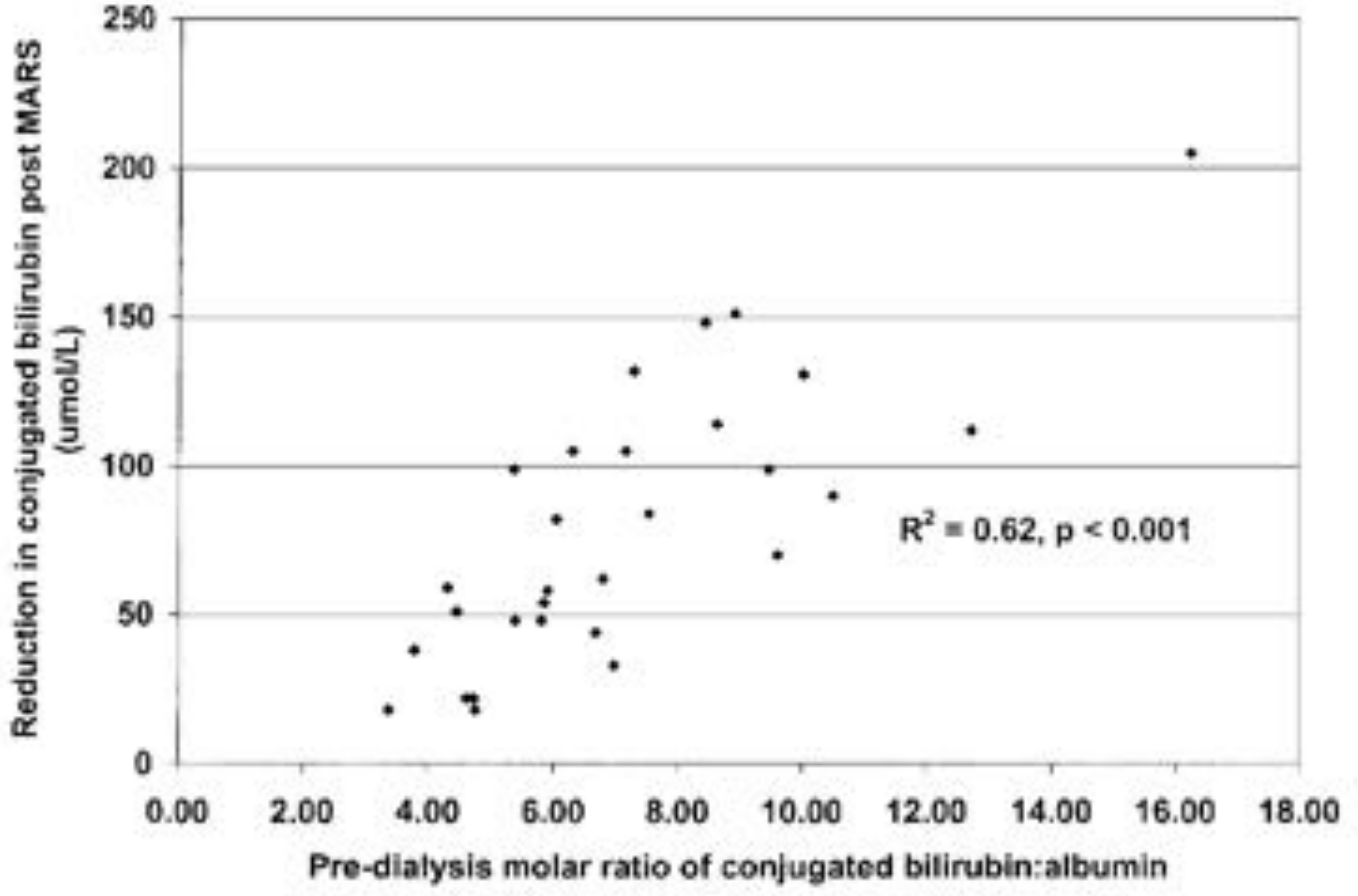
n (PP)	24 Hours	48 Hours	72 Hours	96 Hours	120 Hours	Kaplan Meier
SMT % 31 (29)	0 (0)	ITT $P = 0.045$				
ECAD % 39 (33)	13 (15)	30 (34)	58 (64)	61 (67)	72 (74)	PPP=0.017

Values are percentage of patients reaching a 2-grade improvement at each time after randomization. ( ) represent PP analysis. At any time during the study, patients receiving ECAD achieved a higher response rate than the SMT group.

Source: Hepatology. 2008 Aug;48(2):686-7

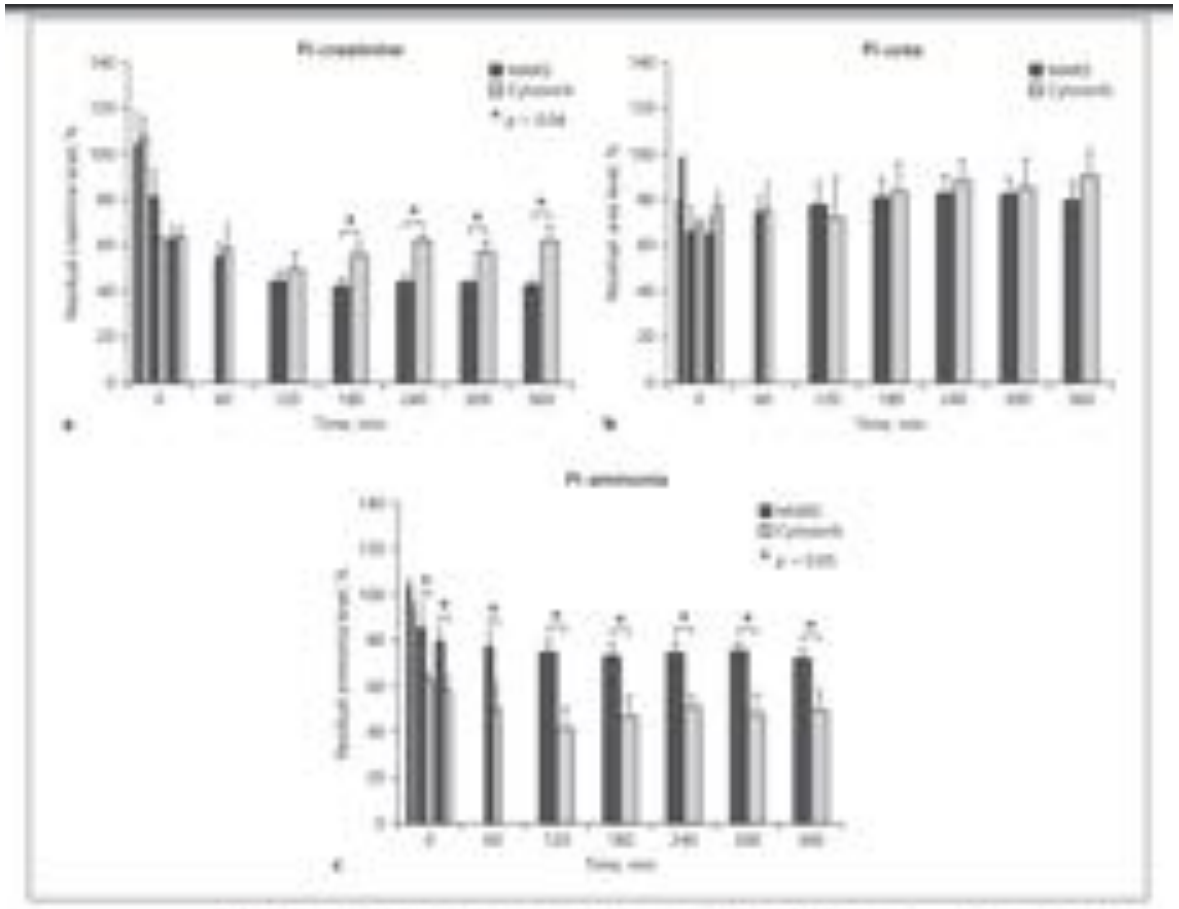
Predicting the Decrease of Conjugated Bilirubin With Extracorporeal Albumin Dialysis MARS Using the Predialysis Molar Ratio of Conjugated Bilirubin to Albumin

