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Plasma exchange treatment (PLEX) in liver failure

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ALF: Acute Liver Failure or…maybe Alien Life Form?

https://en.wikipedia.org/wiki/ALF_(character)

ALF?

- **Acute liver failure (ALF) can develop in a normal liver or in the setting of chronic liver disease (acute on chronic liver failure, ACLF).**
- The most common causes: acetaminophen toxicity and viral hepatitis.
- Other known causes: ingestion of hepatotoxins/drugs/alcohol, autoimmune hepatitis, critical illness, neo plastic infiltration
- **The mortality rate in ALF: 50% to 90%** due to acute metabolic disturbances, hepatic encephalopathy, and severe coagulopathy resulting in multiple organ failure.
- Survival rates improve following liver transplantation (LT).

Table 2. The clinical course of different ALF aetiologies.

Precipitant	Examples	Presentation
Viral	Hepatitis A, E, B (less frequent CMV, HSV, VZV, Dengue)	Acute/fulminant
Drugs/toxins	Paracetamol (acetaminophen), phosphorous, *Amanita phalloides*	Acute/fulminant and subacute/subfulminant
	Anti-tuberculous, chemotherapy, statins, NSAI, phenytoin, carbamazepine, ecstasy, flucloxacillin	Acute/fulminant
Vascular	Budd Chiari	Acute/fulminant and subacute/subfulminant
	Hypoxic hepatitis	Acute/fulminant
Pregnancy	Pre-eclamptic liver rupture, HELLP, fatty liver of pregnancy	Acute/fulminant
Other	Wilson disease, autoimmune, lymphoma, malignancy, HLH	Acute/fulminant and subacute/subfulminant

CMV, cytomegalovirus; HSV, Herpes simplex; NSAI, non-steroidal anti-inflammatory; HELLP, haemolysis, elevated liver enzymes, low platelets; HLH, haemophagocytic lymphohistiocytosis.

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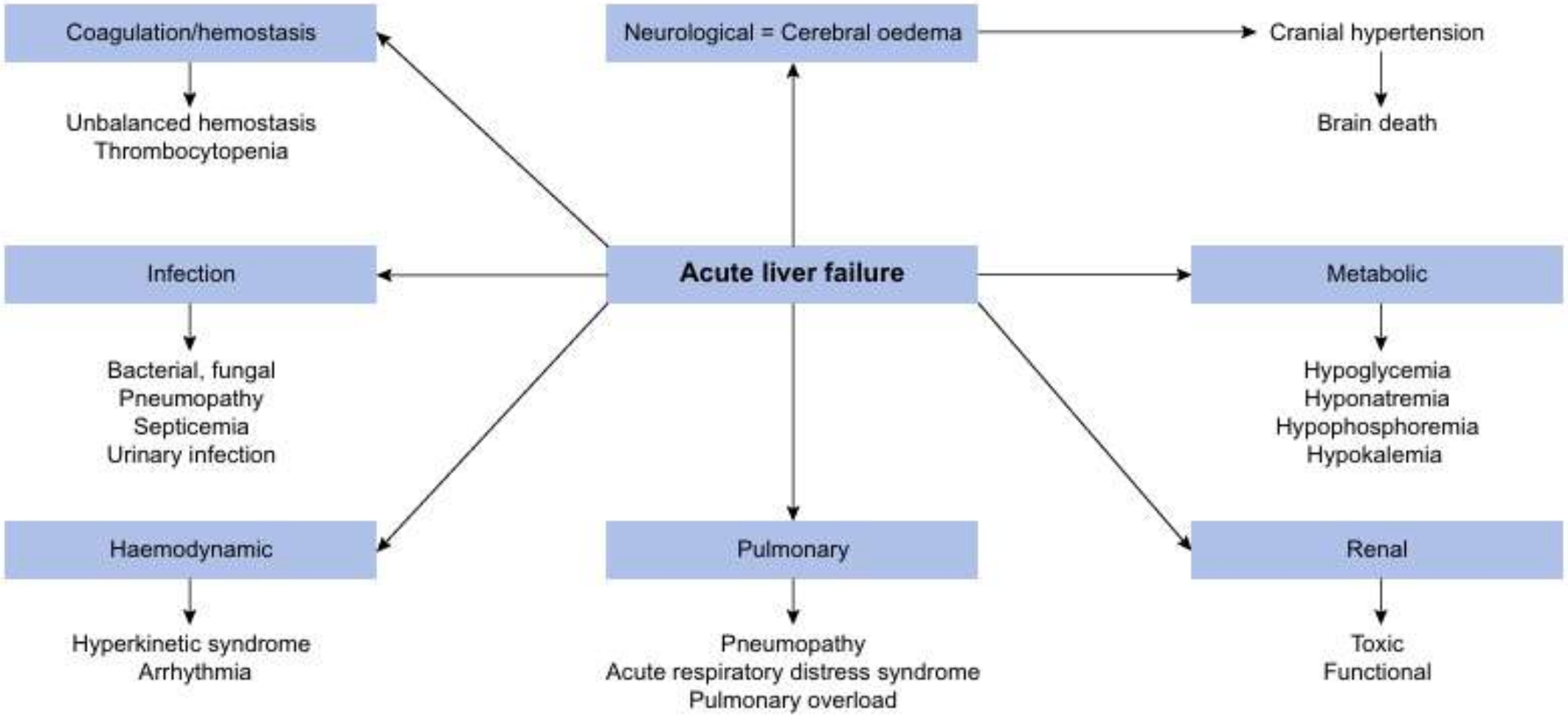
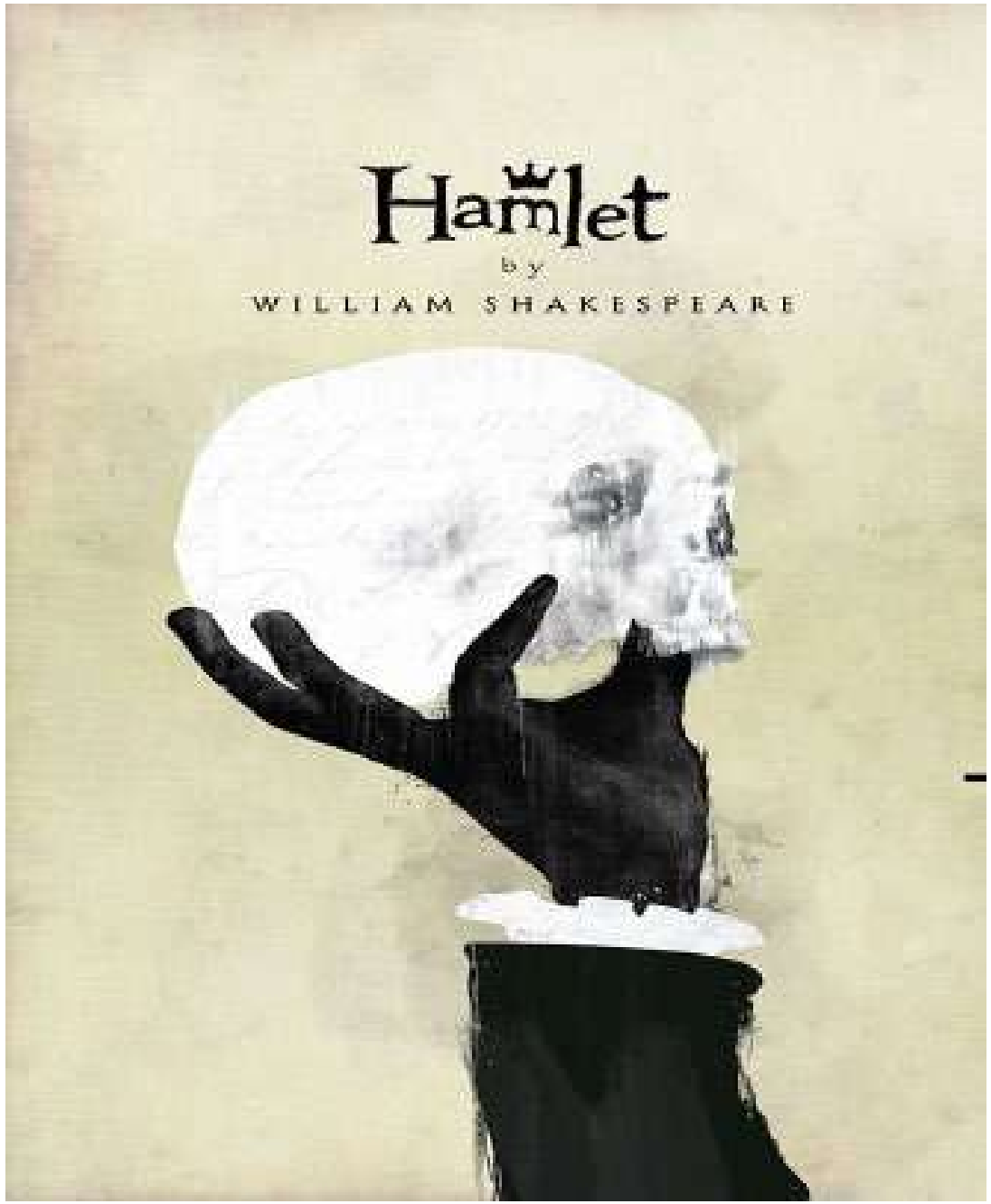


