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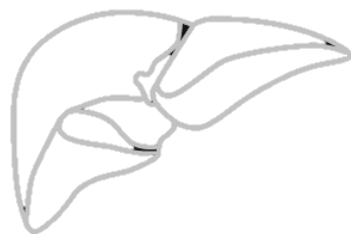
INTERNATIONAL CONGRESS

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JUNE 24-25 2024

PARIS JICP

16 RUE JEAN REY 75015



Blood Purification Techniques: Extracorporeal Blood Purification in Acute Liver Failure

Pr Antoine Monsel

Réanimation Chirurgicale Hépato-Digestive Polyvalente
Département d'Anesthésie Réanimation Pitié-Salpêtrière



AP-HP.Sorbonne Université



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JUNE 24-25 2024

PARIS JICP

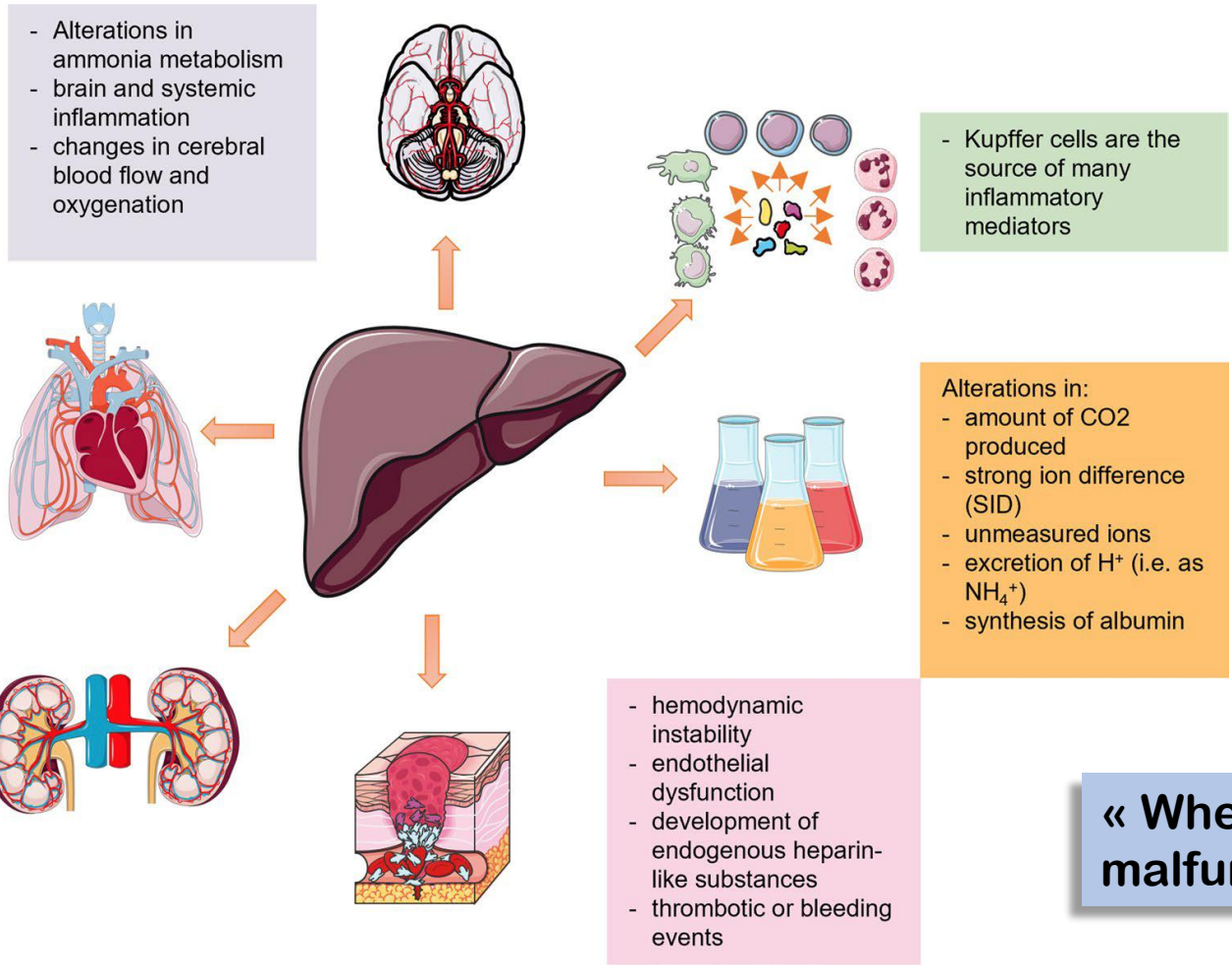
16 RUE JEAN REY 75015



Bénéficiaire ▲	Type de bénéficiaires ▲	Entreprise ▲	Date ▲	Nature ▲	Montant ▲	
MONSEL ANTOINE	Médecin	<u>GILEAD SCIENCES</u>	13/04/2016	REPAS	25 €	Détail
MONSEL ANTOINE	Médecin	<u>MSD France</u>	13/01/2016	INSCRIPTION	390 €	Détail
MONSEL ANTOINE	Médecin	<u>FRESENIUS KABI FRANCE</u>	24/01/2018	Inscription	630 €	Détail
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MONSEL ANTOINE	Médecin	<u>FRESENIUS KABI FRANCE</u>	19/07/2018	AUTRE: STAFF	12 €	Détail
MONSEL ANTOINE	Médecin	<u>AMOMED PHARMA</u>	15/11/2018	Repas	19 €	Détail
MONSEL ANTOINE	Médecin	<u>MSD France</u>	04/06/2018	28/06/2018 - 28/06/2018	Contrat d'expert scientifique, contrat dans le cadre d'une recherche, contrat de consultant	Détail
MONSEL ANTOINE	Médecin	<u>FRESENIUS KABI FRANCE</u>	18/12/2017	24/01/2018 - 26/01/2018	Inscription congrès	Détail
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MONSEL ANTOINE	Médecin	<u>MSD France</u>	13/01/2016	13/01/2016 -	Autre : CONVENTION D'HOSPITALITÉ	Détail

Why using Extracorporeal Liver Replacement/Support Therapy (ELS or LRT) ?

Toxic liver syndrome → refractory multiple organ failures → death within hours



« When the liver fails, all organs malfunction and fail within hours... »

Why using Extracorporeal Liver Replacement/Support Therapy (ELS or LRT) ?

Acute Liver Failure (ALF) and Acute-on-Chronic-Liver-Failure (ACLF) are the 2 main forms of liver failure encountered in ICU

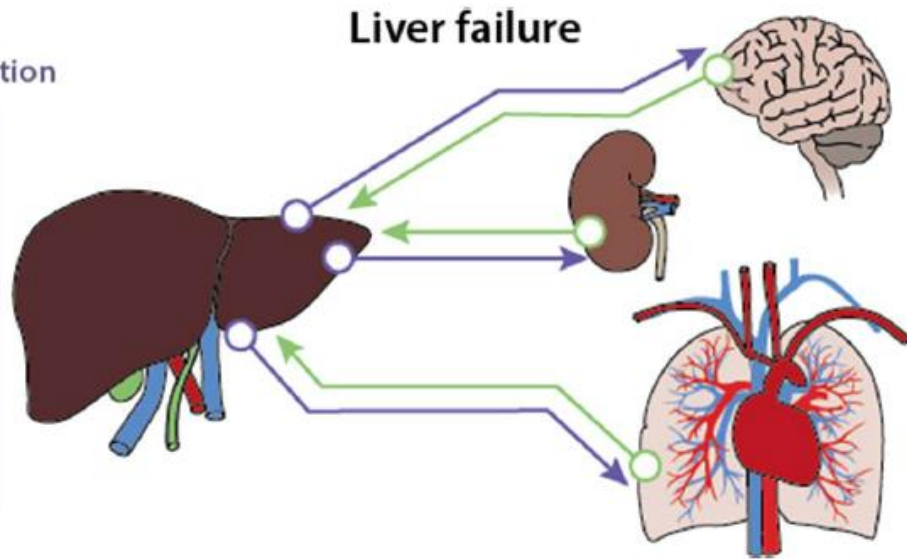
as trigger for clinical deterioration

Acute Liver Failure (ALF)

