The Liver Transplant Symposium 2023

AIG HOSPITALS

Organ support strategies for ACLF: PLEX is the way to go

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24.9.23

Outline

- Differences in ACLF definitions
- Why we need bridging therapies
- Mechanism of ACLF
- How PLEX works
- Impact of EASL vs. APASL definition on PLEX related outcomes
- Impact of etiology on PLEX related outcomes
- Impact of PLEX on post-LT outcomes
- PLEX and history
- Recommendations/guidelines
- Summary

Differences in ACLF definition exist but all imply high short-term mortality

	EASL-CLIF	APASL	NACSELD
Definition	Acute decompensation presenting with extrahepatic organ failure in a patient with cirrhosis.	Jaundice (>5 mg/dl) and coagulopathy (INR>1.5) followed by ascites and/or hepatic encephalopathy within 4 weeks in a patient with known or unknown liver disease	Often infection related extrahepatic organ failure in a patient with cirrhosis.
Liver involvement	Not required (bilirubin >12 mg/dl is considered as organ failure)	Bilirubin > 5mg/dl is must	Not required
Coagulopathy	Not required (INR >2.5 is considered as organ failure)	INR >1.5 is must	Not required
Renal involvement	Must (serum creatinine should be >1.5 mg/dl to identify ACLF and > 2 to define organ failure)	Not required	Renal replacement therapy required
Infection	Most often is a precipitant	Can be a precipitant but usually considered as a consequence	Most often is a precipitant
Reversibility	Unlikely	Possible	Unlikely
Data on liver transplantation	Robust	Few studies	Few studies
Severity scores to predict transplant free-survival	CLIF-C ACLF; CLIF-C OF	AARC	-
Validation of TAM score to predict post-LT outcomes	Yes	No	No
TIPS for variceal bleed	Possible	Not applicable. (Variceal bleed is not considered as a precipitant unless the bleed leads to rise in bilirubin and INR.)	Possible

Kulkarni et al. Clinics in Liv Dis. 2023

Definitions are in continuum

APASL

Requires bilirubin > 5mg/dl and INR >1.5 followed by ascites &/or HE within 4 weeks

Broader definition.

Reversibility possible.

Can include relatively stable patients who may not have high mortality.

EASL

Requires creatinine >1.5 mg/dl with organ failure

Usually ICU patients

Can aid in early prioritization for LT

Reversibility less likely

High mortality

Can miss outpatients with ACLF

NACSELD

Requires >1 extrahepatic organ failure

Applicable for ICU patients

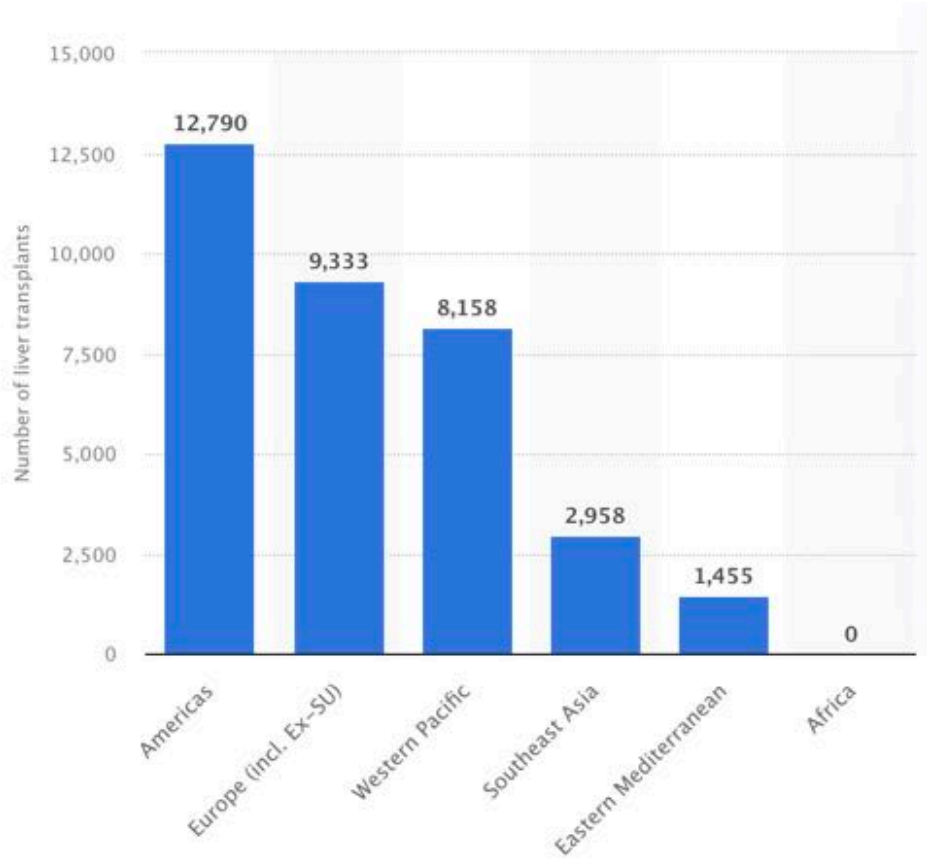
Reversibility not possible

Very high mortality

Can miss outpatients with ACLF

Increasing severity of disease

Why we need bridging therapies?



Source: https://www.statista.com/statistics/398685/liver-transplants-by-world-region/

- The Asia-Pacific region is home to more than half of the global population and accounts for 62·6% of global deaths due to liver diseases.
- 54·3% of global deaths due to cirrhosis and 72·7% of global deaths due to HCC