Fig. 2. Main organ specific complications in ALF.

Journal of Hepatology 2017 vol. 66 j 1047–1081

The standard treatment is supportive care as a bridge to recovery or liver transplantation (LT).

- If LT is not available, other liver support systems have been used but none have been shown conclusively to increase survival in this cohort of patients.
- Liver support systems: cell-based (bioartificial) and non-cell-based therapies.
- cell-based liver support systems: bioartificial liver, extracorporeal whole liver perfusion, extracor poreal liver assist device, and modular extracorporeal liver support)
- Non-cell-based therapies: PLEX , albumin dialysis, liver support systems (such as molecular adsorbents recirculation system (MARS)), fractionated plasma separation and adsorption, single pass albumin dialysis, and selective plasma exchange therapy.



To PLEX or not to PLEX that is the question!

https://www.magicalquote.com/booktheme/question/

The wisdom of the guidelines says…

ACUTE LIVER FAILURE

Incidence: <10/1,000,000/year					
Indication	**Procedure**	**Category**		**Grade**	
Acute liver failure*	TPE-HV	I		1A	
	TPE	III		2B	
Acute fatty liver of pregnancy	TPE	III		2B	
# reported patients: >300	**Procedure**	**RCT**	**CT**	**CS**	**CR**
Acute liver failure*	TPE-HV	1 (183)	2 (52)	2 (71)	NA
	TPE	2 (160)	3 (212)	NA	NA
Acute fatty liver of pregnancy	TPE	0	0	11 (170)	8 (9)

TPE-HV = TPE-high volume; *in select patients bridging to liver transplantation or with expected liver regeneration, excluding acute fatty liver of pregnancy.

Volume treated: 1 to 1.5 TPV; TPE-HV: target 8 to 12L exchange	**Frequency:** Daily
Replacement fluid: Plasma or plasma/albumin	

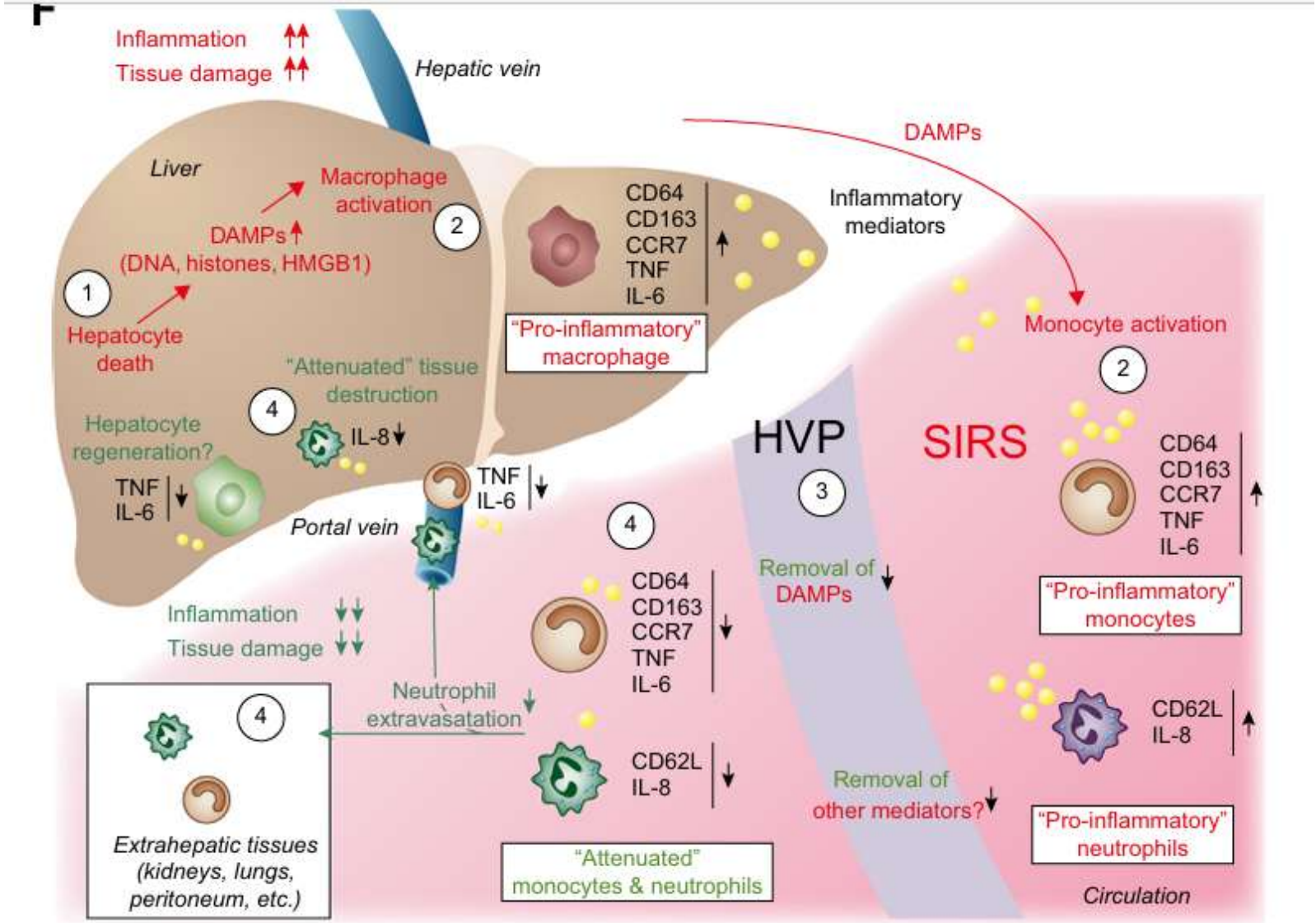
Duration and discontinuation/number of procedures