Incidence (ICU) <1%
Mortality 23 - 53%

Acute-on-Chronic Liver Failure (ACLF)

Incidence (ICU) 1 - 5%
Mortality 13 - 86%
(depending on ACLF severity)



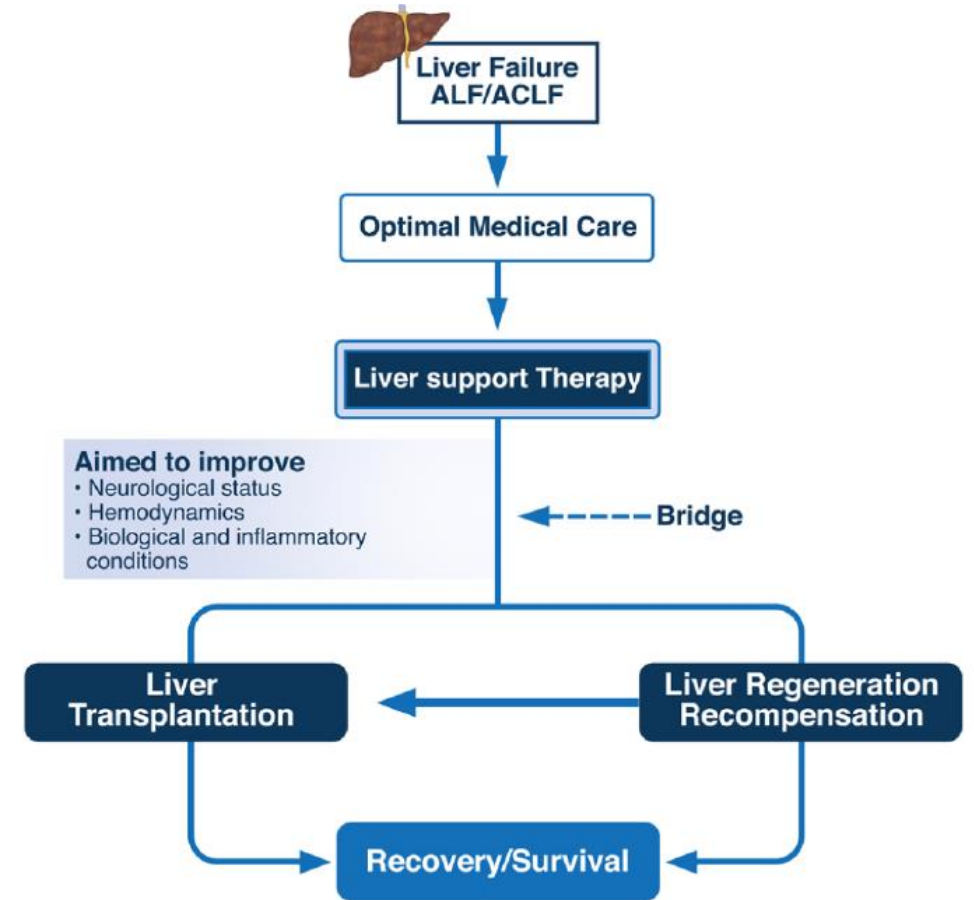
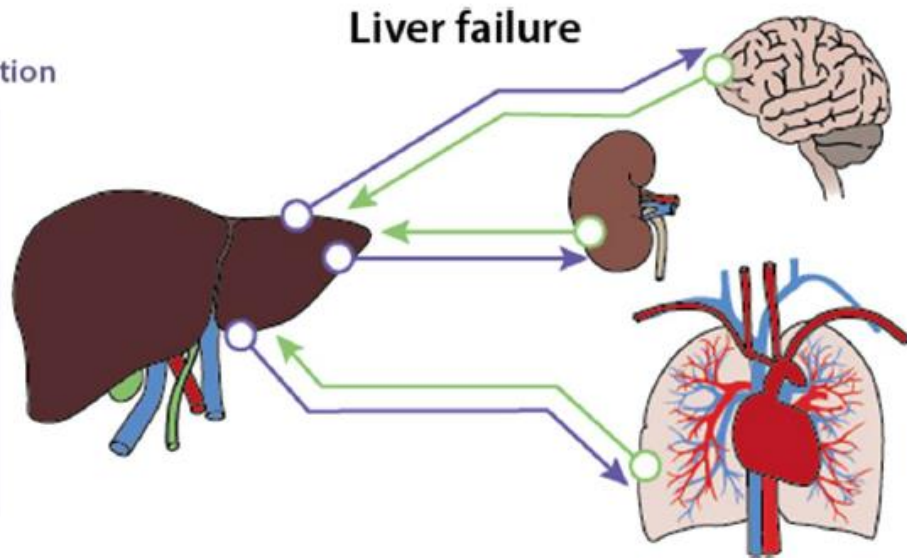
215k ACLF patients/year
eligible to treatment worldwide

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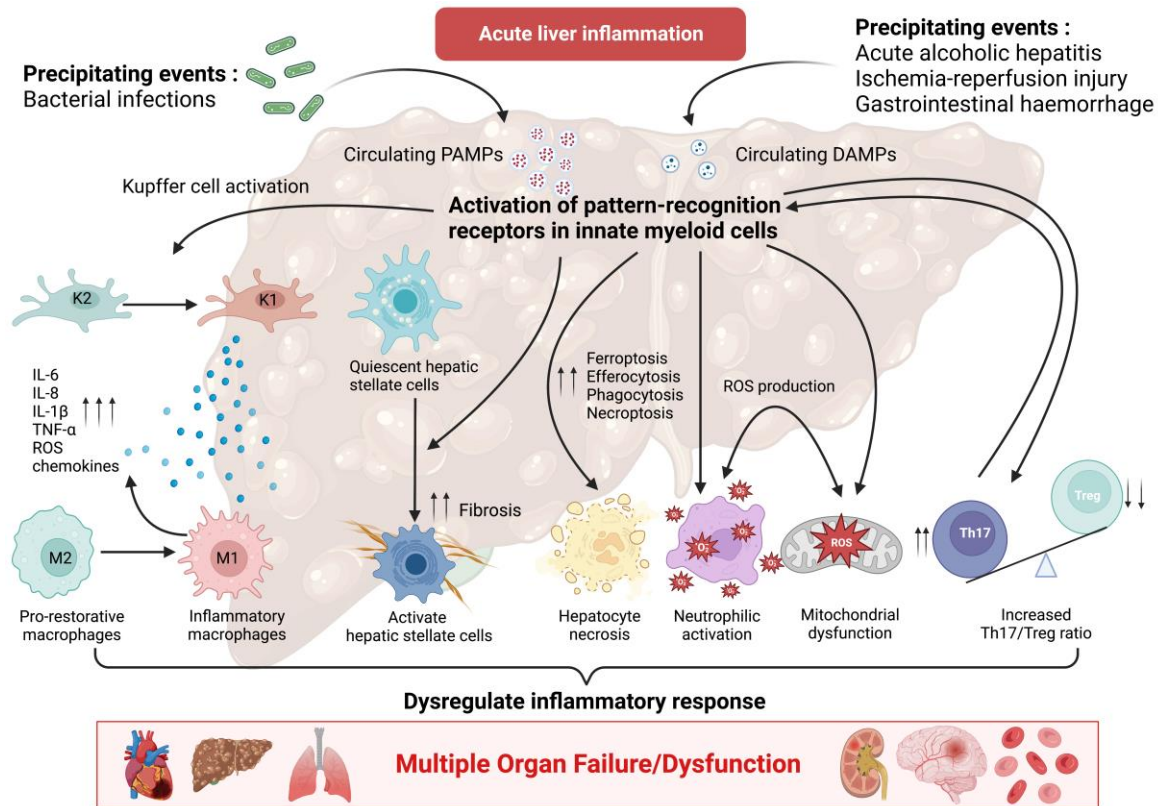
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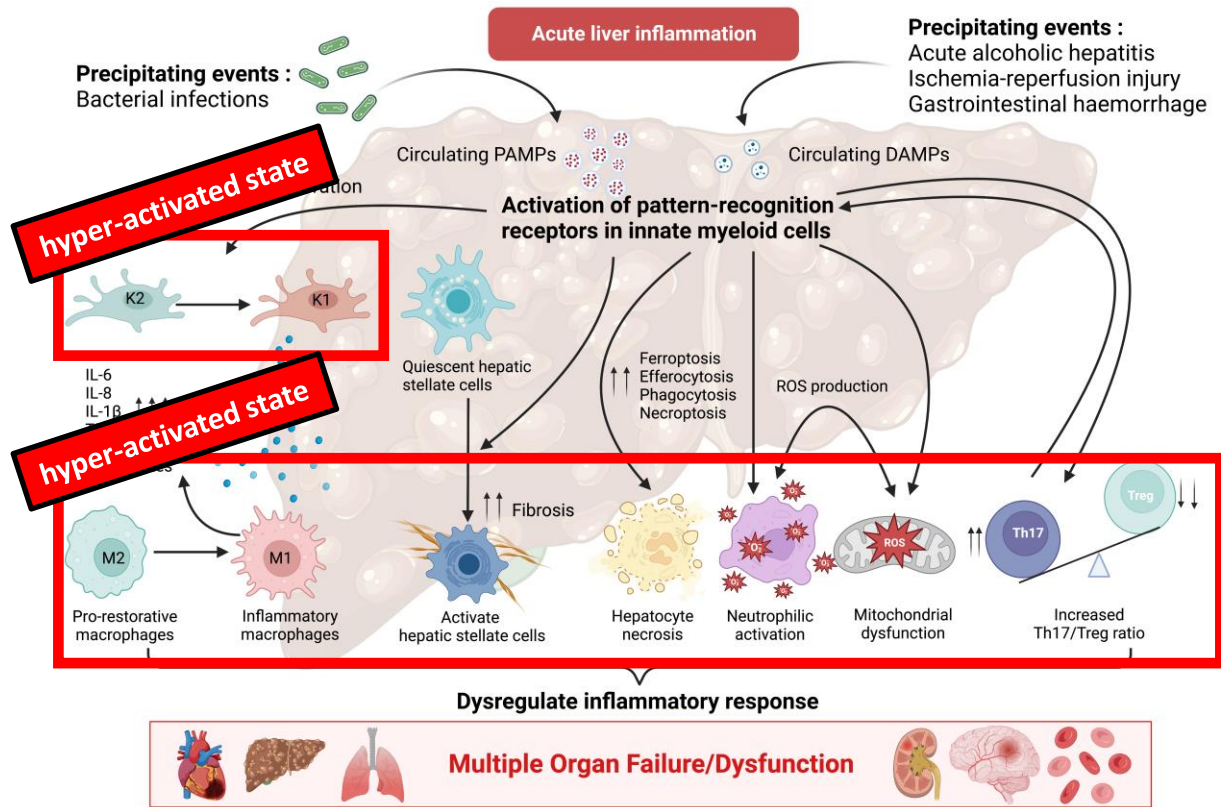