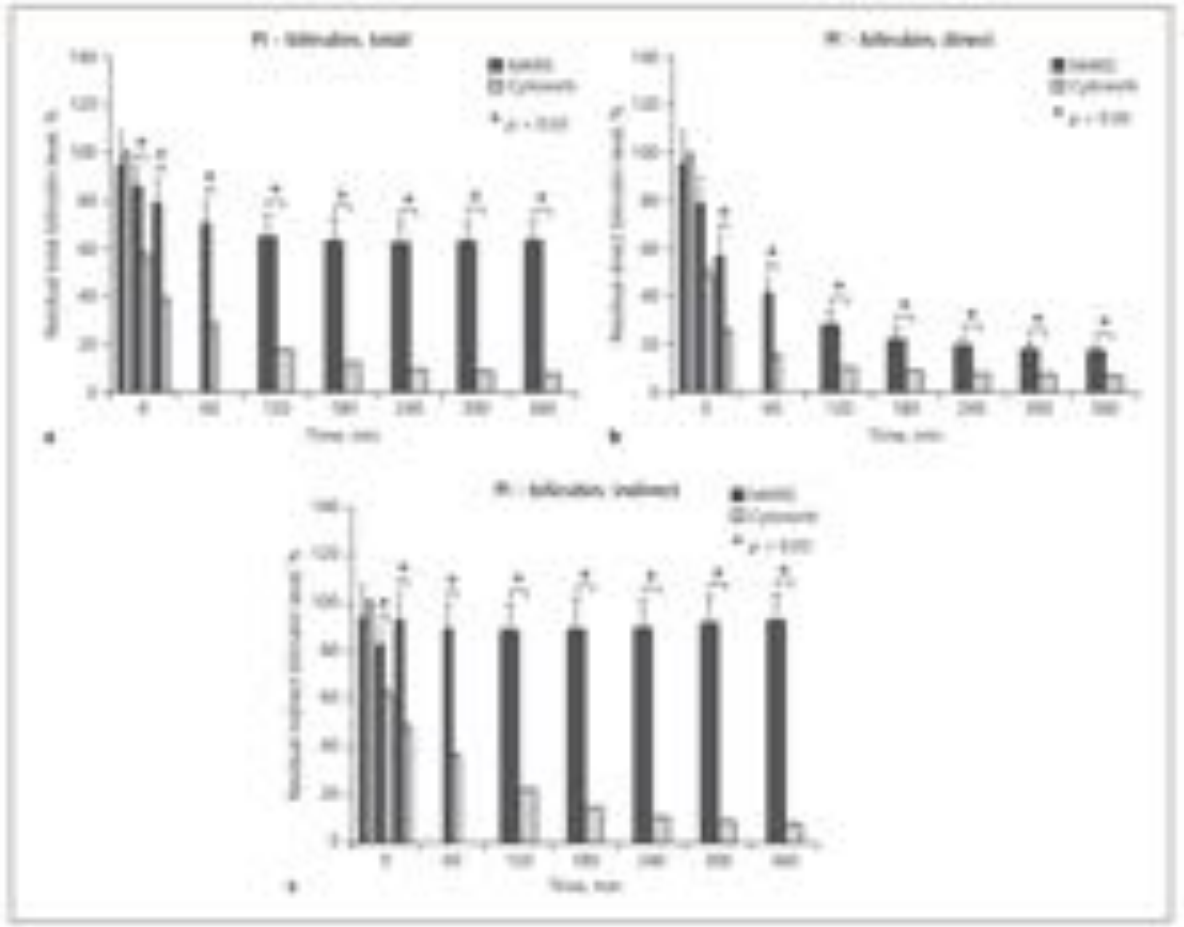
Figure 2. Reduction in conjugated bilirubin as a function of predialysis molar ratio of conjugated bilirubin to albumin. The regression equation is (12.8 × predialysis molar ratio of conjugated bilirubin to albumin − 12.2).



Lee et al. Liver Transplantation 2000;8:591-3.

Similarities, Differences, and Potential Synergies in the Mechanism of Action of Albumin Dialysis Using the MARS Albumin Dialysis Device and the CytoSorb Hemoperfusion Device in the Treatment of Liver Failure





Blood Purif 2021;50:119–128

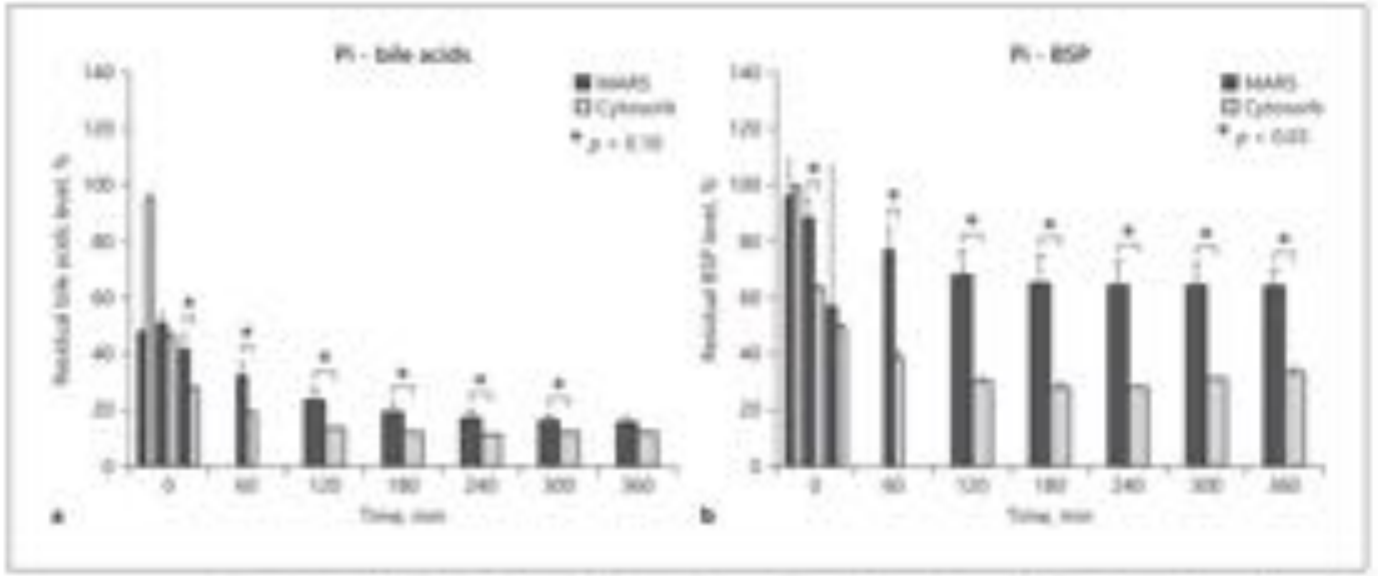


Fig. 4. Residual levels of albumin-bound marker molecules bile acids (chenodeoxycholic acid; **a**) and bromosulphthalein (BSP; **b**) referenced against initial compartment 1 concentrations over time ($n = 3$). Pi, patient inlet.