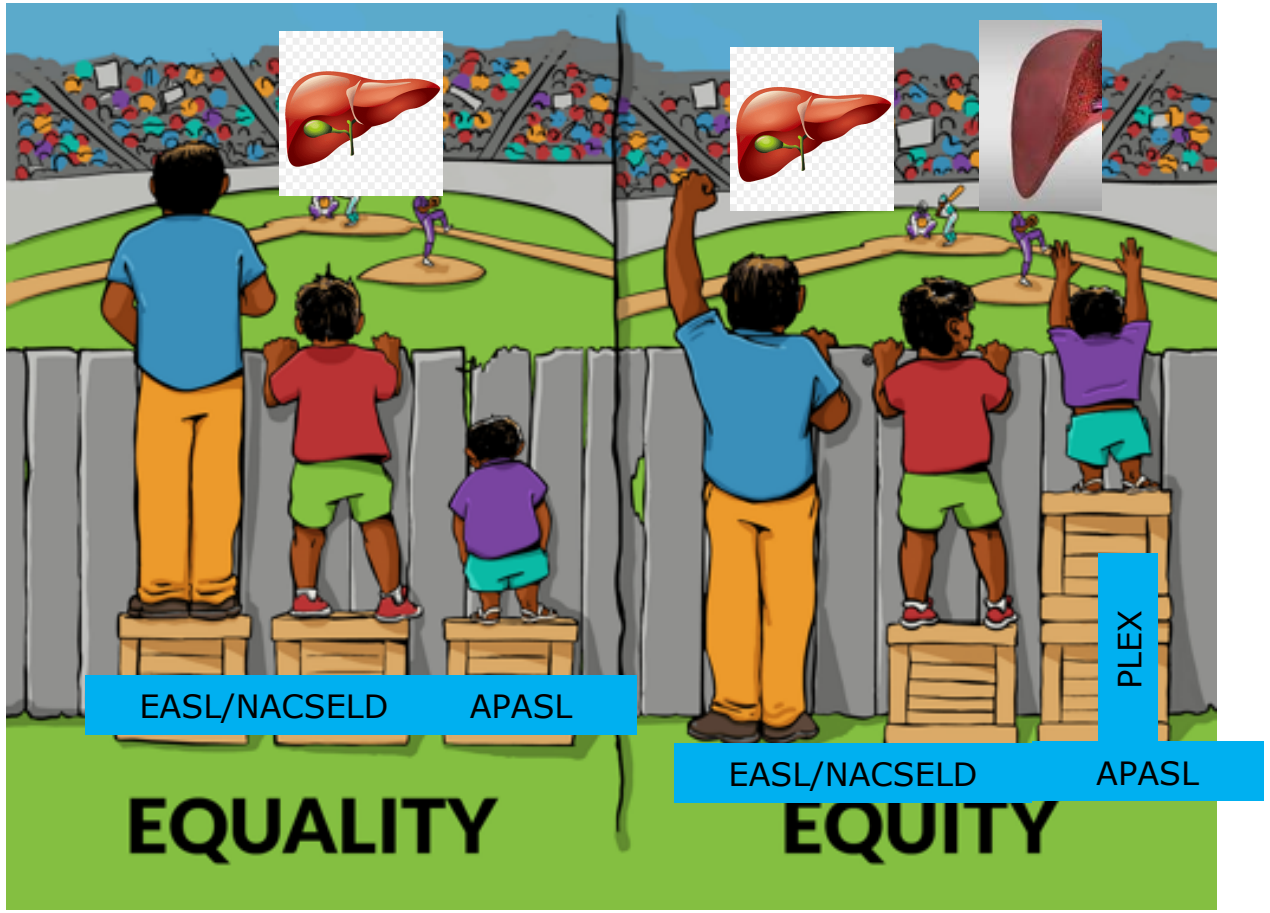
Why we need bridging therapies?

We need measures to

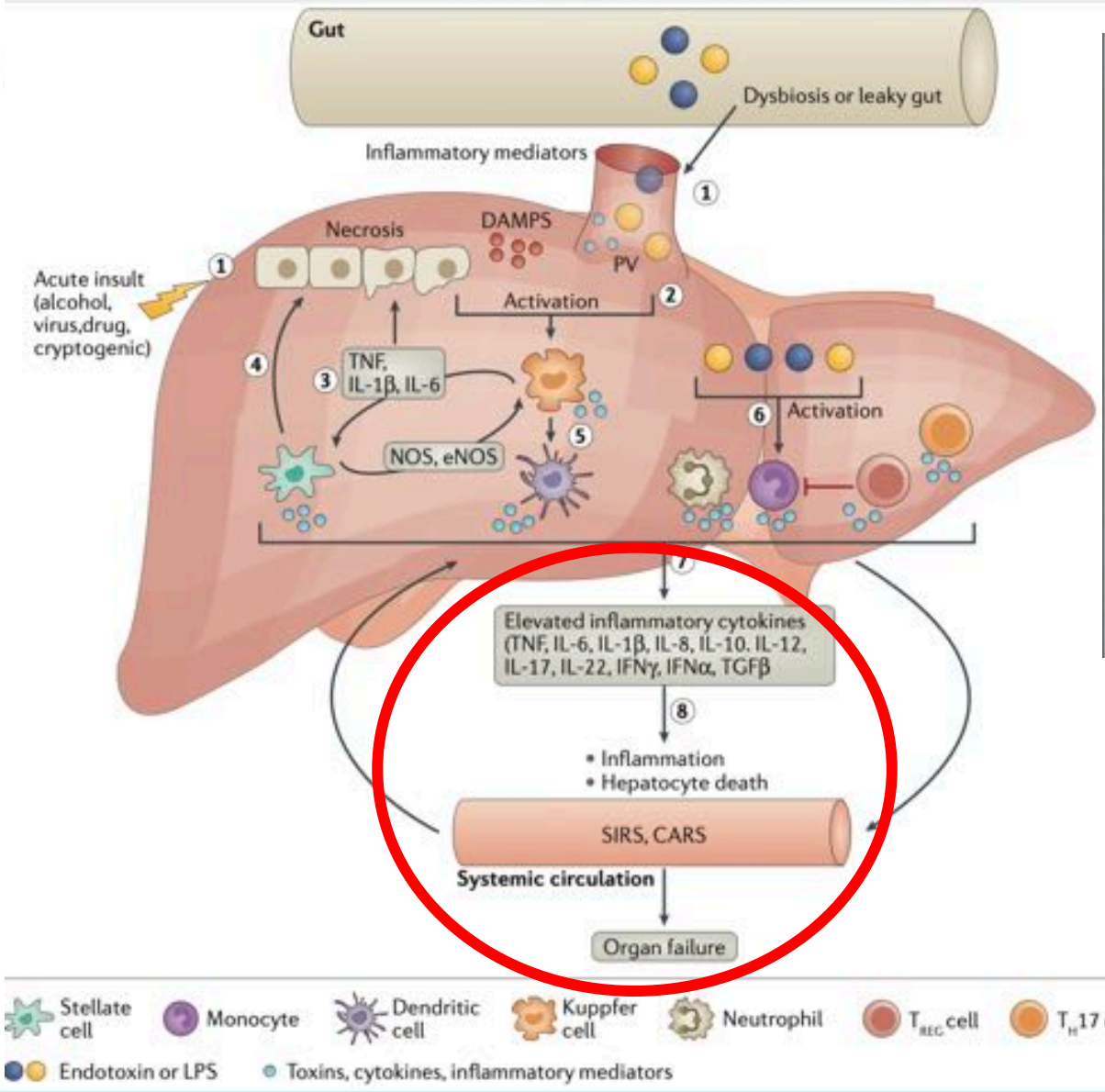
- Stabilize
- Buy time
- Time to counselling