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Dysregulated hyperinflammation: a hallmark signature in acute liver failure

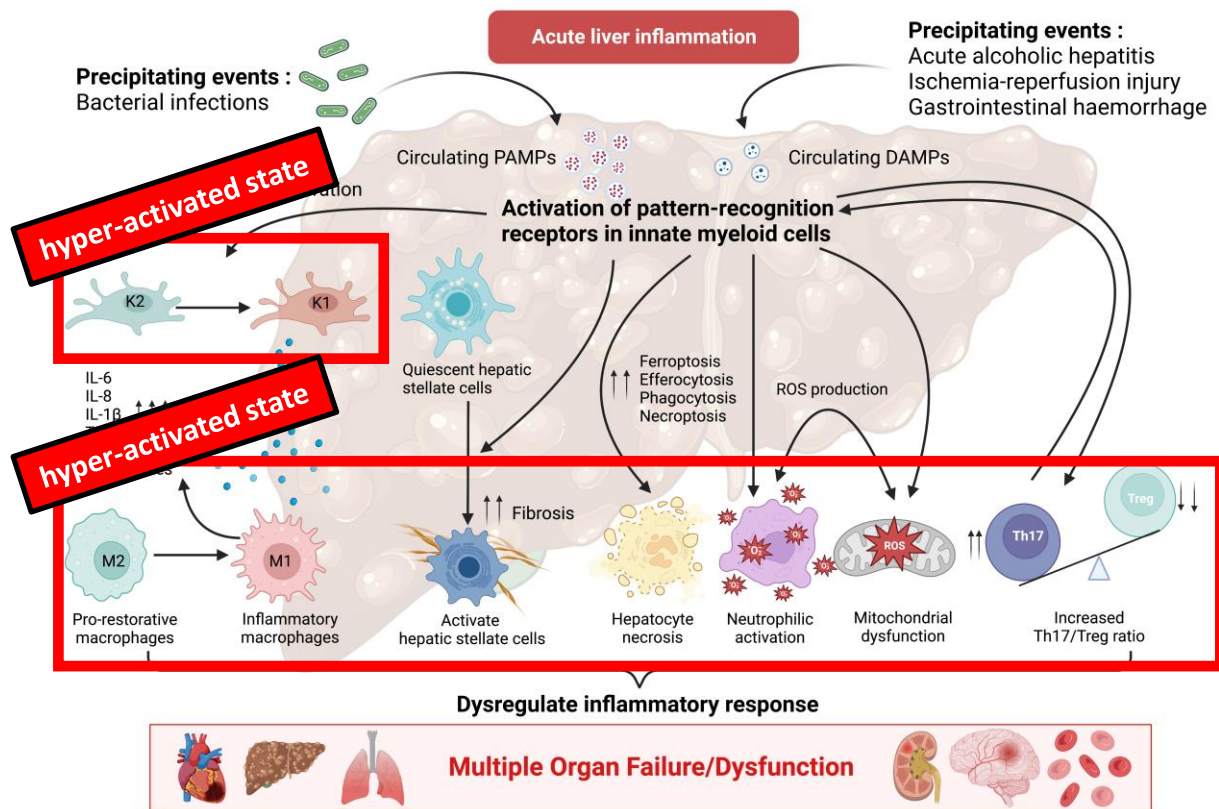


Dysregulated hyperinflammation: a hallmark signature in acute liver failure



Dysregulated hyperinflammation: a hallmark signature in acute liver failure

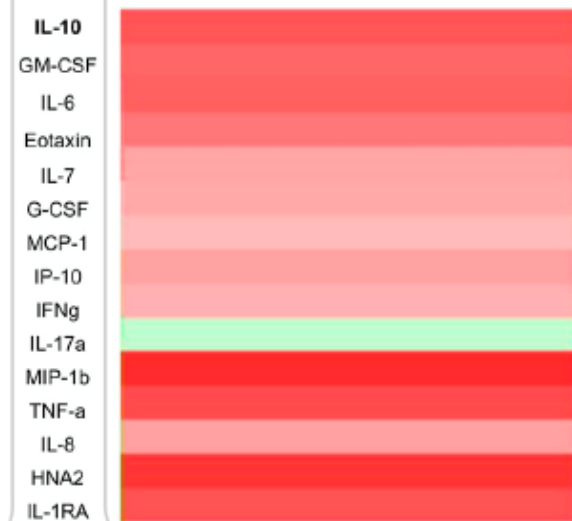
« maladaptive » acute inflammation



Baseline cytokine profile in patients with SDC/UDC



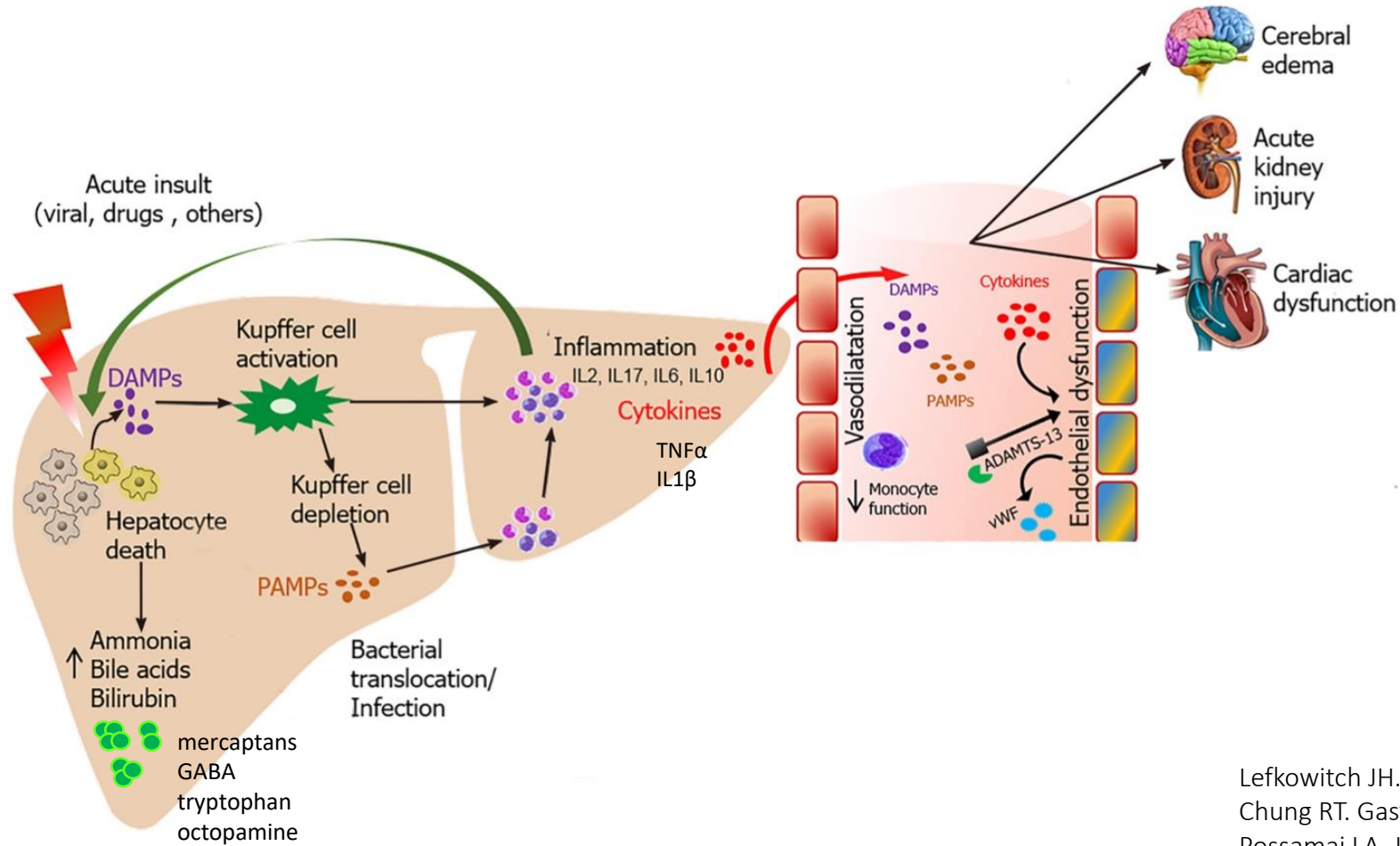
Baseline cytokine profile in pre-ACLF patients



« simple » acute decompensated cirrhosis

ACLF / ALF

Liver dysregulated hyperinflammation translates into systemic compartment leading to remote multiple organ failure