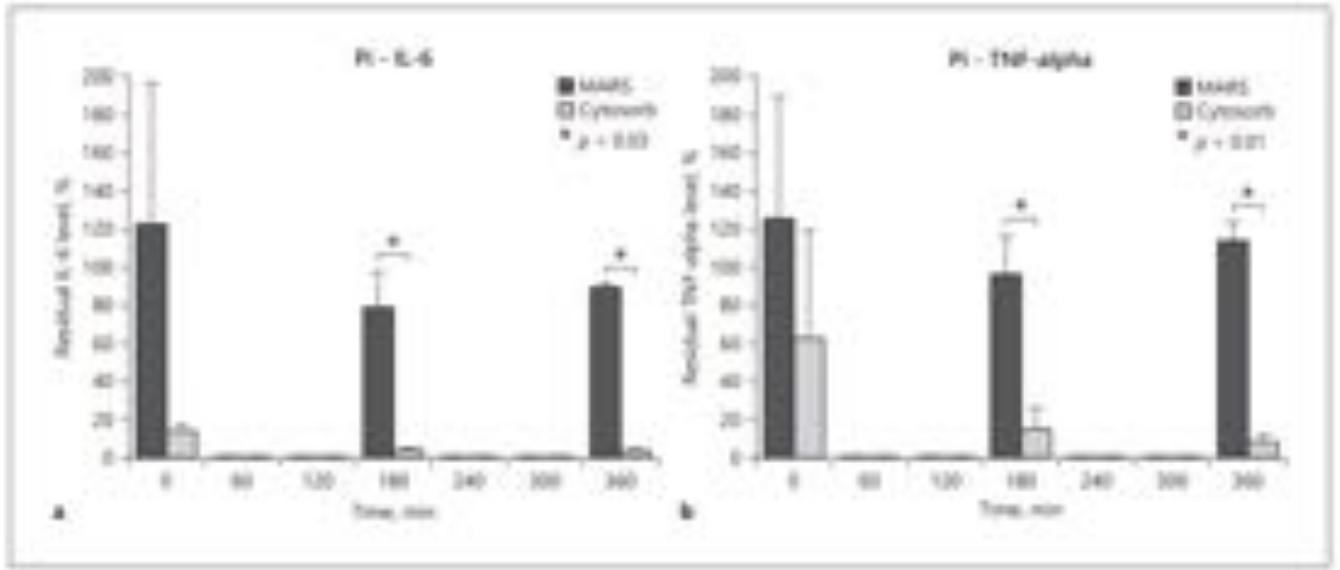
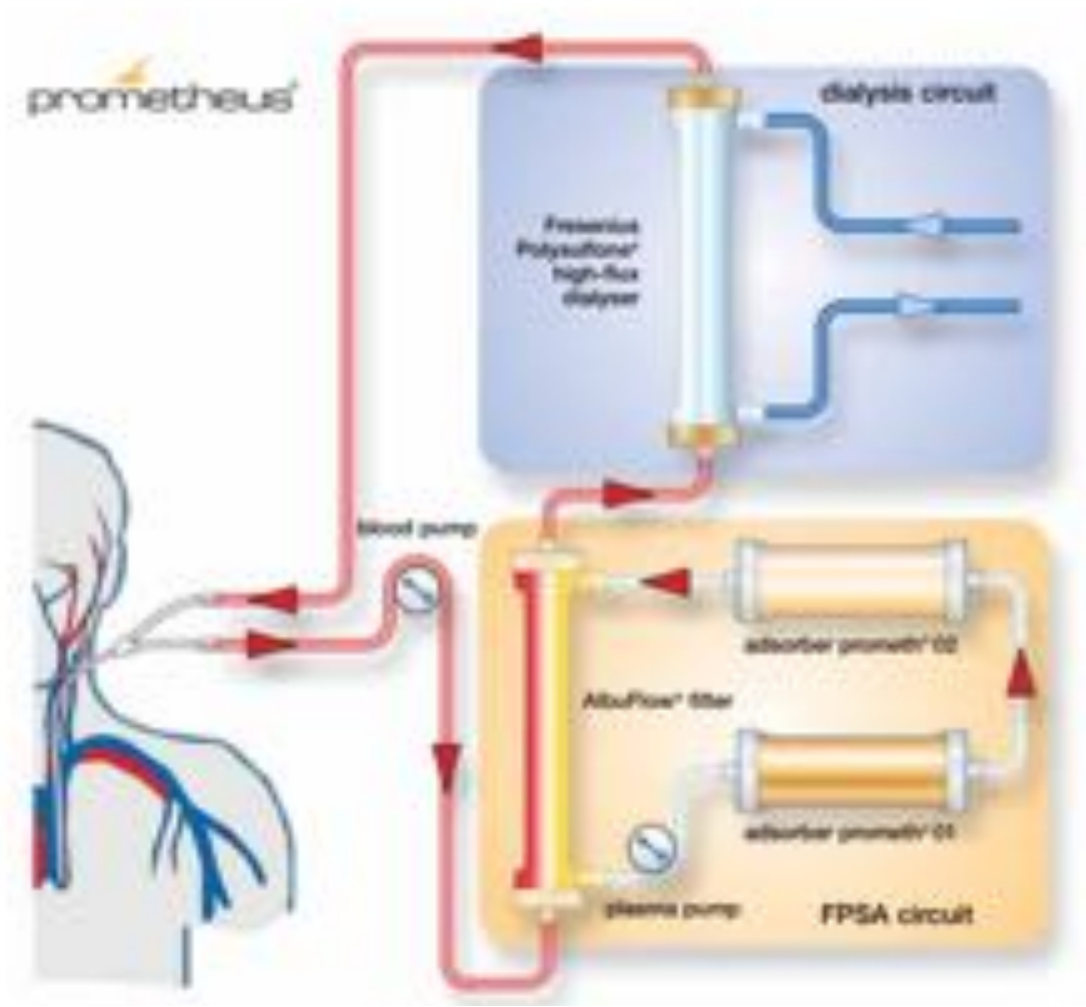


Fig. 5. Residual levels of IL-6 (**a**) and TNF-α (**b**) referenced against initial compartment 1 concentrations over time ($n = 3$). IL, interleukin; TNF-α, tumour necrosis factor-alpha; Pi, patient inlet.