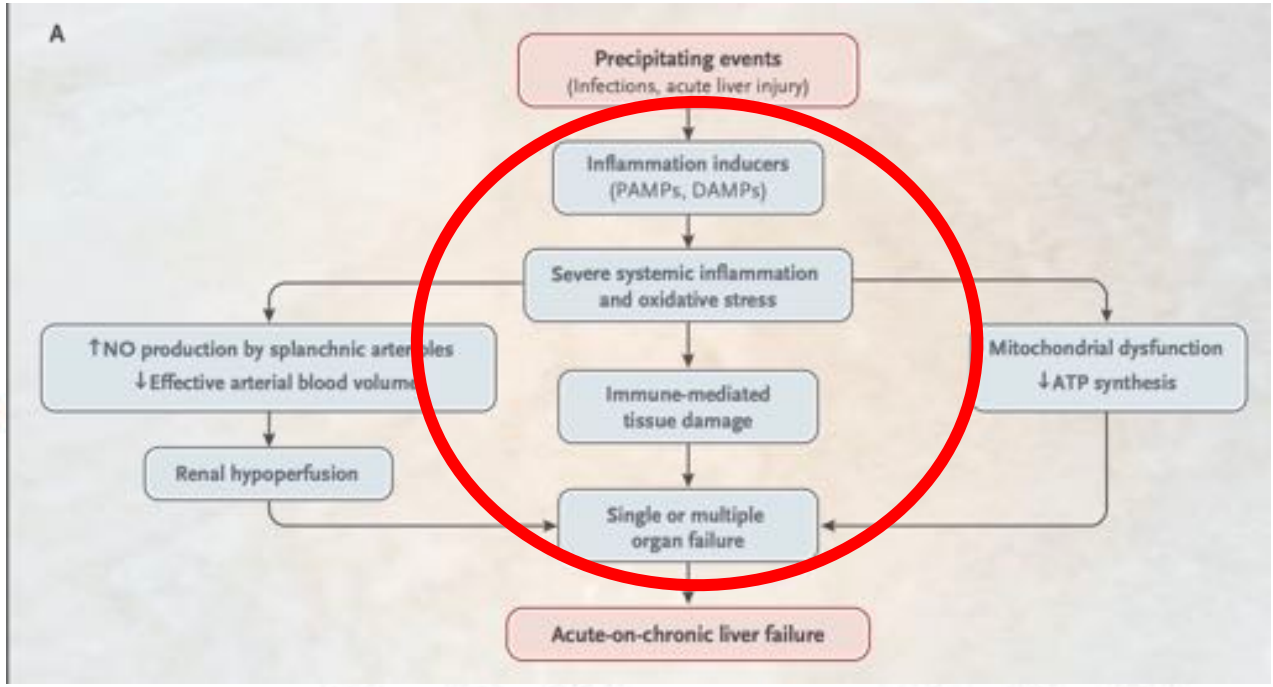
Such measures should be

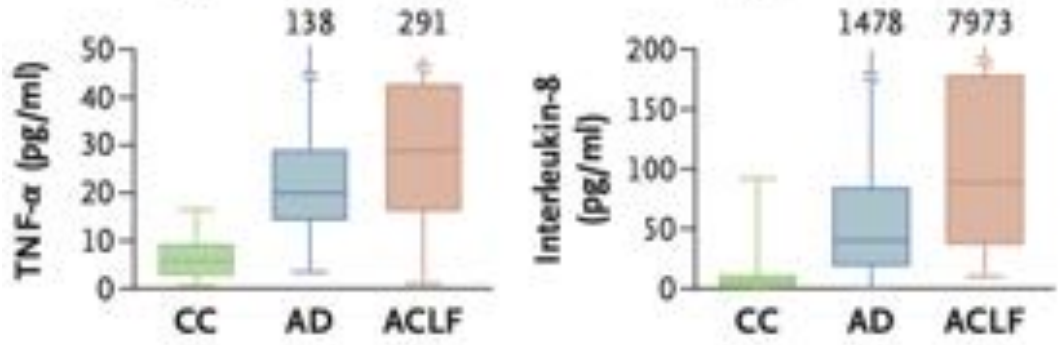
- Cost-effective
- Widely available



Common mechanisms!







Sarin SK. Nature Reviews. 2016

Arroyo V. NEJM. 2020

Thrombo-inflammation, ACLF and OF

> Indian J Gastroenterol. 2016 Nov;35(6):432-440. doi: 10.1007/s12664-016-0708-2. Epub 2016 Nov 8.

Plasma von Willebrand factor levels predict in-hospital survival in patients with acute-on-chronic liver failure

K S Prasanna [1], Ashish Goel [1], G Jayakumar Amirtharaj [2], Anup Rama

vWF levels predicts mortality in ACLF
vWF correlates with OFs (grade of ACLF)

Liver International / Early View

ORIGINAL ARTICLE | Open Access

Von Willebrand factor is an independent predictor of short-term mortality in acutely ill patients with cirrhosis

Bente P. van den Boom, Marilena Stamouli, Jennifer Timon, William Bernal, Annabel Blasi, Jelle Adelmeijer, Javier Fernandez, Ton Lisman, Vishal C. Patel

Ratio of von Willebrand factor antigen to ADAMTS13 activity is a useful biomarker for acute-on-chronic liver failure development and prognosis in patients with liver cirrhosis