In ALF, daily TPE is typically performed for a defined period as a bridge to LT or liver self-regeneration. The biochemical response to TPE should be evaluated in laboratory values drawn the following day (≥12 hours or more after TPE) to address recirculation from the interstitium. Samples drawn immediately after completion of TPE would be expected to appear better compared to pre-TPE levels. In studies, TPE-HV was performed on 3 consecutive days. In AFLP, TPE is used until amelioration and/or delivery.

What is PLEX supposed to FIX in Acute liver failure(ALF)?

DAMPs

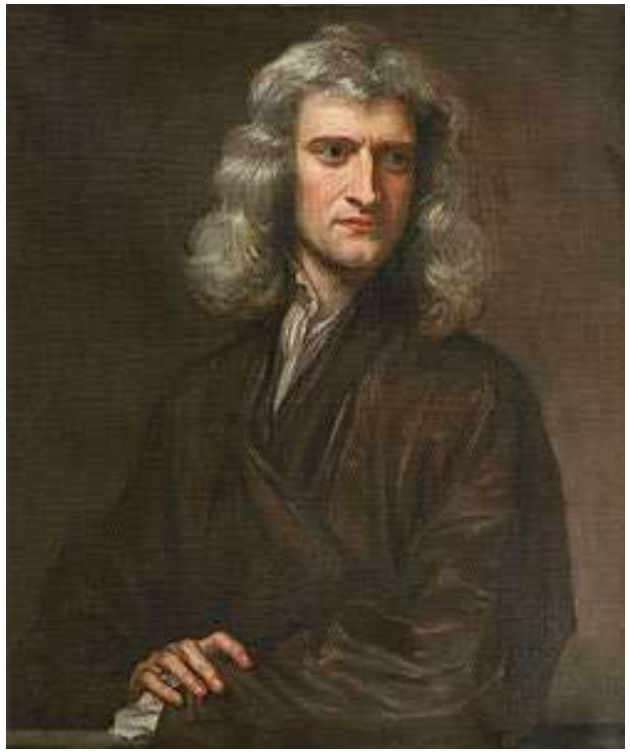
- Damage Associated Molecular P atterns



JournalofHepatology2016vol.64j69–78

Bridging to transplantation?

But how to achieve this?



Sir Isaac Newton
(25 December 1643 – 31 March 1727)

We build too many walls and not enough bridges.

Is High Volume PLEX indeed High Value PLEX?

Research Article

JOURNAL OF HEPATOLOGY

High-volume plasma exchange in patients with acute liver failure: An open randomised controlled trial

Fin Stolze Larsen[1,*], Lars Ebbe Schmidt[1], Christine Bernsmeier[2], Allan Rasmussen[3], Helena Isoniemi[4], Vishal C. Patel[2], Evangelos Triantafyllou[2], William Bernal[2], Georg Auzinger[2], Debbie Shawcross[2], Martin Eefsen[1], Peter Nissen Bjerring[1], Jens Otto Clemmesen[1], Krister Hockerstedt[4], Hans-Jørgen Frederiksen[5], Bent Adel Hansen[1], Charalambos G. Antoniades[2,6,†], Julia Wendon[2,†]

[1]*Department of Hepatology, Rigshospitalet, Copenhagen, Denmark;* [2]*Institute of Liver Studies, King's College Hospital, London, United Kingdom;* [3]*Department of Surgery and Liver Transplantation C, Rigshospitalet, Copenhagen, Denmark;* [4]*Transplantation and Liver Surgery Clinic, Helsinki University Hospital, Finland;* [5]*Department of Anaestesia AN-2041, Rigshospitalet, Copenhagen, Denmark;* [6]*Section of Hepatology, St. Mary's Hospital, Imperial College London, London, UK*

See Editorial, pages 10–12

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Patients and methods

This study was conducted in two parts. Study A: ALF patients randomised to standard medical treatment (SMT) and to SMT plus HVP. Study B: examined the effect of plasma obtained before and after the first HVP session from ALF patients on the circulating immune cell subsets innate and native immune system.

Study A

Trial design

The eligibility criteria were age greater than 18 years and a diagnosis of ALF with at least grade 2 hepatic encephalopathy [21]. All aetiologies including acute Wilson's disease, Budd-Chiari syndrome and acute presentation of autoimmune hepatitis (without clinical or radiological evidence of cirrhosis or chronic liver injury in the later two cohorts) were eligible for inclusion. Twenty-six patients were listed for liver transplantation (LTx) in the HVP treated group *vs.* 30 in the in the control group (NS). Before enrolment into the study, all patients had review of possible aetiological factors and clinical examination. A diagnostic ALF screen was secured incorporating serological tests, hepatitis serology, autoimmune markers, and microbiological cultures, in addition to ultrasound imaging and/or CT imaging as determined by the treating clinician.

HVP data

All patients received at least one treatment session with HVP apart from one patient who was transplanted before HVP could be initiated. All the 182 enrolled patients were included in the ITT analysis.

The mean number of HVP treatments per patient was 2.4 ± 0.8. The mean plasma volume exchanged during the first session was 9.3 ± 1.3 L, 9.2 ± 1.2 L for session 2 and 9.0 ± 1.2 L session 3. The mean administered dose was 0.33 ± 0.12 L/kg of actual body weight per treatment.

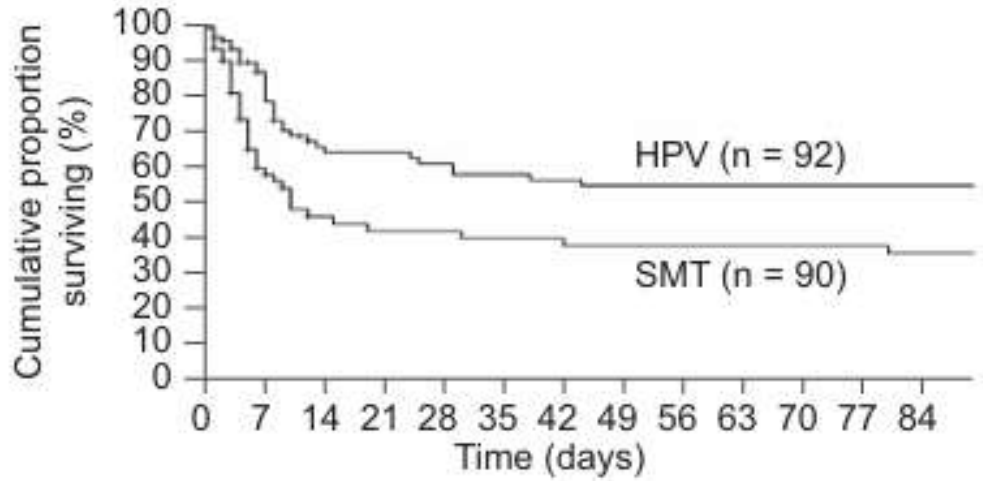


Fig. 1. Main results of the intention-to-treat analysis survival data in the standard medical treated group (SMT) compared to the high-volume plasma exchange (HVP) treated group (LogRank: $p = 0.0058$).