Prometheus from Fresenius



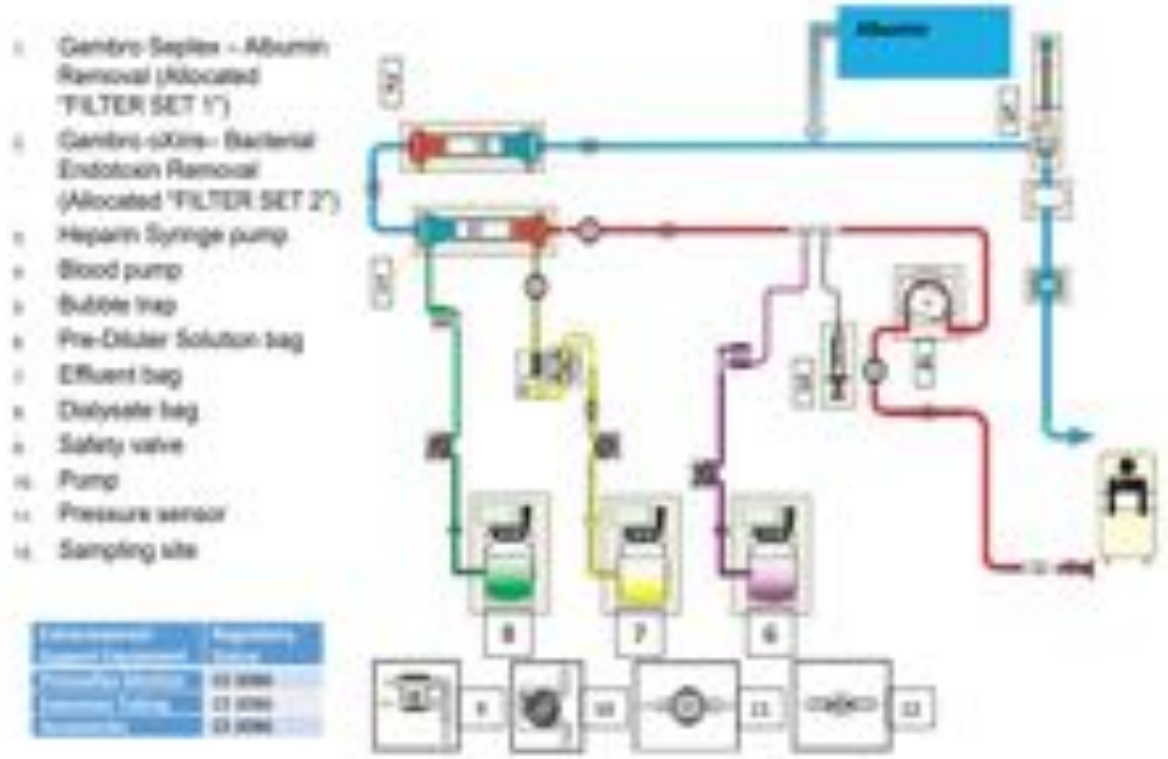
Specifically, the patient's blood first passes through an albumin-permeable biocompatible filter (Albuflow®; molecular weight cutoff of 250kDa), filtering out an albumin rich plasma fraction which then passes through a neutral resin adsorber (Prometh® 01) and an anion-exchanger (Prometh® 02) before being returned to the blood.

The reconstituted blood then undergoes conventional dialysis using a high-flux polysulfone dialyzer.

Reduction in bilirubin and ammonia and improvement in HE and HRS but no outcome benefit.

DIALIVE – combination of Septet and Oxiris

Schematic representation of a prototype of the Dialive LDD system



Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

Randomized, controlled clinical trial of the DIALIVE liver dialysis device versus standard of care in patients with acute-on-chronic liver failure

Authors

Correspondence

Graphical abstract

32 pts with alcohol related ACLF.

There were no significant differences in 28-day mortality or occurrence of serious adverse events between the groups.

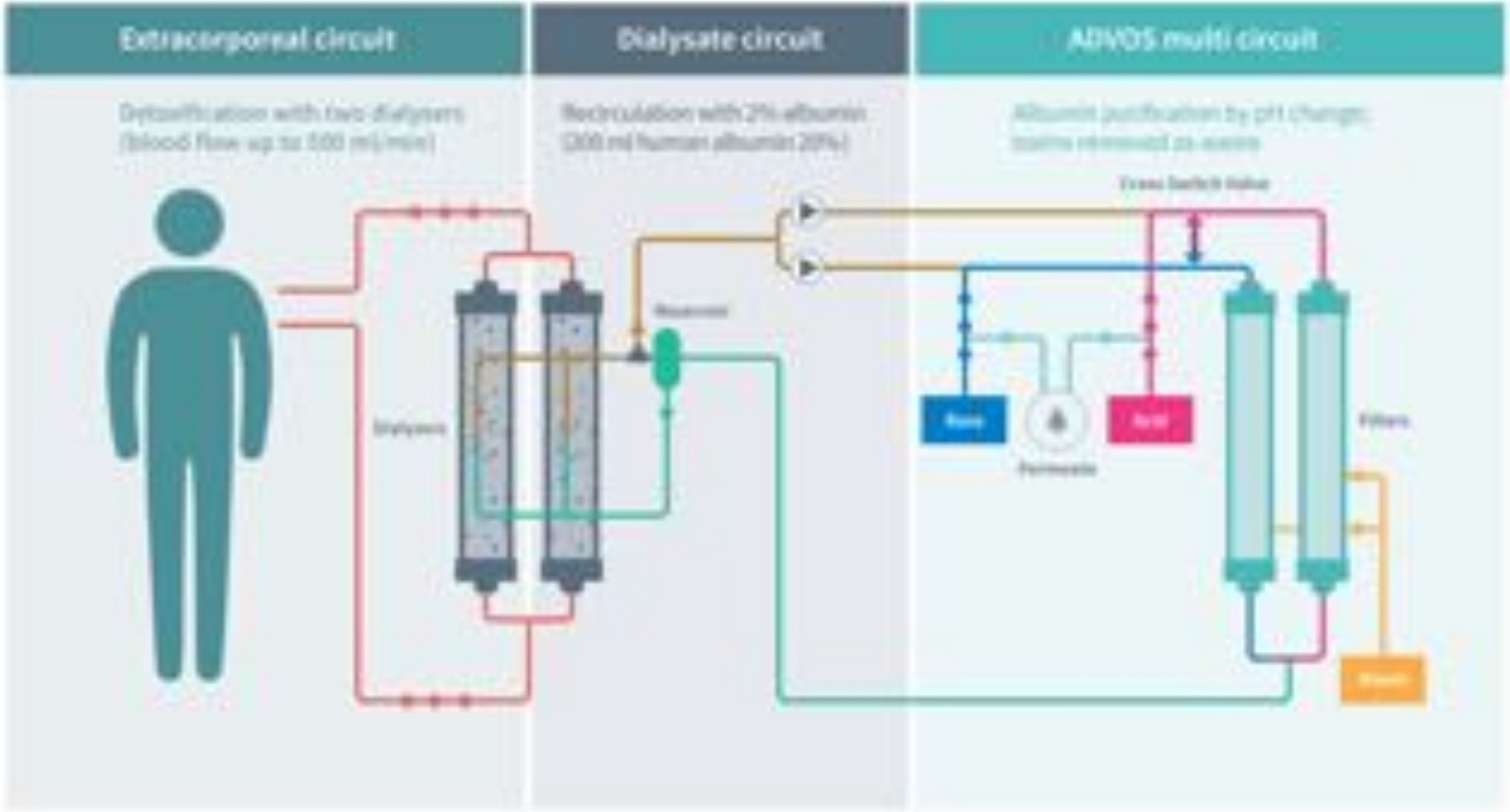
Significant reduction in the severity of endotoxemia and improvement in albumin function was observed in the DIALIVE group, which translated into a significant reduction in the CLIF-C (Chronic Liver Failure consortium) organ failure ($p = 0.018$) and CLIF-C ACLF scores ($p = 0.042$) at Day 10.