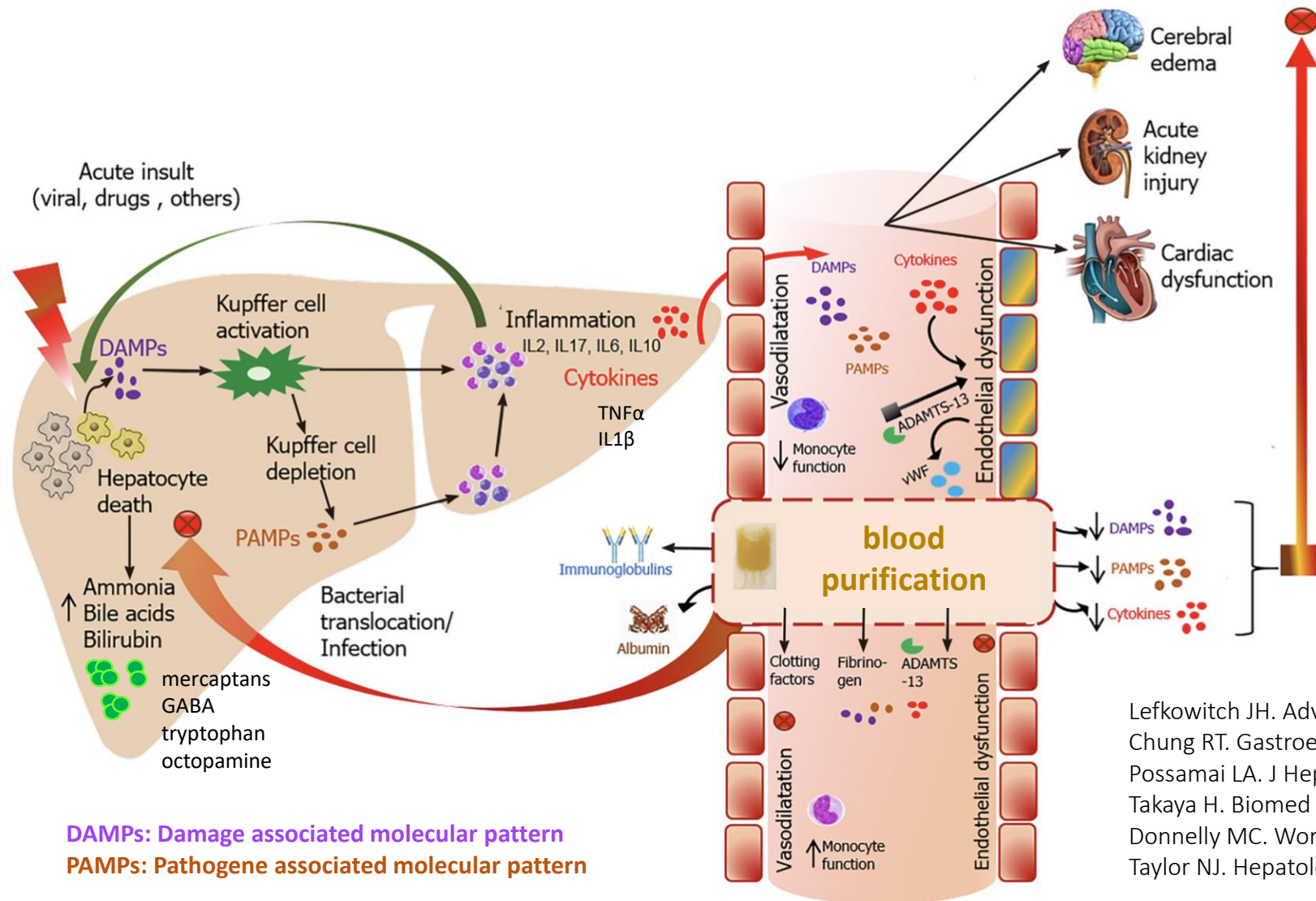


DAMPs: Damage associated molecular pattern

PAMPs: Pathogene associated molecular pattern

- Lefkowitch JH. *Adv Anat Pathol* 2016, 23:144–158
 Chung RT. *Gastroenterology* 2012, 143:e1–e7
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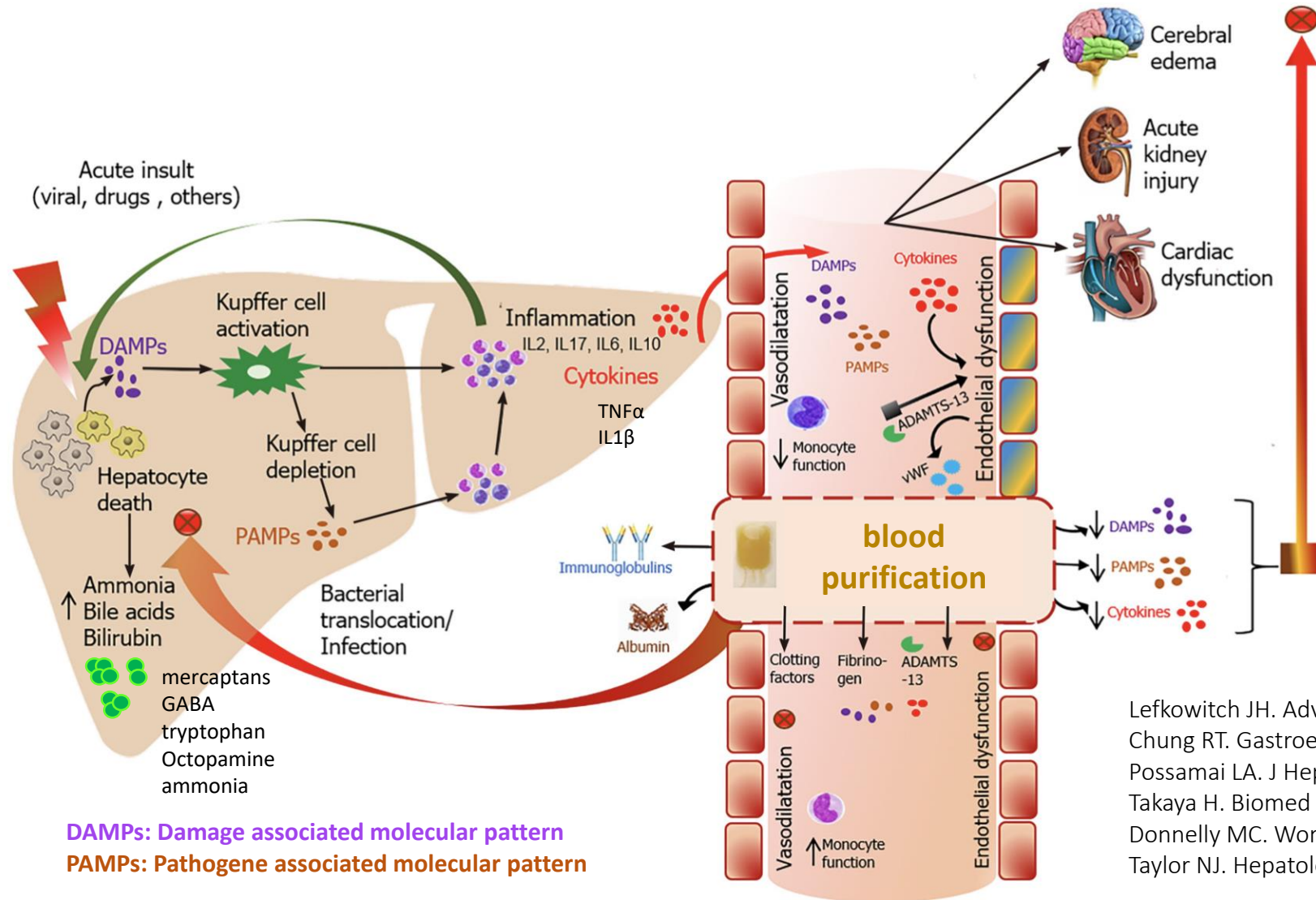
Removing inflammation from the blood to improve outcomes in acute liver failure



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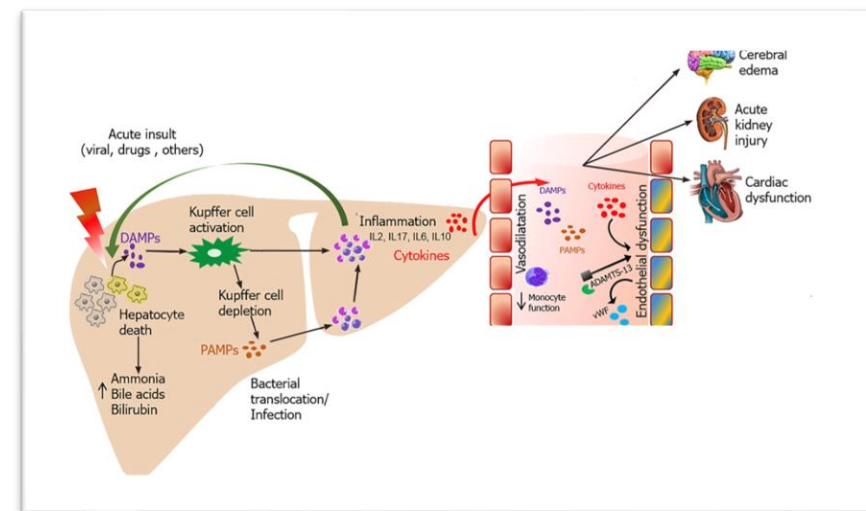