The aim of this open, prospective, randomised, controlled study was to examine if HVP reduces mortality in patients with ALF. We found that exchange of plasma in ALF patients with fresh frozen plasma increases transplant-free survival after 3 months (Fig. 1). The data shows that the main effect of HVP on survival is achieved in the patients that did not undergo emergency liver transplantation (Fig. 2). The data also shows that in those patients, who fulfilled criteria for poor prognosis but were not listed for transplantation due to contraindications, also demonstrated a significant increase in survival after HVP therapy (Fig. 3). Interestingly, patients listed for transplantation, but not offered a liver

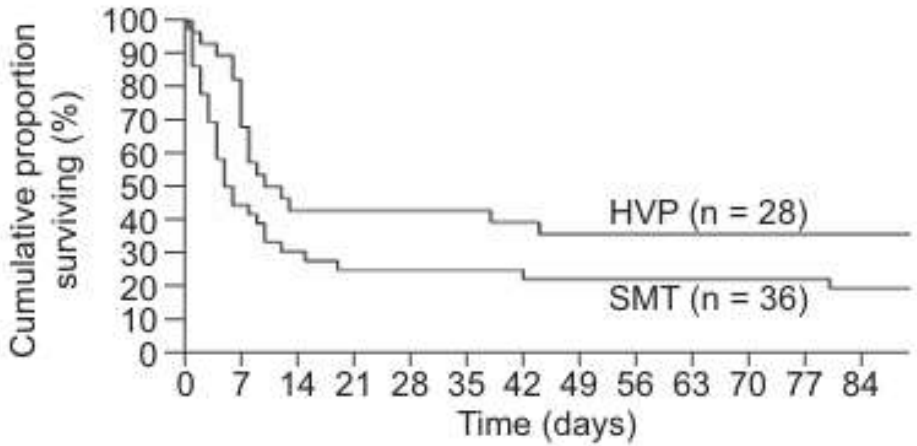


Fig. 3. Survival data in patients fulfilling transplant criteria that received standard medical treated (SMT) only, compared to the SMT treated group that also received high-volume plasma exchange (HVP) (Cox: $p = 0.03$).

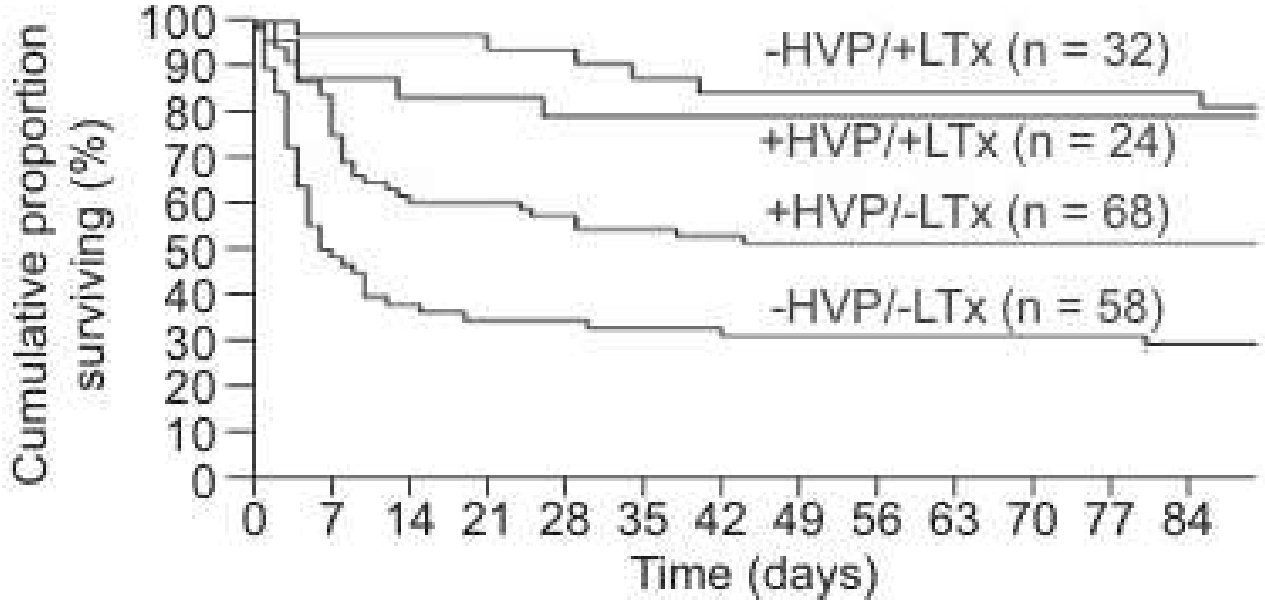


Fig. 2. Survival in the groups, in the two groups receiving SMT (standard medical treated group) with and without emergency transplantation (−HVP +LTx *vs.* +HVP−LTx) and the two group receiving SMT with and without emergency transplantation (−HVP−LTx *vs.* +HVP−LTx) (LogRank: $p = 0.0058$) and Cox proportional hazard: LTx: $p < 0.0001$; HVP: $p = 0.0076$).

Cerebral edema is of crucial concern in patients with hyperacute ALF and is an essential component of the syndrome.[1] A synergistic effect of systemic inflammation on raised intracranial hypertension is documented.[6,7] In an awe-inspiring multicentric study from Europe, high-volume plasma exchange (HVPE) was shown to improve ALF patients' survival.[8] However, the volume of exchange was chosen arbitrarily by the authors for this study. The clearance by PE is inversely related to exchange-volume with higher volumes associated with decreased efficiency, higher chances of transfusion-associated complications, including volume overload, which may worsen cerebral edema.[9] We conducted a randomized controlled trial (RCT) to evaluate the impact of standard-volume PE (SVPE) on 21-day transplant-free survival in ALF patients having cerebral edema with nonacetaminophen etiologies. The secondary endpoints were to assess the effect of SVPE in improving SIRS, hemodynamics, Sequential Organ Failure Assessment (SOFA) scores, duration of mechanical ventilation, and intensive care unit (ICU) stay. We also aimed to investigate the mechanistic basis of SVPE therapy as compared with SMT in a subset of ALF patients.

Standard-Volume Plasma Exchange Improves Outcomes in Patients With Acute Liver Failure: A Randomized Controlled Trial

Rakhi Maiwall,* Meenu Bajpai,‡ Akanksha Singh,* Tanvi Agarwal,§ Guresh Kumar,‖ Ankit Bharadwaj,‖ Nidhi Nautiyal,§ Harsh Tevethia,* Rakesh Kumar Jagdish,* Rajan Vijayaraghavan,* Ashok Choudhury,* Rajendra Prasad Mathur,¶ Ashini Hidam,§ Nirupama Trehan Pati,§ Manoj Kumar Sharma,* Anupam Kumar,§ and Shiv Kumar Sarin*

ometim

A prospective open-label RCT was conducted at the Institute of Liver and Biliary Sciences, New Delhi, from January 2016 to September 2018. The study protocol was registered with ClinicalTrials.gov (NCT02718079). All authors had access to the study data and reviewed and approved the final manuscript.