Time to resolution of ACLF was significantly faster in DIALIVE group ($p = 0.036$).

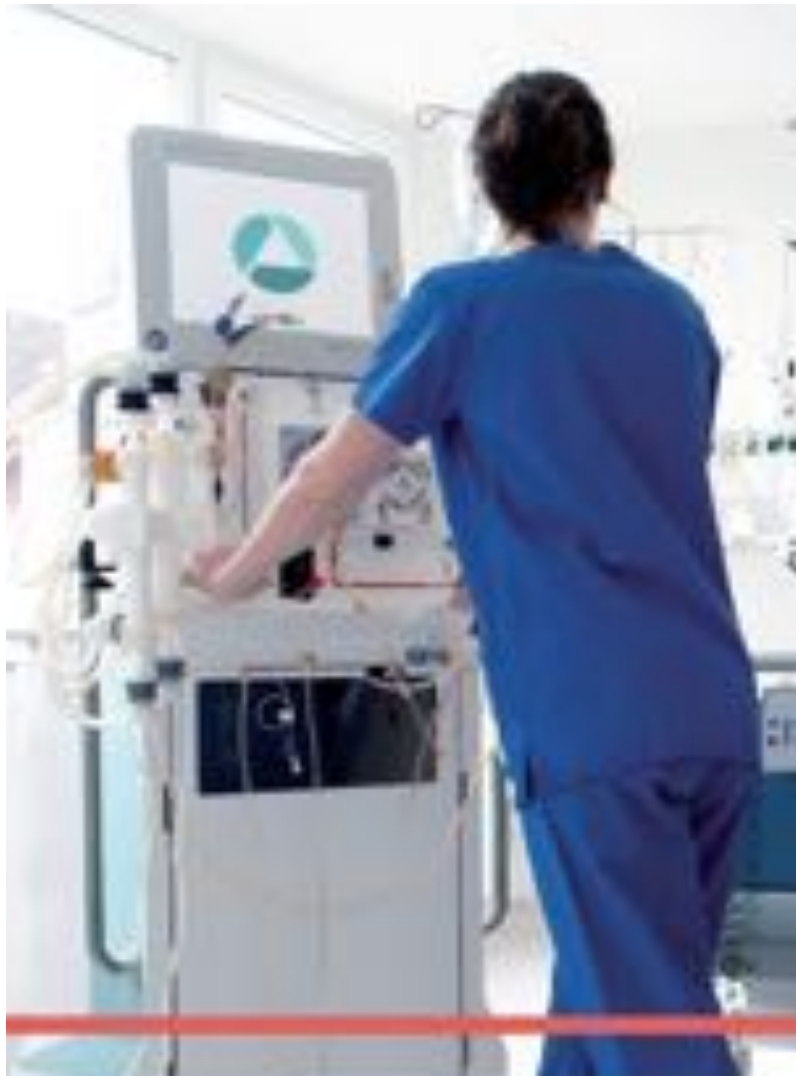
Biomarkers of systemic inflammation such as IL-8 ($p = 0.006$), cell death [cytokeratin-18: M30 ($p = 0.005$) and M65 ($p = 0.029$)], endothelial function [asymmetric dimethylarginine ($p = 0.002$)] and, ligands for Toll-like receptor 4 ($p = 0.030$) and inflammasome ($p = 0.002$) improved significantly in the DIALIVE group