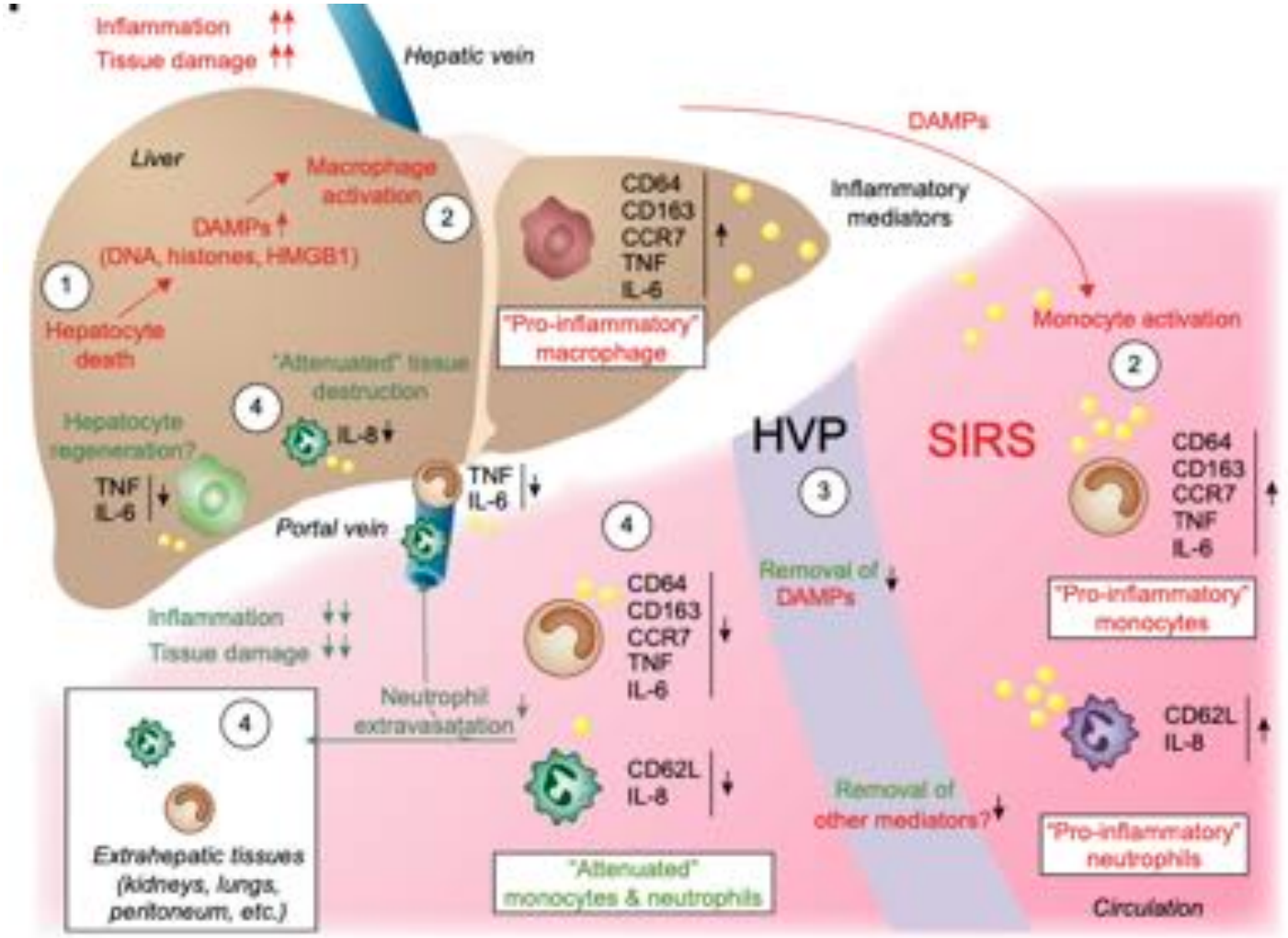
Masahide Enomoto, Hiroaki Takaya, Tadashi Namisaki, Yukihisa Fujinaga, Norihisa Nishimura, Yasuhiko Sawada, Kosuke Kaji, Hideto Kawaratani, Kei Moriya, Takemi Akahane ... See all authors

PLEX and cytokines in ACLF

	Baseline	Post TPE	
	Mean(±SE)	*Mean(±SE)*	*P-value*
Cytokines(pg/ml)			
Pro-inflammatory			
IFN-A2	47.82 (±11.55)	16.56(±2.12)	**.01**
IFN-G	21.90(±7.78)	7.22(±1.26)	**.03**
IL-12	8.02(±2.44)	2.67 (±0.71)	.12
IL-15	10.22(±2.96)	4.40(±1.89)	.17
IL-17	7.06(±2.76)	1.99(±0.35)	**.03**
MCP-3	12.94(±2.99)	9.11(±2.59)	.29
IL-1B	1.71(±0.08)	0.81(±0.11)	**.01**
IL-6	192.77(±23.66)	52.12(±18.19)	**.01**
MCP-1	315.69(±100.68)	183.83(±27.00)	.17
MIP-1A	15.77(±3.56)	8.13(±2.08)	.12
MIP-1B	53.12(±5.64)	35.86(±6.86)	.08
TNF-A	59.98(±16.63)	35.42(±15.59)	.17
TNF-B	2.01(±0.98)	1.11(±0.57)	.29
IL-8	89.92(±8.00)	68.41(±9.73)	.17
RNTS	1060.90(±277.24)	604.97(±216.84)	.17
IP-10	2741.18(±578.23)	1868.22(±389.24)	.17
ETXN	74.35(±9.37)	59.58(±7.85)	.17
Anti-Inflammatory			
IL-2	2.18(±1.11)	0.95(±0.38)	.35
IL-4	39.10(±8.68)	27.47(±10.63)	.17
IL-5	1.54(±0.30)	0.51(±0.12)	**.01**
IL-10	37.47(±6.31)	30.14(±5.30)	.46
IL-1RA	55.11(±5.90)	144.27(±19.01)	**.01**
IL-7	104.13(±79.83)	35.71(±19.49)	.17
Growth factors			
EGF	24.26(±6.80)	12.61(±2.55)	.17
FGF-2	149.02(±11.88)	67.19(±3.14)	**.01**
TGF A	3.95(±0.41)	2.18(±0.34)	**.01**
G-CSF	39.26(±3.28)	15.56(±1.76)	**.01**
GM-CSF	31.95(±10.13)	21.50(±4.81)	.35
PDGF	5819.82(±1063.96)	2253.16(±127.16)	**.02**
DAMPS (ng/ml)			
HMGB1	110.26(±2.93)	69.47(±9.69)	**.01**
Endotoxin(pg/ml)			
endotoxin	33.91(±1.25)	28.54(±0.39)	**.01**