Participants. All patients with confirmed ALF[1] and cerebral edema on computed tomography imaging admitted to the liver ICU (L-ICU) were screened and enrolled. Details of inclusion and exclusion criteria in the Supplementary Appendix.

Randomization and Masking. Randomization was performed by the clinical trial coordinator using block-randomization method (block size of 8 with 5 blocks). Allocation concealment was performed by the SNOSE (sequentially numbered opaque sealed envelopes) technique provided by the clinical trial coordinator.

Maiwall et al Clinical Gastroenterology and Hepatology Vol. 20, No. 4

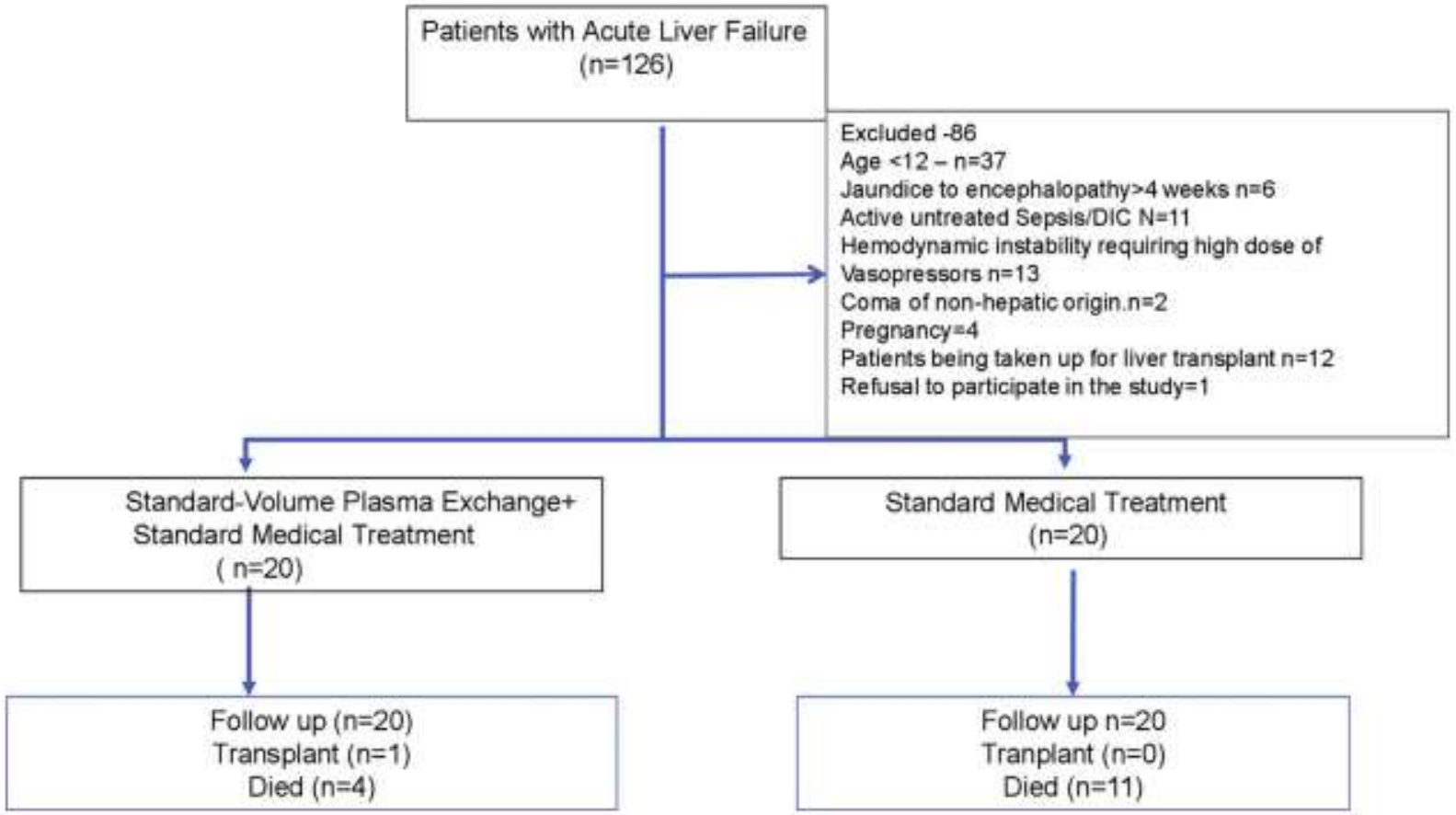
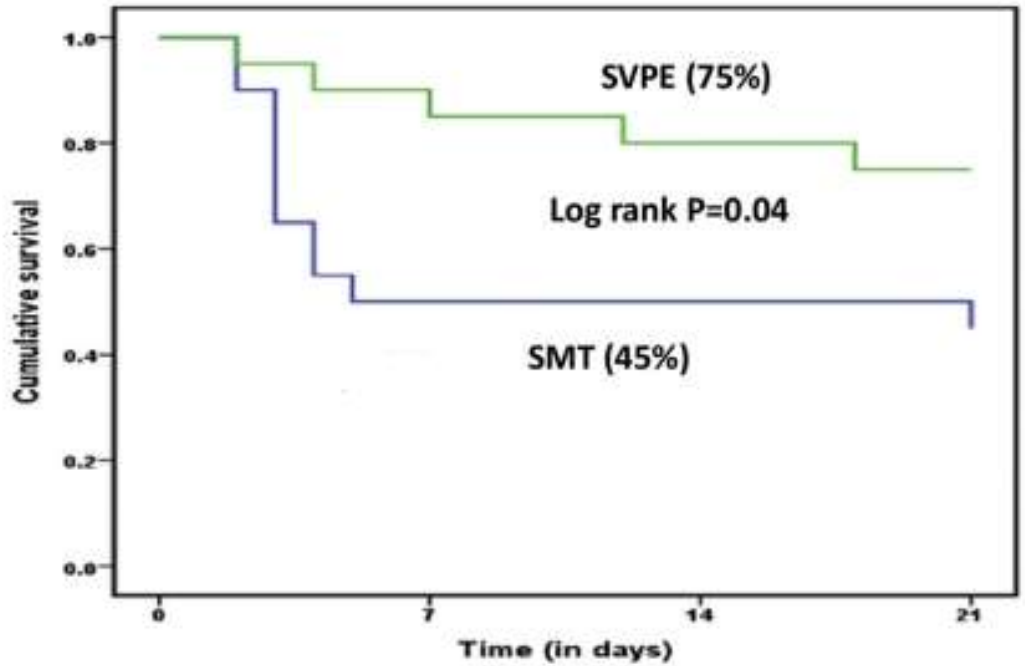


Figure 1. CONSORT diagram of the study cohort.