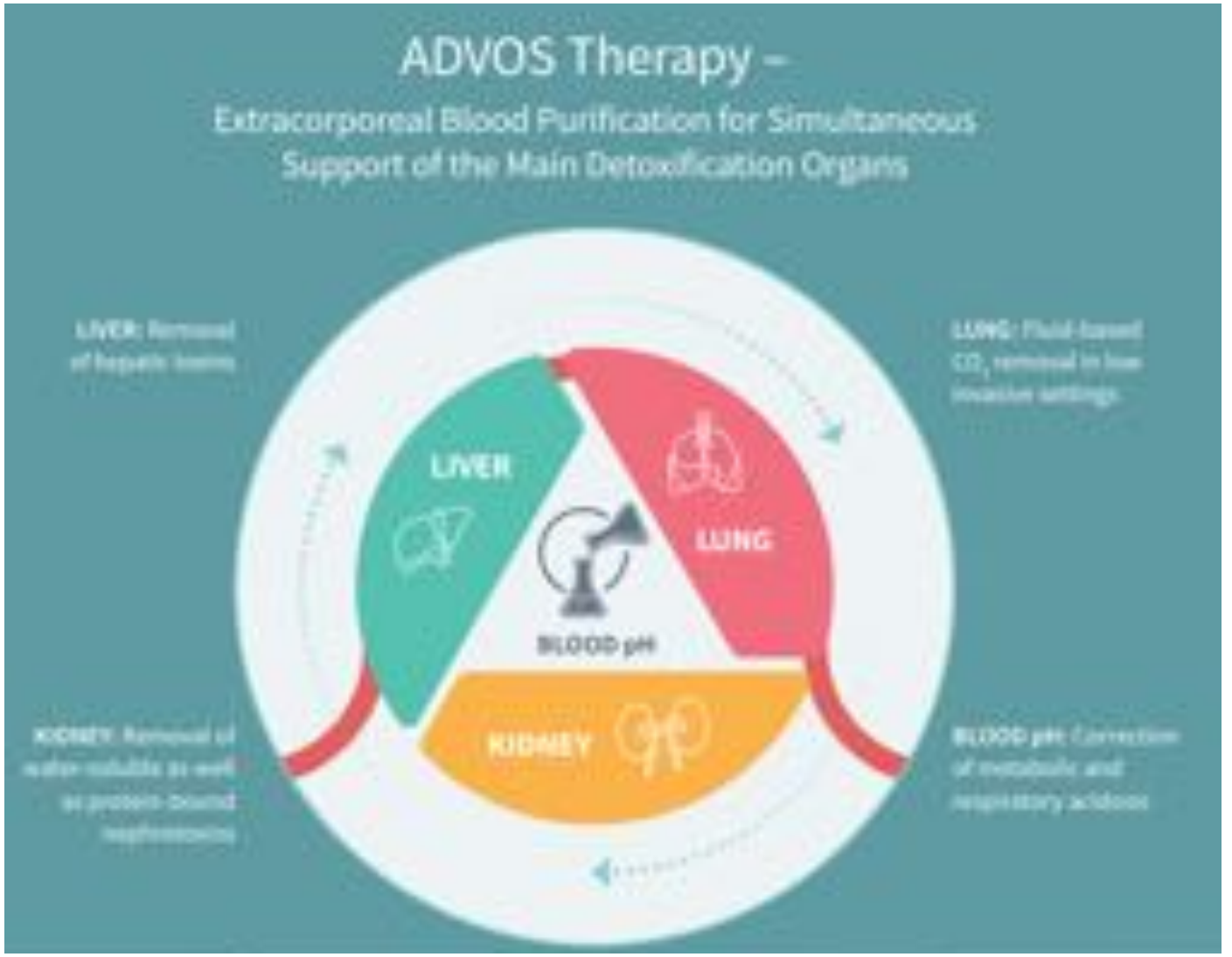
Agarwal et al. J Hep 2023

ADVOS


Extracorporeal circuit
Dialysate circuit
ADVOS multi circuit

The ADVOS procedure (ADVanced Organ Support) provides multi-organ support to the kidneys, liver and lung while simultaneously correcting acid-base disorders in patients.





Successful elimination of bilirubin in critically ill patients with acute liver dysfunction using a cytokine adsorber and albumin dialysis: a pilot study.

Scharf et al. Scientific Reports May 2021

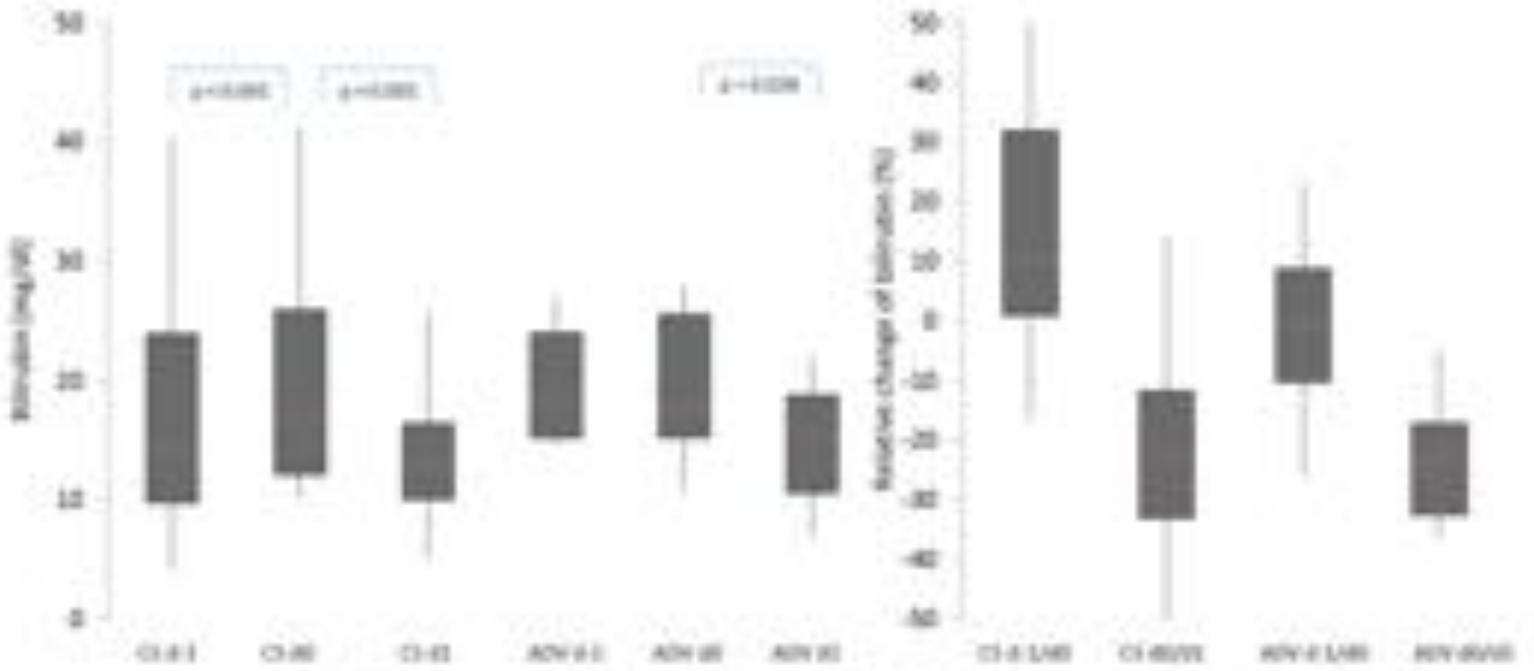


Figure 2. Development and relative reduction in bilirubin levels in patients with CytoSorb and ADVOS therapy. d-1: day before treatment, d0: shortly before treatment, d1: directly after treatment, CS: CytoSorb, ADV: advanced organ support; orange line represents the median, grey boxes the interquartile range and the whiskers are limited to 1.5 times the interquartile range

39 patients (33 CS, 6 ADVOS) were included (> 90 minutes of treatment).

The median bilirubin at d0 was 16.9 and 17.7 mg/dl and at d1 was 13.2 and 15.9 mg/dl, in the CS and ADVOS group, respectively.

There was a significant bilirubin reduction as well in the CS group ($p < 0.001$, median relative reduction: 22.5%) as in the ADVOS group ($p = 0.028$, median relative reduction: 22.8%).

Extracorporeal removal

- Bilirubin & bile acids
- Ammonia
- Cytokines
- Endotoxin
- Fluids
- Electrolytes
- Glucose
- Antimicrobials (Antibiotics, antifungals, antivirals) ?? Therapeutic drug monitoring

Prismasol (CRRT replacement fluid) – note possible 0 glucose

NDA 21-703
Page 4

in mEq/L except where noted	PrismaSol BK 0/3.5	PrismaSol BGK 2/0	PrismaSol BGK 2/3.5	PrismaSol BGK 4/2.5	PrismaSol BGK 4/0	PrismaSol BGK 0/2.5	PrismaSol BK 0/0
Calcium Ca^{2+}	3.5	0	3.5	2.5	0	2.5	0
Magnesium Mg^{2+}	1.0	1.0	1.0	1.5	1.5	1.5	1.5
Sodium Na^{+}	140	140	140	140	140	140	140
Chloride Cl^{-}	109.5	108.0	111.5	113.0	110.5	109.0	106.5
Lactate	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Bicarbonate HCO_3^{-}	32	32	32	32	32	32	32
Potassium K^{+}	0	2.0	2.0	4.0	4.0	0	0
Dextrose	0	100 mg/dL	100 mg/dL	100 mg/dL	100 mg/dL	100 mg/dL	0
Theoretical Osmolarity	287 mOsm/L	291 mOsm/L	296 mOsm/L	300 mOsm/L	296 mOsm/L	292 mOsm/L	282 mOsm/L

Calcium chloride, USP, is chemically designated calcium chloride dihydrate ($CaCl_2 \cdot 2\,H_2O$).
Magnesium chloride, USP, is chemically designated magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$).
Dextrose, USP, is chemically designated D-Glucose anhydrous ($C_6H_{12}O_6$) or D-Glucose monohydrate ($C_6H_{12}O_6 \cdot H_2O$).
Lactic acid, USP, is chemically designated $CH_3CH(OH)COOH$.
Sodium chloride, USP, is chemically designated NaCl.
Potassium chloride, USP, is chemically designated KCl.
Sodium bicarbonate, USP, is chemically designated $NaHCO_3$.