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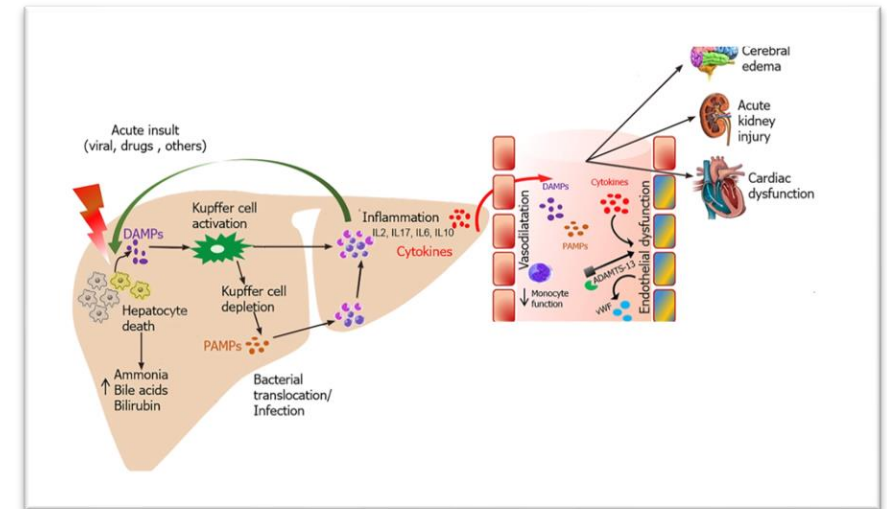
Role of the ELS / ELRT in 2024: we changed targets

rebalancing inflammation



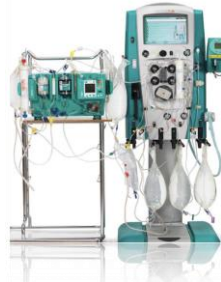
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Extracorporeal Artificial Liver Support ... publication history

Albumin Dialysis



MARS®

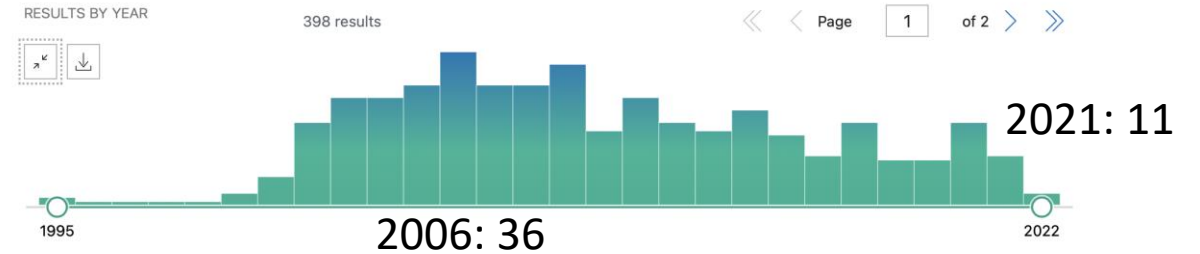


PROMETHEUS®



SPAD

...