Maiwall et al Clinical Gastroenterology and Hepatology Vol. 20, No. 4

21-day transplant-free survival between standard-volume plasma-exchange and standard me



Days		0	7	14	21
SMT	At risk	20	10	10	9
	Died	0	10	10	11
SVPE	At risk	20	17	16	15
	Died	0	3	4	5

Background

The only randomized controlled trial, performed in Europe by Larsen et al, comprised 182 patients with acute liver failure (ALF) randomized to high-volume plasma exchange (HVPE) vs standard medical treatment and showed improved clinical outcomes with HVPE. Majority of patients included in this trial were due to acetaminophen etiology. A high-volume, filtration-based, fixed-protocol strategy of plasma exchange (3 sessions per patient) was performed.

Findings

Our study provides data on effectiveness of plasma exchange in nonacetaminophen etiology of ALF patients with cerebral edema. Standard-volume plasma exchange (SVPE) using centrifugation technique and response-guided strategy improved overall clinical outcomes. A reduction in the levels of proinflammatory cytokines, damage-associated molecular patterns and amelioration of systemic inflammatory response syndrome was observed with SVPE as compared with standard medical treatment. SVPE improved tissue microcirculation and systemic hemodynamics in ALF patients by clearing arterial lactate, restoring the balance between plasma ADAM metalloproteinase with thrombospondin type-1 motif member 13 and von Willebrand factor.

Implications for patient care

A lower-volume strategy of plasma exchange (SVPE) could effectively improve outcomes in patients with ALF by ameliorating systemic inflammation, improving microcirculation, and reducing cerebral edema. SVPE could be routinely recommended for management of nonacetaminophen patients of ALF with cerebral edema.

…PLEX in pediatric ALF?

Is therapeutic high-volume plasmapheresis (HVP) beneficial in children with acute liver failure?

Twenty-two children with acute liver failure

Age 4 days – 17 years including 4 neonates

Body weight 2.5kg – 106kg

HVP with 1.5-2.0 times the patient's estimated plasma volume

Median of 2 cycles

FFP

HVP using fresh frozen plasma

Complications: Hypothermia, haemolysis, reduction in platelets

Three patients died, 7 survived with native liver and 12 following liver transplantation. Overall survival of 86%.

HVP in PALF…

- … was feasible and safe
- … led to haemodynamic stability
- … improved markers of liver failure
- … reduced inflammatory marker

Hilberath et al. Role of High-Volume Plasmapheresis in the Management of Paediatric Acute Liver Failure. J Pediatr Gastroenterol Nutr. (2024)

JPGN

…as they say in Ellīnikī Dīmokratía:

"οι πολλές γνώμες
βουλιάζουν το καράβι

"Too many opinions sink the
boat"

https://en.wikipedia.org/wiki/Flag_of_Greece

A bridge too far…?

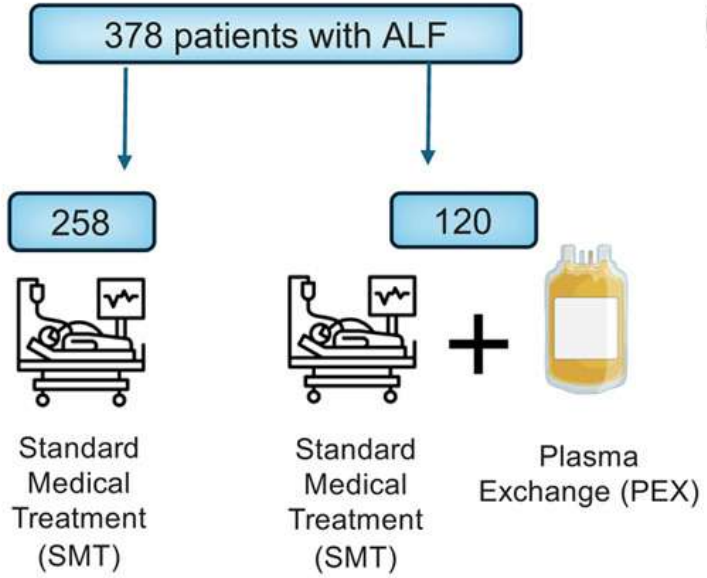
https://www.rottentomatoes.com/m/bridge_too_far

Plasma exchange does not improve overall survival in patients with acute liver failure in a real world cohort

Study design

All UK liver transplant centres (n = 7) between June 2013 and December 2021

Patients admitted to ICU with Acute liver failure (ALF) from all aetiologies



Outcomes

68.7% of patients with ALF survived to hospital discharge (44.7% transplant-free survival)

Heterogeneity between centres in use and indication for starting PEX

Predictors of receiving PEX :

- Paracetamol aetiology
- Increasing age
- Fulfilling Kings College criteria
- Receiving higher doses of noradrenaline

Significant improvement in haemodynamic parameters following PEX: median noradrenaline dose 0.35 µg/kg/min (0.19-0.70 µg/kg/min) to 0.16 µg/kg/min (0.08-0.49) (p = 0.001)

Propensity score matching:

No difference between PEX and SMT groups in :

- Overall survival (51.4 % and 62.6 % respectively, p = 0.12)

or

- Transplant-free survival (42.6 % and 53.1 %, p = 0.24)

Conclusions

PEX was associated with a significant improvement in haemodynamic parameters but no survival benefit demonstrated.

A further prospective study is needed to guide and define the future application and indications for PEX in patients with ALF.

DOI: 10.1016/j.jhep.2024.09.034

Posttransplantation period…PLEX to the rescue

TRANSPLANTATION, LIVER

Incidence: rare

Indication	Procedure	Category	Grade
Desensitization, ABOi LDLT	TPE	I	1C
Desensitization, ABOi DDLT*/AMR**	TPE	III	2C
AMR/Immune suppression withdrawal	ECP	III	2B
Desensitization, ABOi	ECP	III	2C

# reported patients: >300	Procedure	RCT	CT	CS	CR
Desensitization, ABOi LDLT	TPE	0	0	>10 (>200)	NA
Desensitization, ABOi DDLT/AMR	TPE	0	0	12 (116)	NA
AMR/Immune suppression withdrawal	ECP	0	3 (457)	NA	NA
Desensitization: ABOi	ECP	0	2 (31)	0	0

ABOi = ABO-incompatible; LDLT = living donor liver transplant; DDLT = deceased donor liver transplant; AMR = antibody mediated rejection; *TPE based desensitization is not indicated in the setting of group A-subtype (e.g., A_2) into group O DDLT; **includes ABOi and donor-specific antibody (DSA) directed against human leukocyte antigen (HLA).

Volume treated: TPE: 1-1.5 TPV; ECP: varies

Replacement fluid: TPE: albumin, plasma; ECP: NA

Frequency: TPE: daily or every other day. ECP: one cycle weekly or every 2-8 weeks for several months

J Clin Apher. 2023 Apr;38(2):77-278. doi: 10.1002/jca.22043.