The pH of the final solution is in the range of 7.0 to 8.5.

Solutions in contact with the plastic container can leach out certain of its chemical components in very small amounts within the expiration period, e.g. di 2-ethylhexyl phthalate (DEHP), up to 3 parts per million; however, the safety of the plastic has been confirmed in tests in animals according to USP biological tests for plastic containers as well as by in-vitro toxicity studies.

Liver Transplantation
Volume 9, Issue 9, September 2003, Pages 949-953

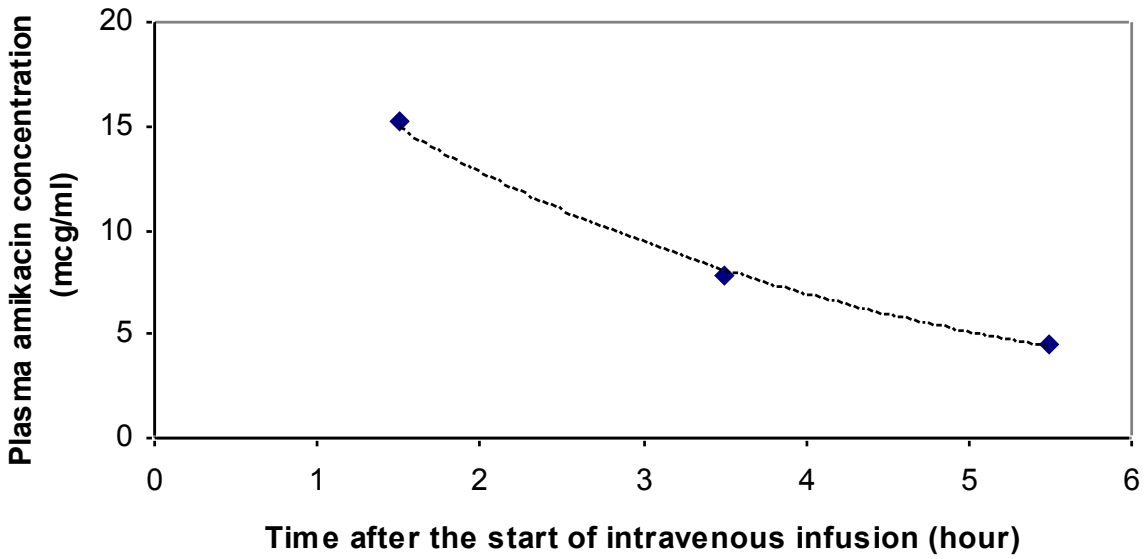
Original Articles

Hypoglycemia in nondiabetic patients undergoing albumin dialysis by molecular adsorbent recirculating system ☆

Ai-Leng Khoo [*], Lai-San Tham [*], Gek-Kee Lim [*], Kang-Hoe Lee [‡‡]

the period of MARS treatment. Glucose loss in dialysate fluid was quantified hourly by measuring the total volume of dialysate fluid and assaying the glucose concentration in dialysate fluid. Mean glucose removal during a 6-hour MARS session was 37.19 ± 5.58 g. Mean glucose removal rate was 6.20 ± 0.93 g/h. In

Anti-infective removal during Extracorporeal treatment



Concentration-time curve of amikacin (500 mg infused over 30 minutes) during the second MARS treatment.

For plasmapheresis, drugs with low volume of distribution have high removal with PE.

Table 1. Additional clearance of anti-infective agents provided by Cytosorb®; from Schneider AG et al., modified.

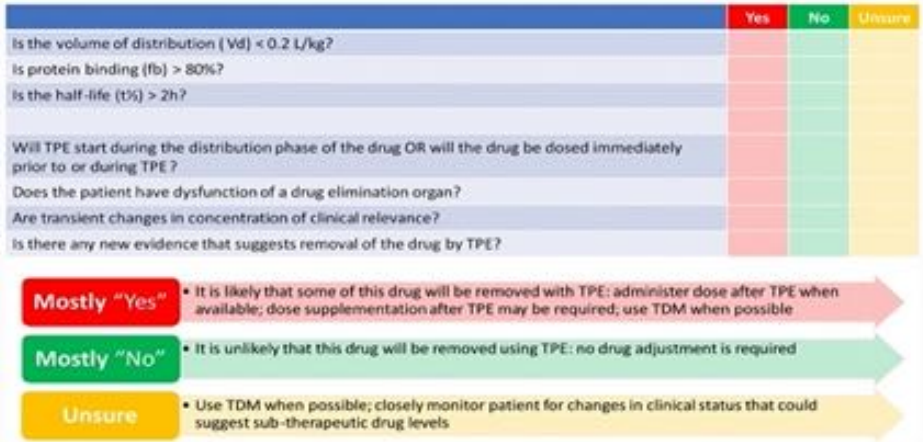
Agent	Variation (%)
Liposomal Amphotericin B	74.9
Anidulafungin	22.7
Cefepime	1.2
Ceftriaxone	5.2
Ciprofloxacin	14.5
Clarithromycin	4.7
Clindamycin	6.4
Flucloxacillin	15.9
Fluconazole	282.2
Linezolid	114.6
Meropenem	6.3
Metronidazole	15.4
Piperacillin	19.4
Posaconazole	32.0
Teicoplanin	30.7
Tobramycin	5.5

Table 1 Summary of the effect of therapeutic plasma exchange (TPE) on antimicrobials