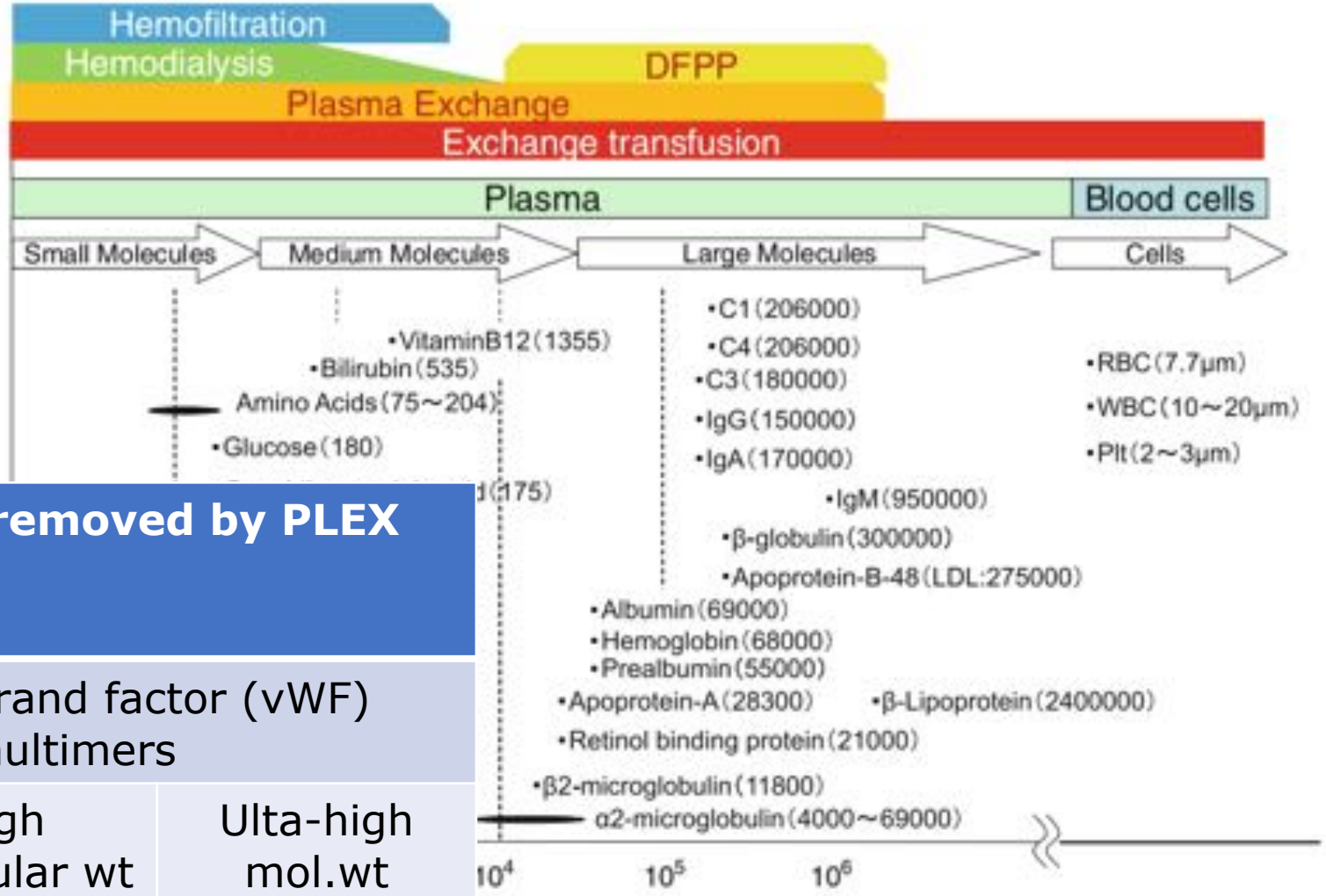
Maiwall et al. Liv Int. 2021

Removal of DAMPs and inflammatory cytokines by PLEX



Larsen et al. JHEP. 2016

How PLEX works?



Molecules removed by Dialysis	Molecules removed by PLEX		
< 60 kD	Von Willebrand factor (vWF) multimers		
	Dimers	High molecular wt	Ulta-high mol.wt
	500 kD	5000-10,000 kD	> 20,000kD

EASL-CLIF

Author. Year, type of study	N	Etiology	Outcomes
Swaroop et al. 2022. Single center retrospective	38 matched pairs	Mixed	30 days mortality: 21% vs 50% in SMT, P = 0.008; 90 day mortality:36.8% vs P = 0.166
Chen et al. 2021. Multicenter. Prospectiv cohort study			l at: 69.50 vs. , p = 0.006 48.70 vs. 40.70%, p = 1-year, 42.20 vs. 31.30%, p = 0.014
Stahl et al. 2020. Single center retrospective study	31 matched pairs	Mixed	Death at 5 days: 33.3% vs. 66.7% in SMT (P=0.04). Reduction in OF and CLIF-C score Similar proportion bridged to LT

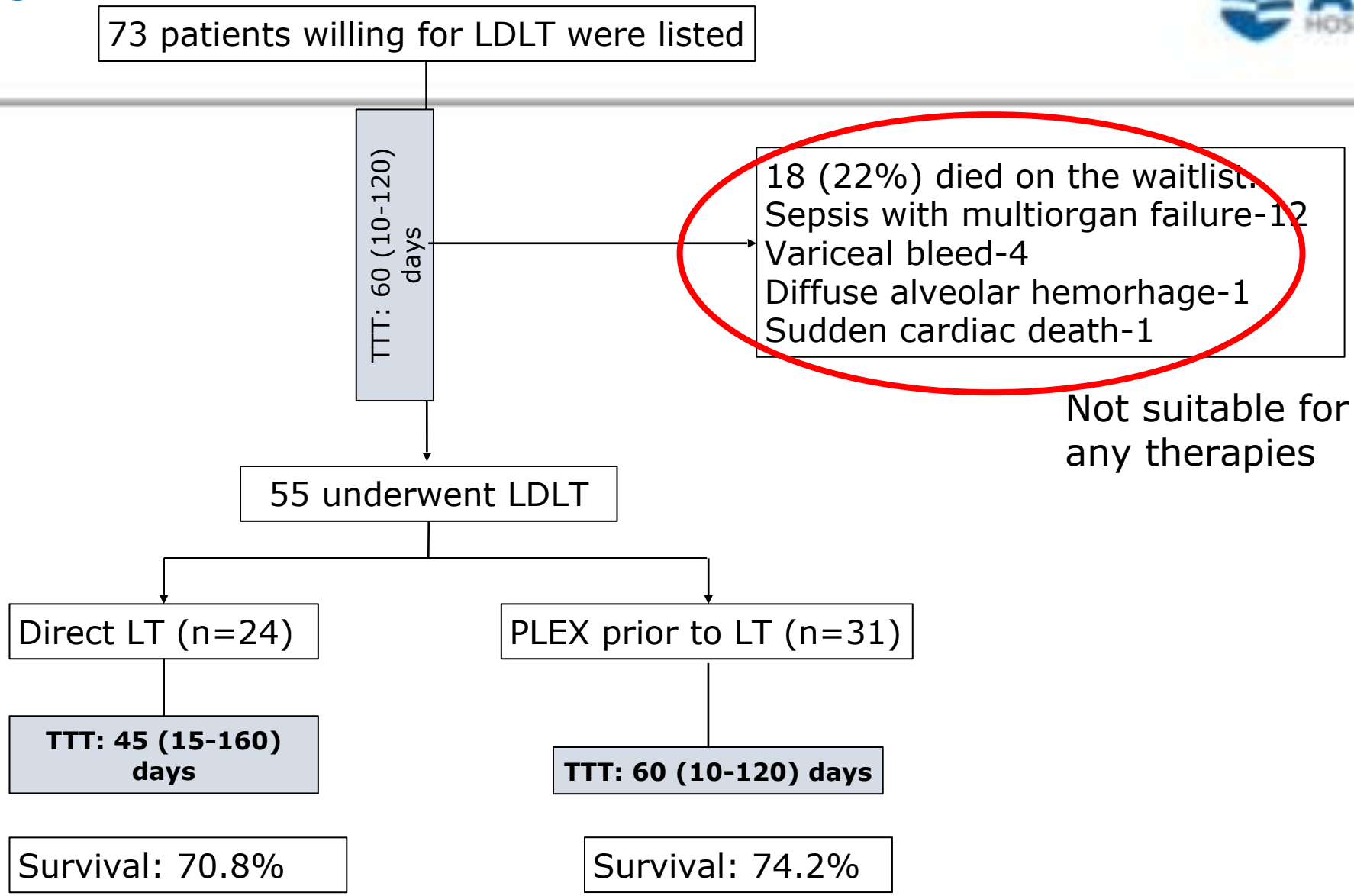
PLEX IS ASSOCIATED WITH
✓ REDUCTION IN ORGAN FAILURE
✓ REDUCTION IN CLIF-C SCORE
✓ IMPROVED SURVIVAL (SHORT TERM)