1970. , male

- Sudden onset icterus (1 week); last 3 days swelling of the abdomen
- Last three months feeling unwell, earlier alcohol abuse
- Hepatic involvement first noticed - 12/2024
- 7/2025. – ALT 159, AST 188, GGT 462, viral serology ok
- Hypertension; Th: Valsartan/HCT 80/12,5mg, alcohol weekly

- 3.11.2025. - GE dept. – ICU
- ALT – 92 – 44
- AST – 238 – 149
- GGT - 915 – 259
- Bilirubin – 327 – 499
- PT - 73% - 40%

oliguria, elevated creatinine
terlipresin - good response
urinary tract infection
Rota virus, C. diff.
encephalopathy

- ALF / ACLF (biopsy not possible)??
- HRS - AKI
- 4.11. - ACLF grade 2, CLIF-C ACLF 50, MELD- Na 37, CTP C11
- 12.11. - ACLF gr 2, CLIF-C ACLF score 53, MELD-Na 38, CTP C12
- 1 month mortality 34%

- Corticosteroid therapy not advised
- Liver Tx not possible – no abstinence period

5 HV-TPE

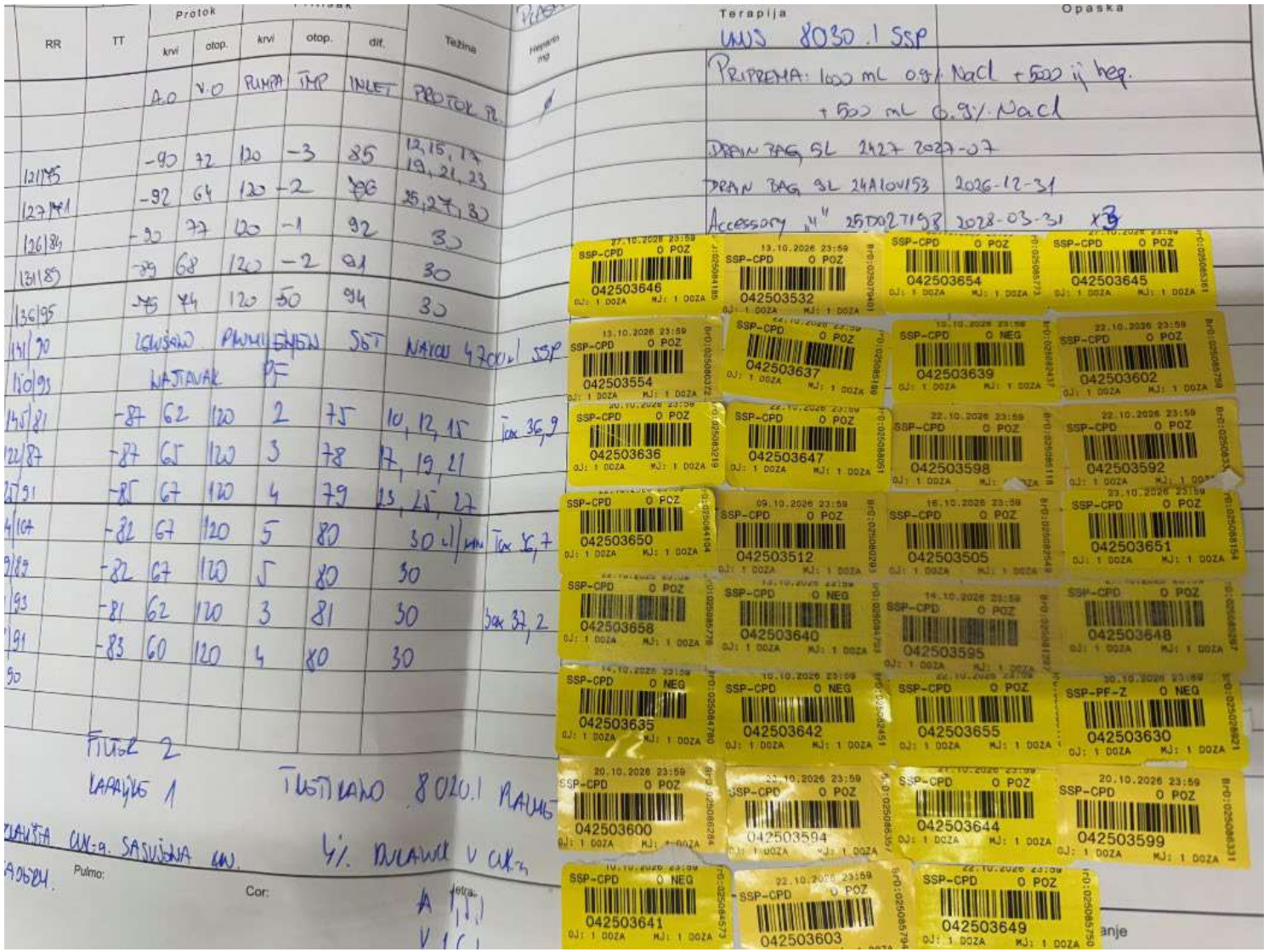
8000ml of FFP

No anticoagulans

Blod flow 120ml/min

2 sets

No adverse events



- HC – Pseudomonas aerug.
- UC – K pneumoniae OXA, E. coli ESBL

- 25.11.2025.
- Bilirubin 136,8 umol/L – stabile over 4 days
- AST 153 U/L, ALT 36 U/L, GGT 96 U/L, PT

- What comes next?

If PLEX is too PERPLEXING….

ELSEVIER

Selective Bilirubin Removal by Plasma Treatment With Plasorba BR-350 for Early Cholestatic Graft Dysfunction

G.L. Adani, D. Lorenzin, G. Currò, M. Sainz-Barriga, C. Comuzzi, V. Bresadola, C. Avellini, and U. Baccarani