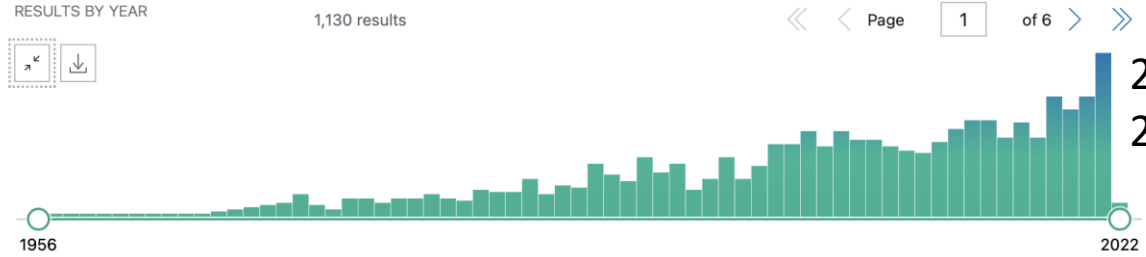
CRRT



...

Extracorporeal Artificial Liver Support ... > 2016

Plasma Exchange



Albumin Dialysis



MARS®



PROMETHEUS®



SPAD

...

CRRT



...

Extracorporeal Artificial Liver Support ... > 2022

Plasma Exchange



Hemoadsorption
Plasmafiltration Coupled
with Hemoadsorption



RESULTS BY YEAR

32 results

2021: 11



CRRT

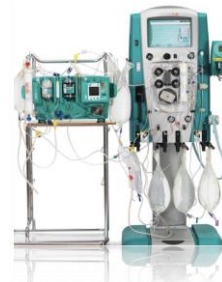


...



SPAD

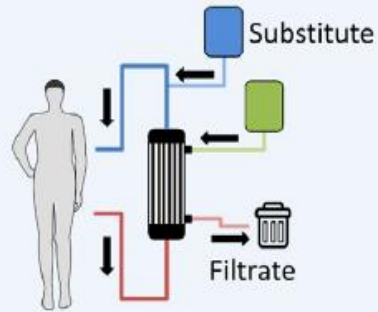
Albumin Dialysis



...

Extracorporeal Artificial Liver Support: let's talk about techniques

Extracorporeal Blood Purification Techniques



Convection Therapies

High Cut-Off Membranes (HCO)

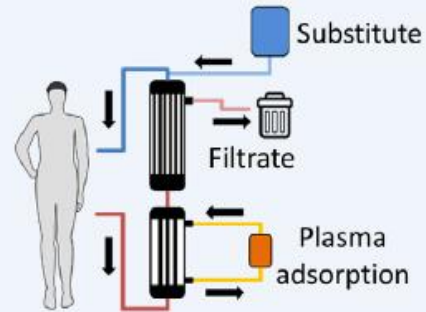
High Volume Hemofiltration (HVHF)



Adsorption Therapies

Specific Adsorption
Polymyxin B (PMX)
LPS Adsorber

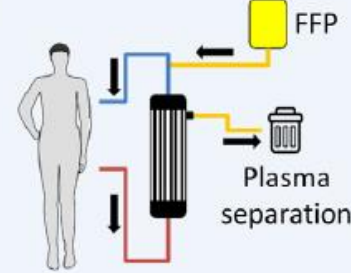
Unspecific Adsorption
Hemoadsorption
(e.g. CytoSorb®)



Combination Therapies

Combined filtration and Adsorption
(e.g. oXiris®)

Coupled Plasma Filtration Adsorption (CPFA)

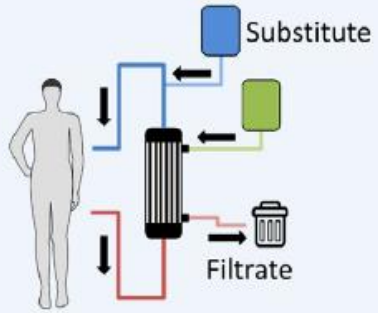


Other Therapies

Plasma Exchange

Extracorporeal Artificial Liver Support: let's talk about techniques

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Convection Therapies

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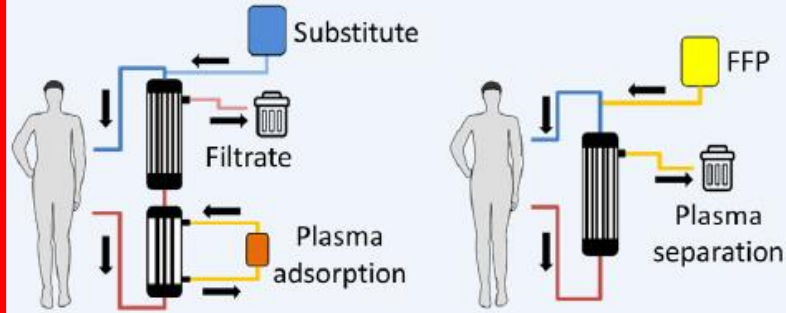
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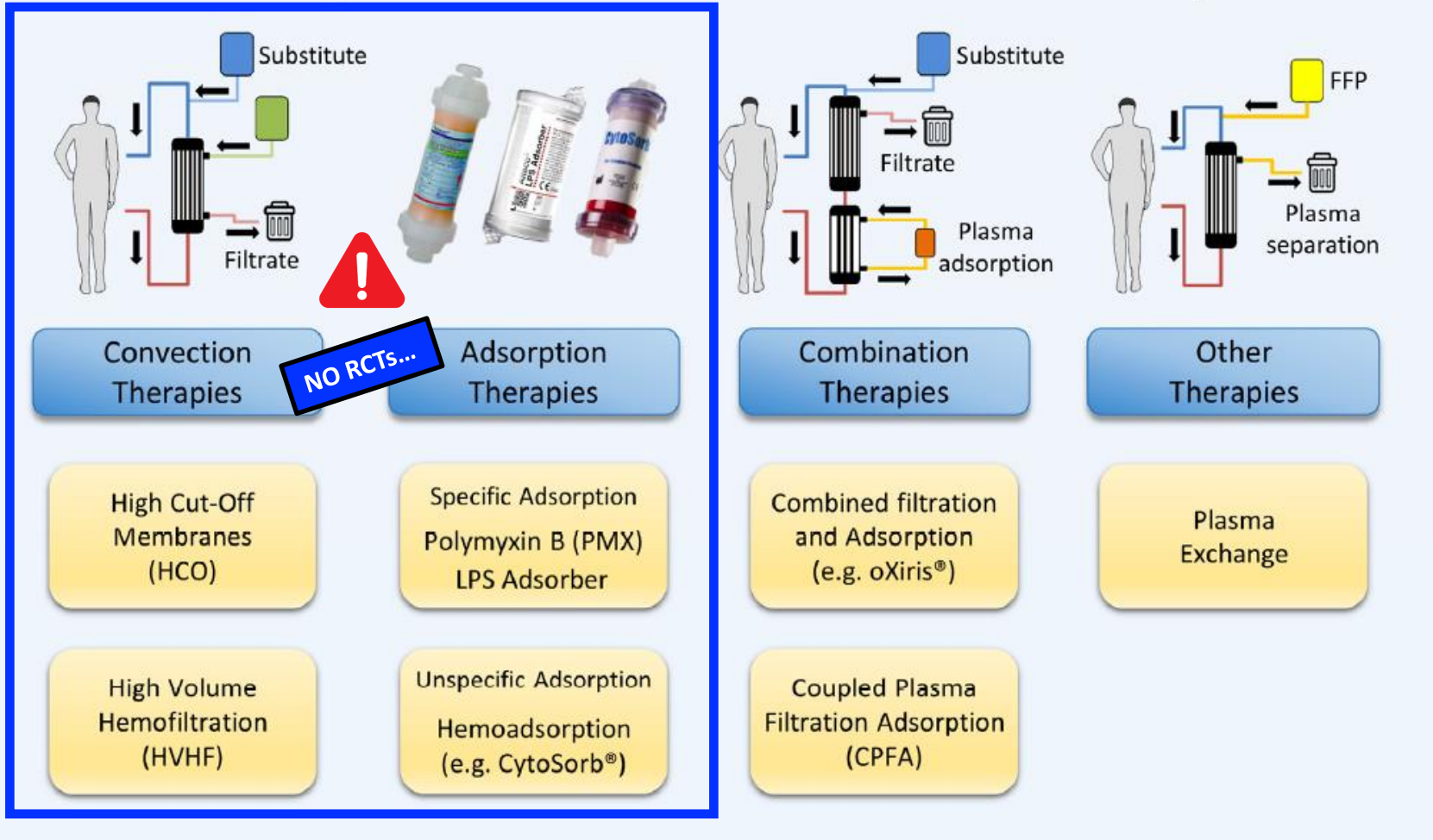
Plasma Exchange