APASL

Authors	N	Etiology	Outcomes
Kumar et al. 2022 Retrospective	21 in PLEX vs. 29 SMT	All alcohol	60% renal/HE recovery Survival at 30 day: 66% vs. 16.6% Survival at 1 year: 20.3% vs. 11%
Maiwall et al. 2021 Retrospective data	119 in ALSS vs. 89 in SMT	Mostly alcohol	Higher resolution of SIRS (OR, 92.3 [3.42-24.8]) and delayed MOF (HR, 7.1 [4.5-11.1) Improved survival
Tang et al. 2020	2		Survival at 21,28 and 90 days: 72.5% vs. 60.3%, 68.3% vs. 57.4%, 55.9% vs. 48.5%, respectively, P < 0.05
Liu et al. 2020 Retrospective	78 in ALSS vs. 54 in SMT	All HBV	Mortality at 28 days: 23% vs. 48.2% At 90 days: 33.34% vs. 57.5% (P<0.05)
Fan et al. 2017. Retrospective	338 vs. 222 patients in SMT	All HBV	30 day mortality: 28.4% vs. 55.4%

PLEX IS ASSOCIATED WITH
✓ RENAL RECOVERY
✓ HE RESOLUTION IN UPTO 60%
✓ REDUCED ORGAN FAILURE AND
✓ IMPROVED SURVIVAL

Bridging to LT



Difference between SMT vs. PLEX

Variables	No PLEX (n=24)	PLEX (n=31)	P
AARC score at admission*	9 (7-11)	10 (8-12)	<0.001
AARC grade at admission (n,%) I II III	2 (8.3%) 20 (83.3%) 2 (8.3%)	0 22 (71%) 9 (29%)	
AARC score at LT*	8.5 (7-10)	9 (8-11)	<0.001
AARC grade at LT (n,%) I II III	3 (12.5%) 21 (87.5%) 0	0 27 (87.1%) 4 (12.9%)	0.03
Time from diagnosis to LT*	45 (15-60)	60 (10-120)	0.02
MELD NA at diagnosis*	31 (27-34)	32 (26-40)	0.04
MELD NA at LT*	28 (11-36)	28 (21-34)	0.77

SICKER PATIENTS WITH LIVER FAILURE CAN BE BRIDGED TO LT

Provide time to recovery

Post LT outcomes			
Variables	No PLEX (n=24)	PLEX (n=31)	P
	7%)	16 (51.6%)	0.26
	)	4 (13%)	0.21
Readmissions post-LT (n,%)	11 (45.8%)	8 (25.8%)	0.12
Infections post-LT (<3m) (n,%)	11 (45.8%)	14 (45.2%)	0.96
Infections post-LT (>3m) (n,%)	4 (16.7%)	3 (9.7%)	0.35
Survival post-LT (n,%)	17 (70.8%)	23 (74.2%)	0.78
Cost pre-LT	8,96,248.83±9,79,443.16	15,52,450±12,27,481.1	0.03

Kulkarni et al. Hep Int. 2023

Network meta-analysis

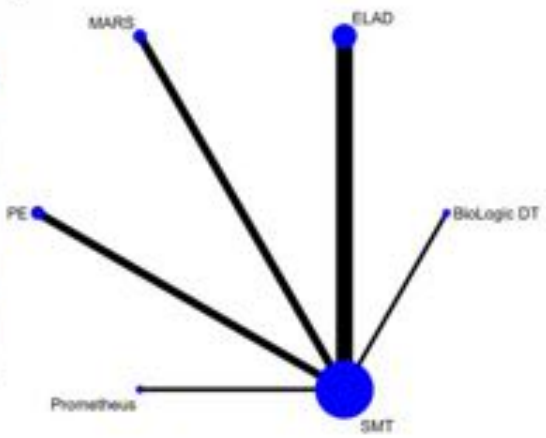
Plasma exchange demonstrated a statistically significant survival benefit compared to SMT in the analysis for 3-month OS (RR 0.74; CrI 0.60 to 0.94)

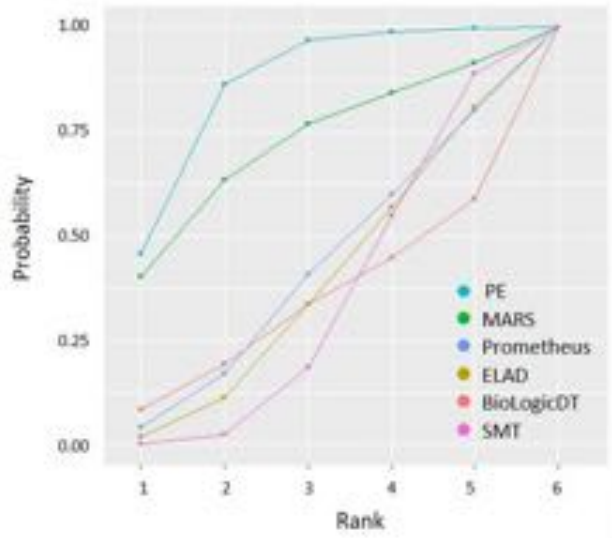
Treatment 1 / RR (95% CrI)	MARS	Prometheus	ELAD	BioLogicDT	SMT
PE	0.95 (0.53, 2.0)	0.81 (0.36, 1.5)	0.98 (0.63, 1.6)	0.95 (0.46, 1.9)	1.0 (0.55, 2.1)
MARS	0.76 (0.50, 1.2)	0.79 (0.37, 1.5)	0.93 (0.43, 1.9)	0.99 (0.76, 1.3)	**0.74 (0.60, 0.94)**
Prometheus	0.75 (0.53, 1.1)	0.78 (0.38, 1.4)	0.97 (0.68, 1.4)		
ELAD	0.72 (0.35, 1.4)	0.75 (0.28, 1.7)			
BioLogicDT					