From: Drug Dosing in Patients Undergoing Therapeutic Plasma Exchange

Fig. 3

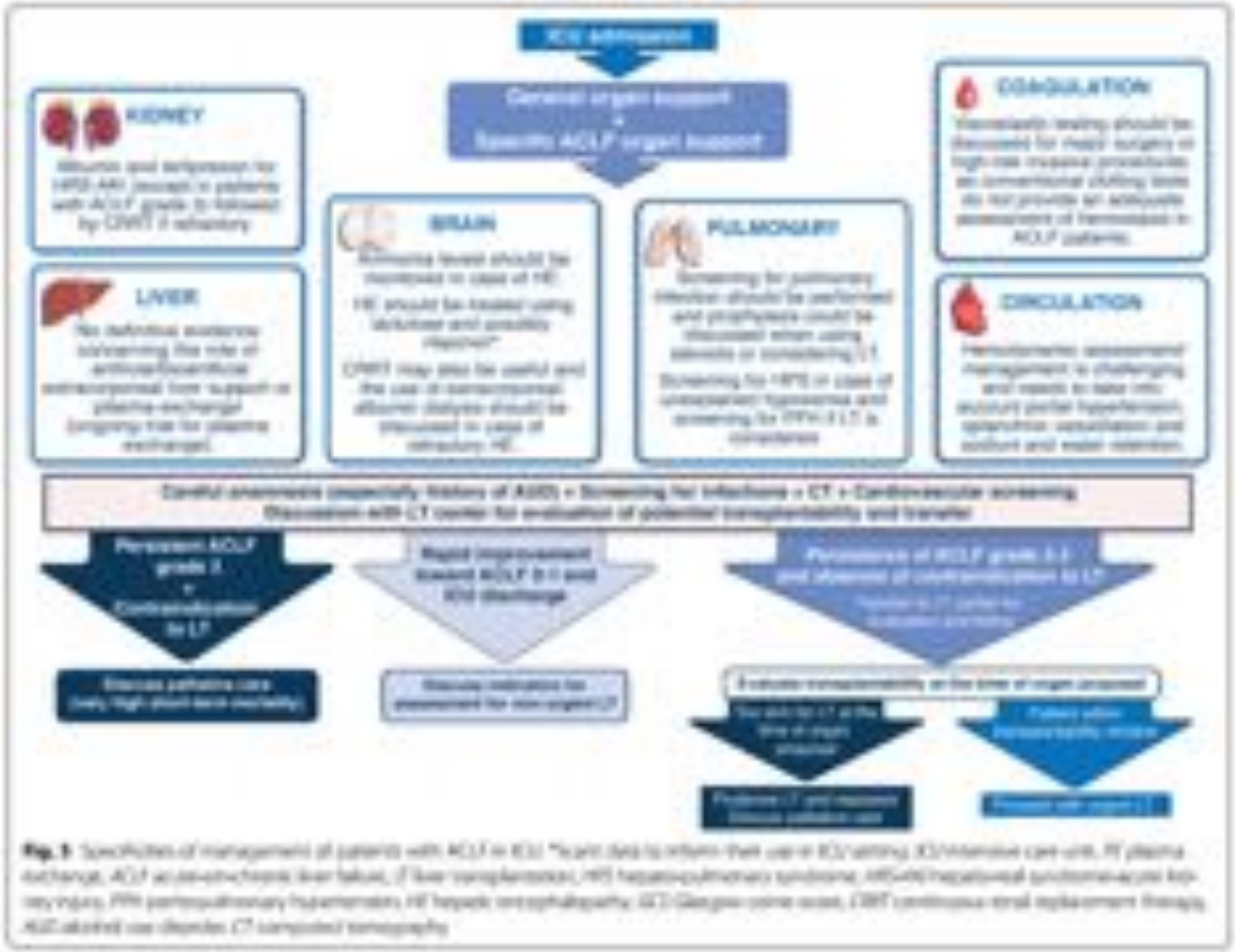
From: Drug Dosing in Patients Undergoing Therapeutic Plasma Exchange



Checklist to determine how likely drugs are removed by therapeutic plasma exchange (TPE)

Coagulation

- Plasmapheresis has FFP replacement (even up to 10L per day in Larsen study)
- Without plasmapheresis, please adjust support accordingly.
- Otherwise, rapid rise in INR and may result in bleeding.
- Can consider Octaplex (prothrombin complex concentrate - contains freeze dried human derived Factors II, VII, IX, X and Proteins S and C) instead of FFP



Intensive care management of acute on chronic liver failure.

Perricone et al. Intensive Care Med 2023.

Liver Transplantation Considerations

- Candidate or not
- Cadaveric vs Live donor options
- Referral to a liver transplant centre for consideration
- Otherwise, palliative care options
- Transplant workup takes time
- Ethics approval (TEC) is required for all live donor liver transplantation
- Urgent transplant listing (criteria)
- Extracorporeal support while waiting for Ltx ?? Indications for starting (HRS, HE, or biochemical). Goals of care ?

Important points to consider for Plasmapheresis

- Transplant vs non transplant candidate
- Timing of transplant
- Patient factors: Cerebral oedema/ hepatic encephalopathy, renal failure plus electrolyte issues
- Dose / volume (30 litres in 3 days or 5 litres or 3.5 litres) of PE
- Filtration based or Centrifugation based
- Replacement (Fresh frozen plasma) strategy
- Intermittent therapy – daily or spaced
- Additional extracorporeal interventions (MARS, CRRT or hemoperfusion)

Plasma Exchange in Acute and Acute on Chronic Liver Failure.

Maiwall and Sarin. Semin in Liver Dis 2021.

Table 3 The techniques of therapeutic plasma exchange (TPE)

	Technique of TPE	
	Filtration-based	Centrifugation based
Blood flow rates (mL/h)	150–200	50
Filtration fraction (%)	~30	~80
Technique	Membrane which separates the cellular from acellular components	Centripetal force of blood rotation separates the cellular from the acellular components based on the specific gravity
Time	Slower	Faster clearance achieved in one-third of time
Priming (min)	~23–40	~171
Procedure time (min)	~120–160	~90–120
Plasma removal efficiency (%)	Less efficient 27–53	More efficient 80–93
Anticoagulation	Usually heparin based	Citrate based

Note: Adapted from references.[112–114]

Anticoagulation for extracorporeal circuit

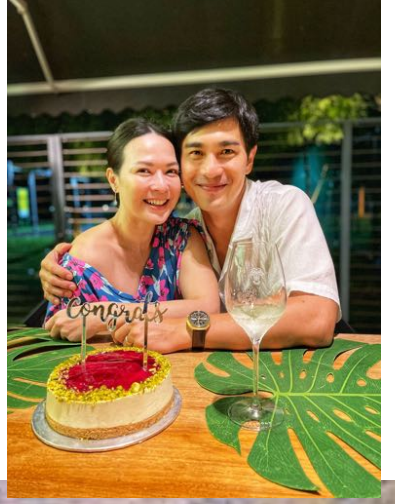
- None – high INR (? Viscoelastic)
- Heparin priming alone
- Continuous hepatin (target PTT or ACT)
- Citrate (accumulation with liver failure)
- Higher blood flow
- Prefilter fluid replacement
- Adsorption cartridge ?

Conclusions

- Severe ACLF (high CLIF-C ACLF score) needs **urgent liver transplantation**
- Extracorporeal liver support systems (non biological) currently have NO demonstrated survival advantage to SMT
- Removal of “hepatotoxins” can be achieved
- Removal of “cytokines” can be achieved
- Improvement in HE (clinical) can be aided by extracorporeal liver support
- **Combination of modalities** should be studied further
- CRRT plus/minus additional adsorption cartridge is available in most ICUs – just ensure appropriate clearance **(DOSE)**
- Be cautious of removing“goodies” (anti-infectives)
- Value proposition ????

“The original phrase is

God is in the details.”



Small things matter in critically ill patients.

Continuous and meticulous care with a team of professionals working together creates the final tapestry of success.

One note does not make a symphony; one artist does not make an orchestra.

Plasma exchange for acute and acute-on-chronic liver failure: A systematic review and meta-analysis

Beran et al. Liver Transpl. 2023 Aug 3.

- In conclusion, PE is associated with improved survival in ALF and could improve survival in ACLF.
- PE may be considered in managing ALF and ACLF patients who are not liver transplant (LT) candidates or as a bridge to LT in otherwise eligible patients.
- Further randomized controlled trials are needed to confirm the survival benefit of PE in ACLF.