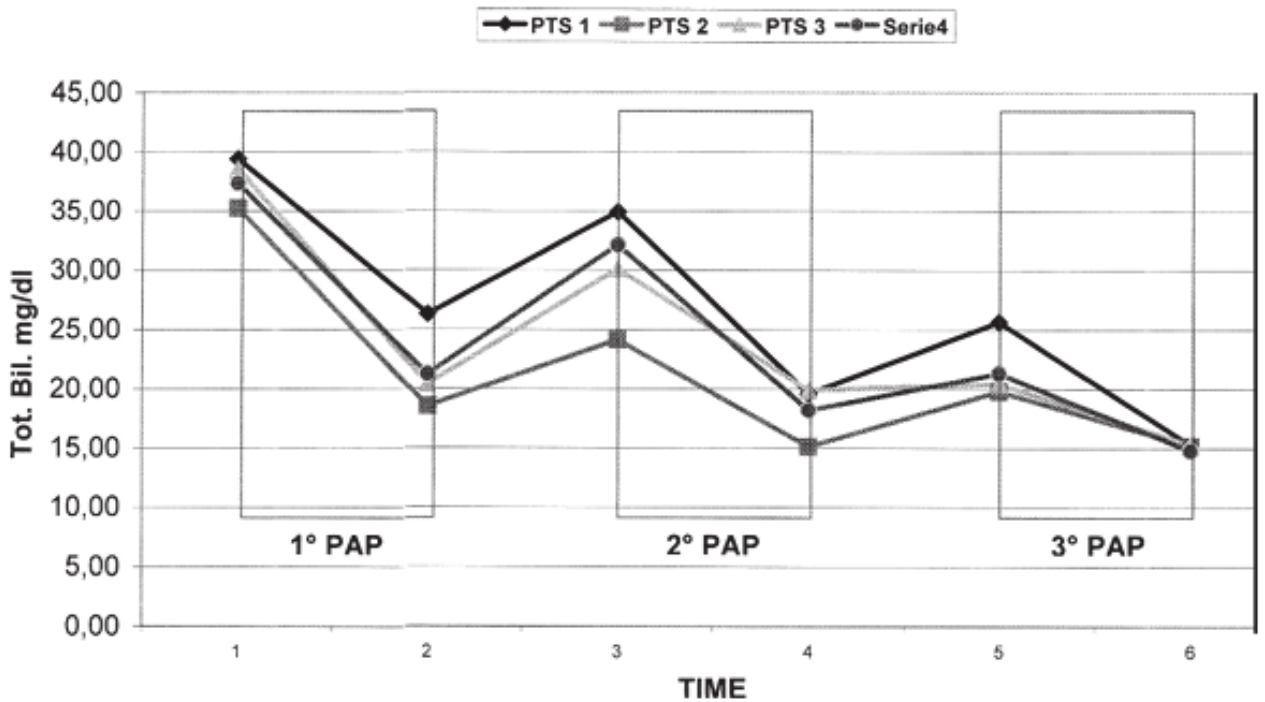
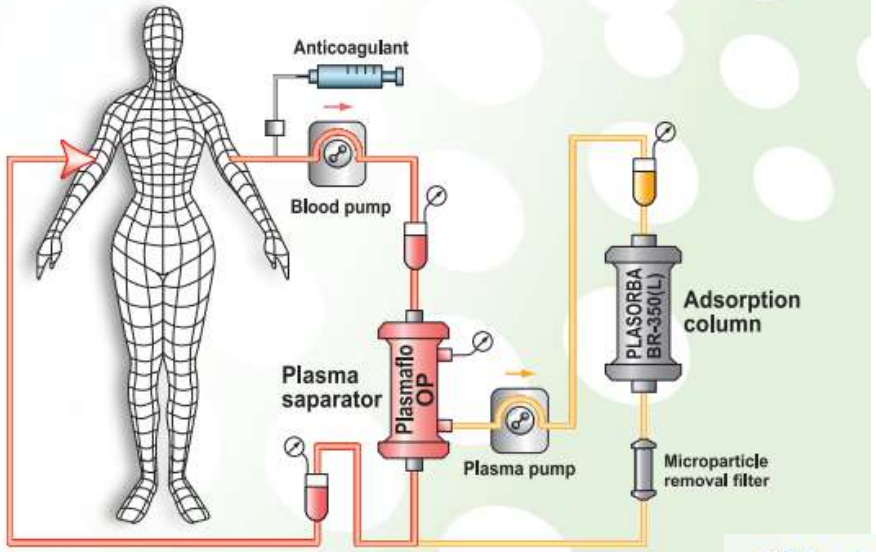


Fig 1. Total bilirubin level during PAP with Plasorba BR-350.

Transplantation Proceedings, 39, 1904–1906 (2007

Circuit Diagram

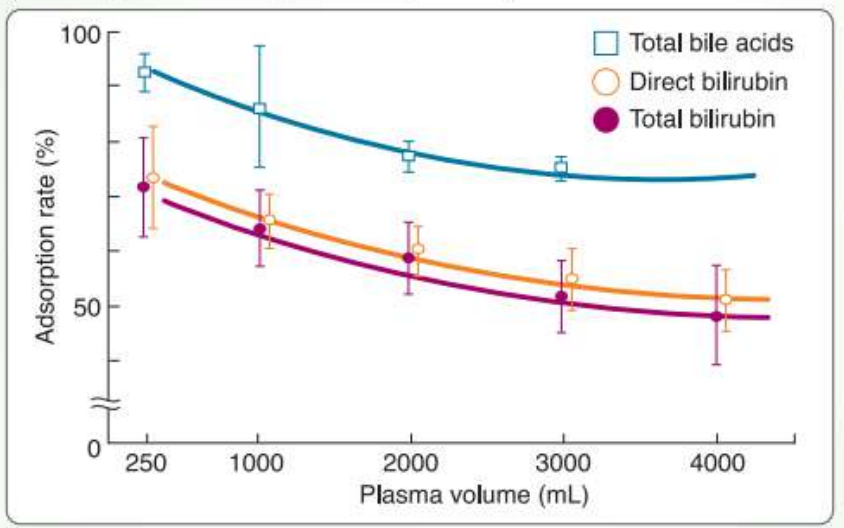


3 patients in Dubrava University Hospital

TPE / adsorption ???

Clinical Course

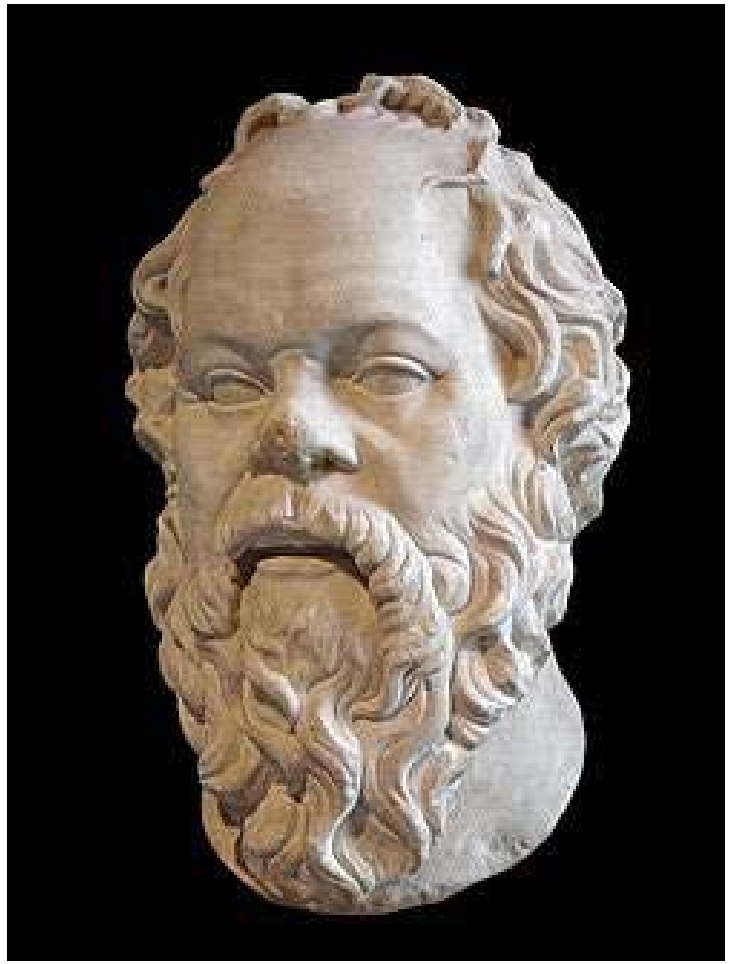
Changes of adsorption rate *(in vivo)*



Patients : n=6
Total treatments : 29 times

First Department of Surgery. Okayama University, Japan

"Education is the kindling of a flame, not the filling of a vessel"



Socrates (c470 – 399 BC)

Thank you!

durlenivan@gmail.com