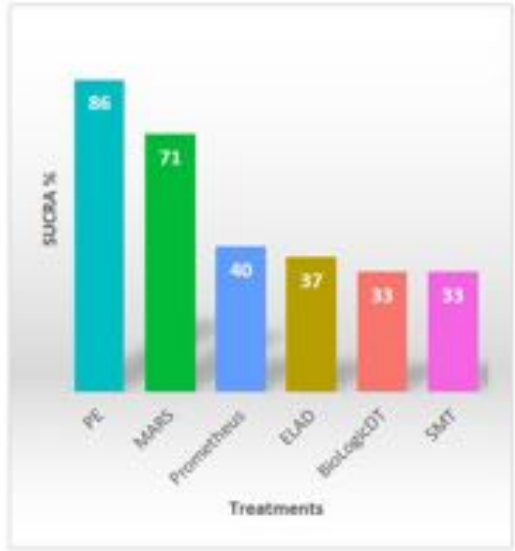
b

Study ID	Intervention(s)	Patients/group
Thompson (2018)	ELAD/SMT	96/107
Hillebrand (2010)	ELAD/SMT	14/4
Teperman (2012)	ELAD/SMT	25/28
Pyrsopoulos (2019)	ELAD/SMT	78/73
Qin (2014)	PE/SMT	104/130
Yu (2008)	PE/SMT	140/140
Ellis (1999)	BioLogicDT/SMT	5/5
Sen (2004)	MARS/SMT	9/9
Mitzner (2000)	MARS/SMT	8/5
Kribben (2012)	Prometheus/SMT	77/68

c







SR MA

- 20 studies
- 5705 patients – 2856 PE vs. 2849 in SMT
- **Patients in PE group had higher MELD scores than SMT group**
- Etiology: 12 studies only HBV; 2 only alcohol and 6 mixed etiology

Outcomes

- PE was associated with higher 30-day survival (61% vs. 45.5%, respectively; RR 1.36, 95% CI 1.22–1.52) **consistent across EASL/APASL**
- Better 90-day survival: (53.6% vs. 45.3%, respectively; RR 1.21, 95% CI 1.10–1.34)
- **HBV better survival** (RR 1.36, 95% CI 1.19–1.56).
- **Alcohol no effect on survival** (RR. 1.71, 95%CI, 0.54-5.35; P=0.36)
- 2.1% (122/5705) underwent LT.

Alcohol-associated hepatitis and PLEX

- 54 patients with SAH (not willing for LT)
- age-40.67 ± 8.04 years
- males-100%
- mDF score-119.75 ± 65.72
- MELD-32.08 ± 5.43
- Survival 76% and 57.4% at 1 and 3 months.

Adverse events- manageable

- Allergic reactions rash
- Hypotension
- Bleeding from access site
- Hypocalcemia
- Thrombocytopenia

PLEX is

Time tested

Annals of Internal Medicine

Article | 1 January 1968

Treatment of Hepatic Coma in Cirrhosis by Plasmapheresis and Plasma Infusion (Plasma Exchange)

STANLEY SABIN, M.D., JOHN A. MERRITT, M.D.

Author, Article, and Disclosure Information

https://doi.org/10.7326/0003-4819-68-1-1

PDF | Tools | Share

Abstract

Three patients with proved active fatty nutritional cirrhosis were treated with plasma exchange after at least 72 hr of refractory hepatic coma. In each case coma cleared after this treatment. The role of plasma exchange in hepatic coma is discussed.

1st PLEX-15 February 1913

Vadim Alexandrovich Yurevich (16/10/1872 to 26/02/1963)

Nikolay Konstantinovich Rosenberg (1/12/1876 to 24/11/1933)

"For the Question Regarding Washing of Blood Outside of the Body and the Vitality of Red Blood Cells".


Русскій Врачъ.

8509

Еженедѣльный журналъ,

посвященный всѣмъ отраслямъ клинической медицины, общественной и частной гигіенѣ и вопросамъ врачебнаго быта.

Органъ, основанный въ память В. А. МАНАССЕИНА.

Подъ редакціей д-ра С. В. ВЛАДИСЛАВЛЕВА.

ТОМЪ XIII.

ПЕТРОГРАДЪ
ИЗДАНІЕ О. А. РИКЕРЪ.
1914 г.

Infectious disease dept Russian Imperial Medical Surgical Academy located in Saint-Petersburg

Plasmapheresis

- **“Plasma Removal With Return of Corpuscles (Plasmapheresis)” coined by John Adel from Department of Pharmacology John Hopkins, USA in 1914**

Journal of Clinical Apheresis ASFA

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Guidelines on the Use of Therapeutic Apheresis in Clinical Practice – Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue

ASFA: More than 30 various indications

PLEX can be used as a first-line or second-line as a stand-alone treatment (or in conjunction with other modalities).

Indications for Liver disease as per ASFA

1. ALF (Category I)
2. Wilson Disease (Category I)
3. Erythropoietic protoporphyria, liver disease (category III)
4. Hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP Syndrome) (Category III)
5. Liver Transplantation: Desensitization (Category I)
6. Liver transplantation: Antibody-mediated rejection (Category III)

Asia Pacific (APASL) guidelines

Recommendations

7.3.1. Plasma exchange appears to be a promising and effective bridging therapy in patients with ACLF to liver transplant or spontaneous regeneration [1, C]

7.3.2. Plasma exchange can be safely undertaken in patients with ACLF in specialized liver units [2, B].

7.3.3. Plasmapheresis may be considered as a specific therapy for patients with Wilson's disease and patients with severe flare of autoimmune liver disease (deemed unsuitable for steroids) [2, B].

7.3.4. Combination of PE with therapies to potentiate liver regeneration should be evaluated in patients with ACLF [2, C].

Sarin et al., Hep Int. 2019

European (EASL) guidelines

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**).