RCTs

RCTs

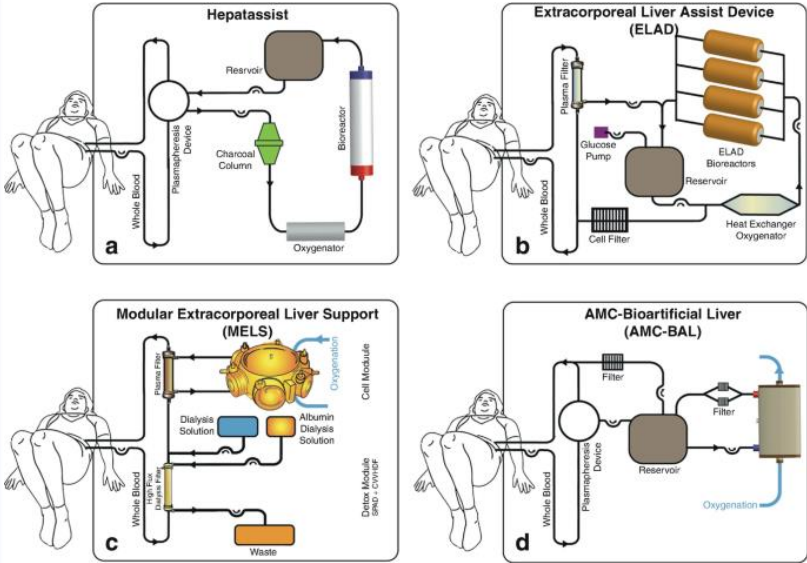
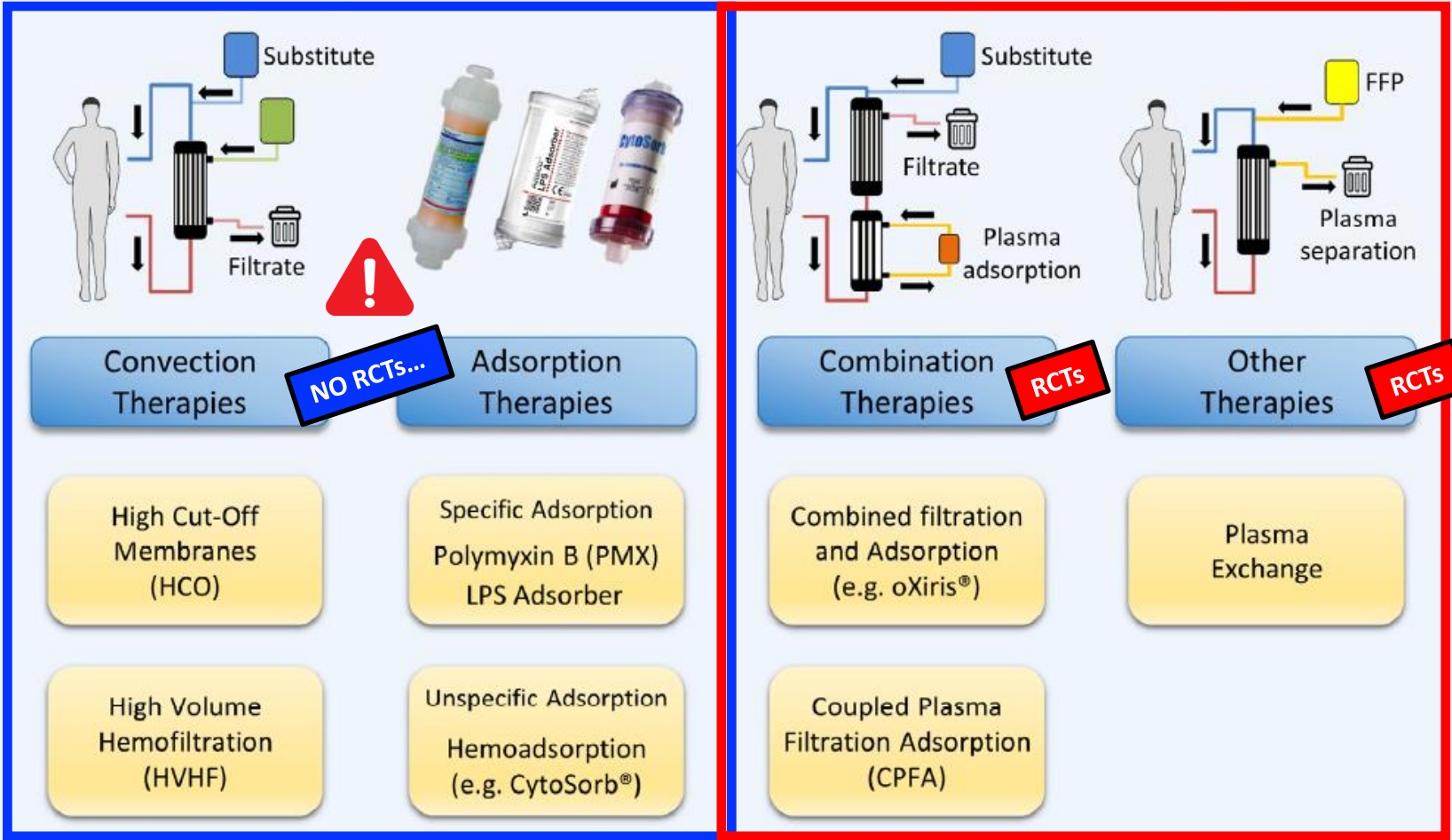
Extracorporeal Artificial Liver Support: let's talk about techniques