WHY IS THIS CORRECT?
PLEX CAN CORRECT COAGULOPATHY/HYPERBILIRUBINEMIA-NOT NECESSARY FOR EASL DEFINITION
SEPSIS IS THE USUAL TRIGGER FOR ACLF WHICH IS A CONTRAINDICATION FOR PLEX

Moreau et al., JHEP. 2023

American guidelines

Summary of evidence: Improvement in short-term survival has been demonstrated using plasma exchange in patients with hepatitis B infection and ACLF. The APASL definition of ACLF was used in this study. Therefore, the results cannot be directly translated to patients in the west, and further studies are needed

Liver-assist devices

Key concept statements

1. Artificial liver support systems, with or without a biological component, theoretically can take over some of the functions of the liver, but whether they provide any clinical benefit is still unclear.
2. Plasma exchange has been shown to improve survival in patients with acute liver failure; however, its effect in ACLF is unknown.

WHY IS THIS CORRECT?
Contraindications for PLEX: allergy to FFP, anticoagulants, **hemodynamic instability and septicemia**
NACSELD DEFINED ACLF REQUIRES INFECTION TO BE THE TRIGGER AND MUST HAVE 2 OFs

SV vs. HV PLEX

We prefer SV PLEX

- SV low volume of plasma required
- Equal efficacy
- More safe
- Less cost
- Less time consuming

Summary

- PLEX can give a window of opportunity to survive and bridge to LT
- PLEX is time tested
- Easily available
- Economical (50k INR/850 SD)
- PLEX is the only way to go!

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Thank you

The Liver Transplant Symposium 2023

Basic concepts : Plasma Volume

- **55% of the total blood volume of the body**.
- 39 mL/kg of the body weight (M) and 40 mL/kg (F)

Total Blood volume = Weight x 70 Kg (M) / 65 kg (F)

Plasma volume : (1 – Hematocrit) x Total Blood volume

Red Cell Vol : TBV x Hematocrit

Eg : 60 kg dry body weight male with Hct 29

TBV = 60 x 70 = 4200 ml

Plasma Volume = 4200 x (1-0.29)
= 4200 x 0.71
= 2982 ml (round off : 3000ml)

Standard volume = 1 x plasma volume = 3000 ml

High volume = 1.5 x plasma volume = 4500 ml

1: 3 Albumin : FFP = 1000 ml albumin + 3500 ml FFP

1000 ml Albumin 20% = 2x(100 ml albumin + 400 ml NS)

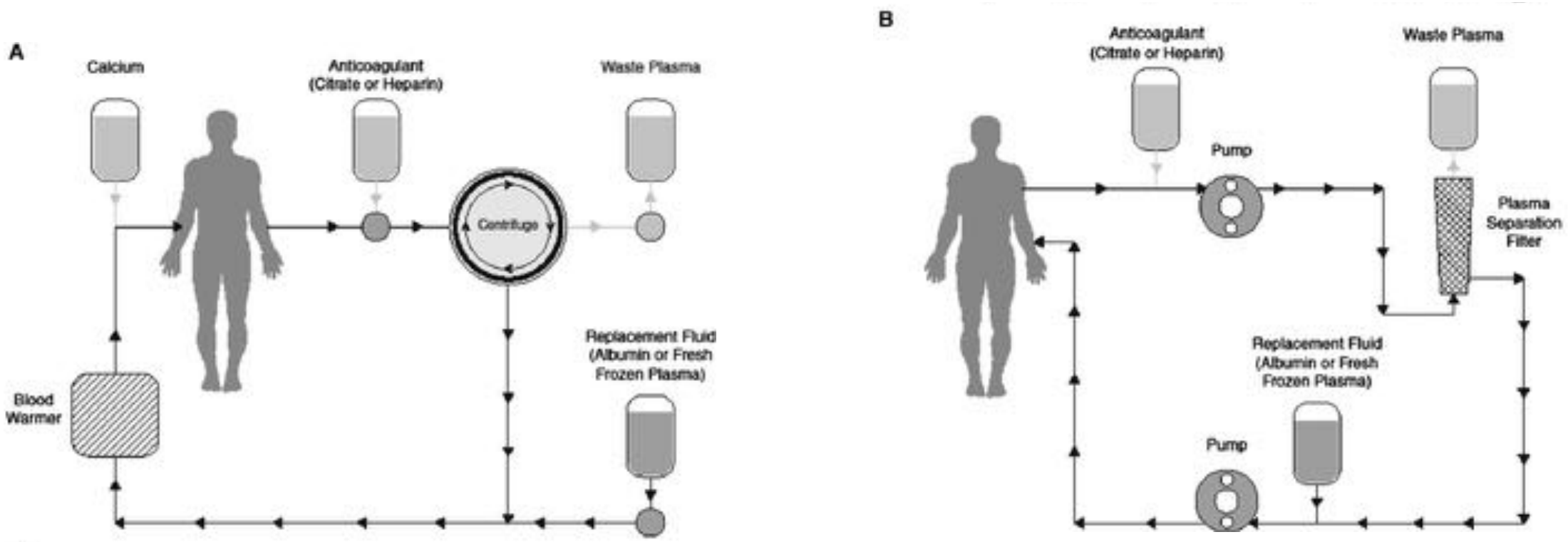
Types of PLEX

	Centrifugal PLEX	Membrane PLEX
Mechanism	Apheresis based on molecular density	Apheresis based on molecular size
Access	Two	One
Time	Less required	More time consuming
Methods	centrifugation separates incoming whole blood into plasma, red blood cell, and white blood cell components	blood plasma is separated from the cellular components using a filter that prevents the passage of cellular components and enables whole plasma removal.
Anticoagulant	Citrate– hypocalcemia	Heparin-thrombocytopenia
Machine	Blood bank based (COM.TEC/Spectra optia)	Dialysis machine (can do CRRT simultaneously)
Return of fluid	the remaining cell-rich blood is mixed with a replacement fluid (e.g., albumin or fresh frozen plasma) and returned to the patient to prevent hypovolaemia.	

Types of PLEX

	Centrifugal PLEX	Membrane PLEX
Plasma removal efficiency (measure of the fraction of plasma removed during TPE in relation to the amount of plasma processed)	70-93% with blood flow rate of 50-80 ml/min	27-53% (~35%) with blood flow rate of 82-150 ml/min
Time to exchange 1L plasma	25-33 minutes	36-38 min
Set up (priming time)	~10 minutes	30-40 min
Total procedure time	90-120 minutes	130-140 minutes
Circuit failure	Unusual	Common due to blood clotting and protein clumping
Adverse events	Less	More

CPLEX vs. MPLEX



Molecular Weight Substances