Extracorporeal Blood Purification Techniques



Extracorporeal Artificial Liver Support: let's talk about techniques

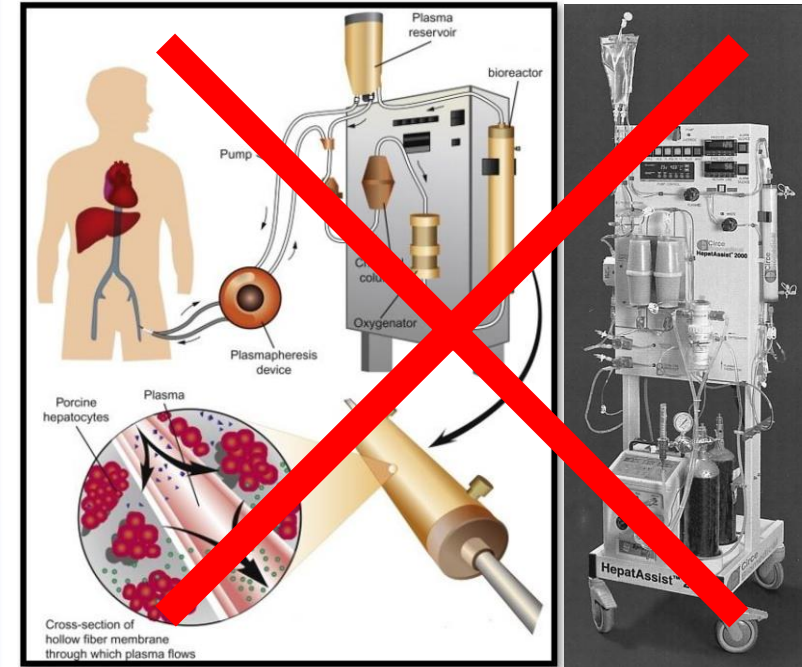
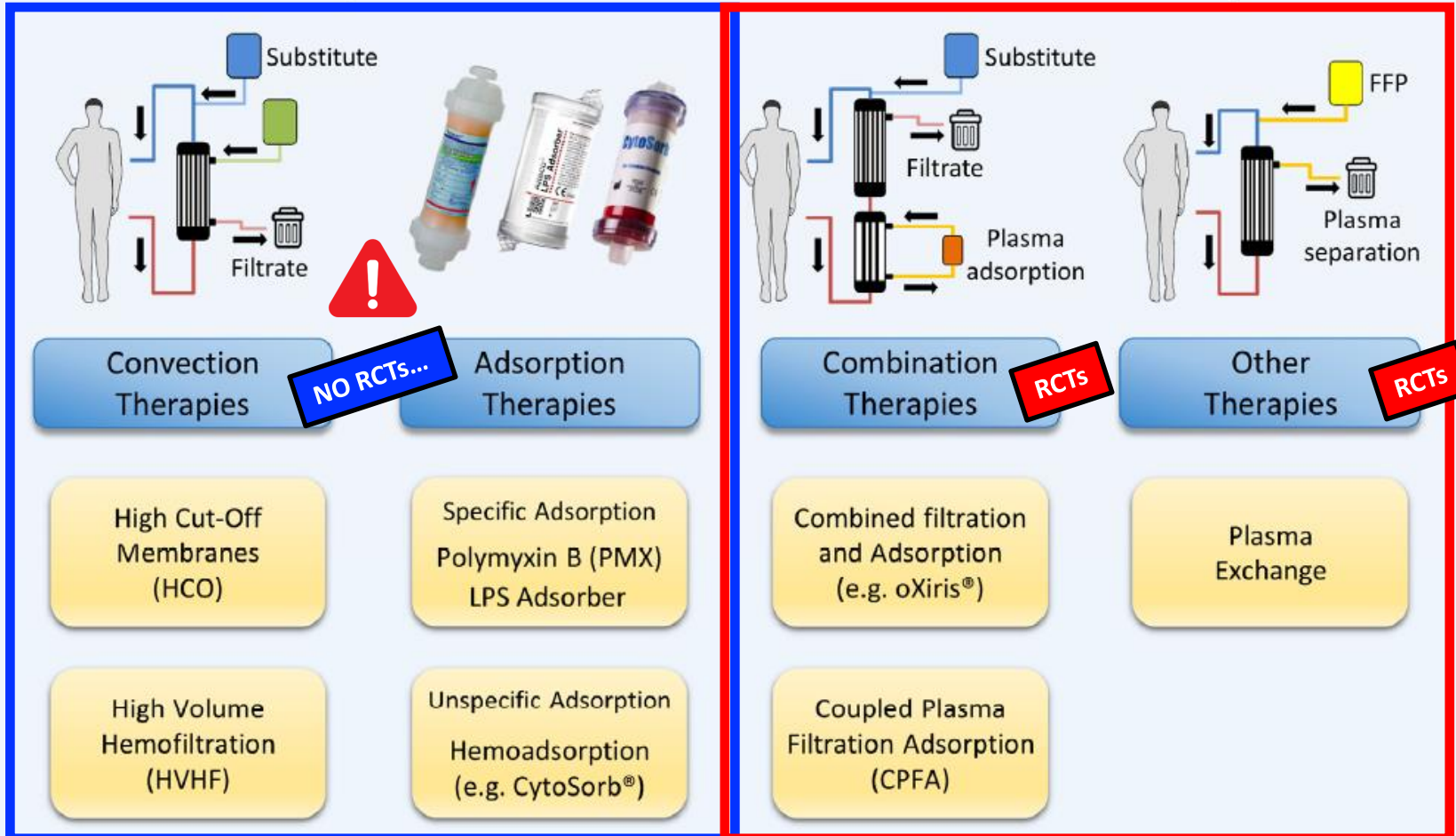
Extracorporeal Blood Purification Techniques



Extracorporeal Bioartificial Liver Devices
 Hepatassist®
 ELAD®
 MELS®
 AMC-BAL®

Extracorporeal Artificial Liver Support: let's talk about techniques

Extracorporeal Blood Purification Techniques



Extracorporeal Bioartificial Liver Devices

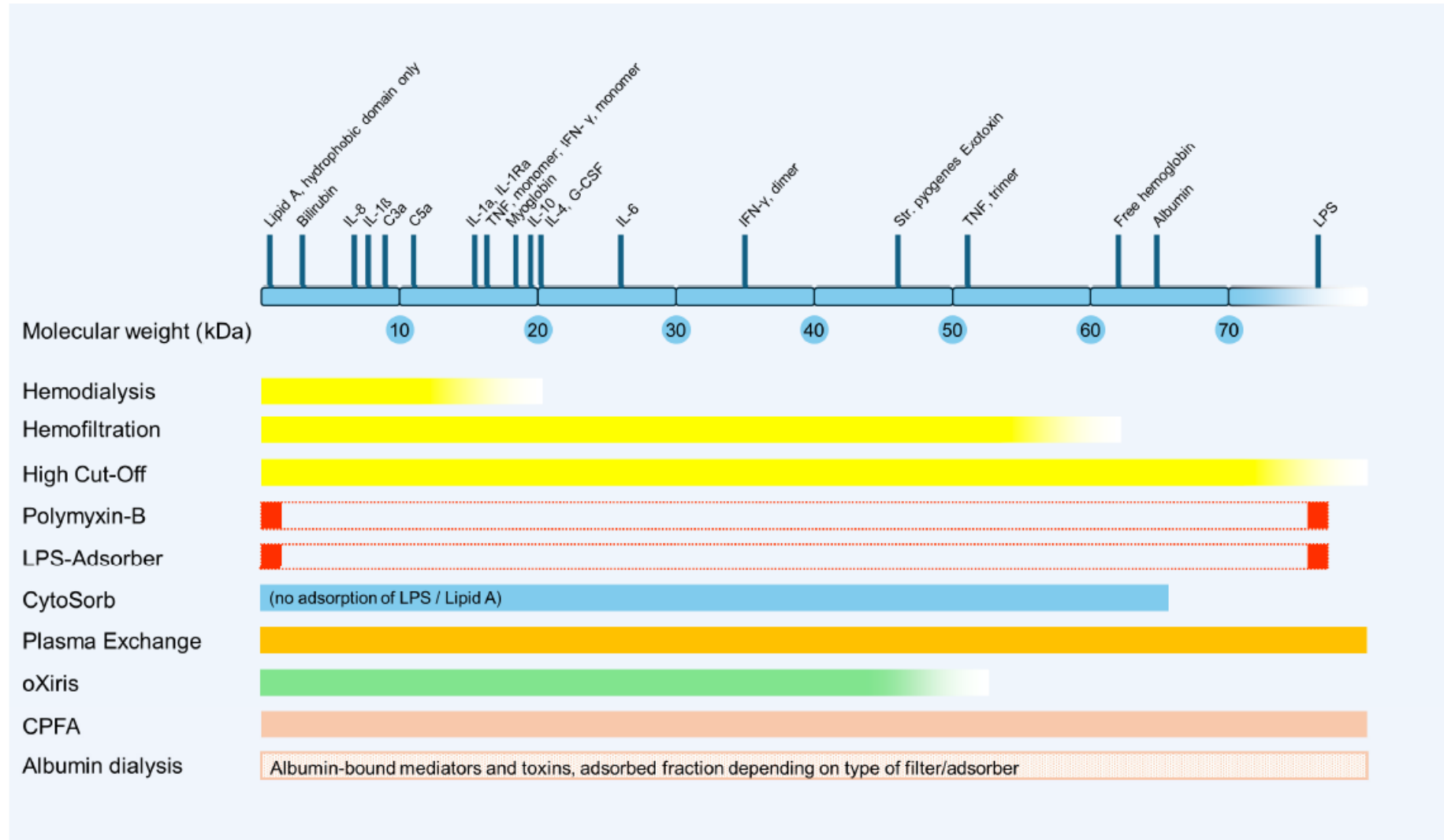
Hepatassist®

ELAD®

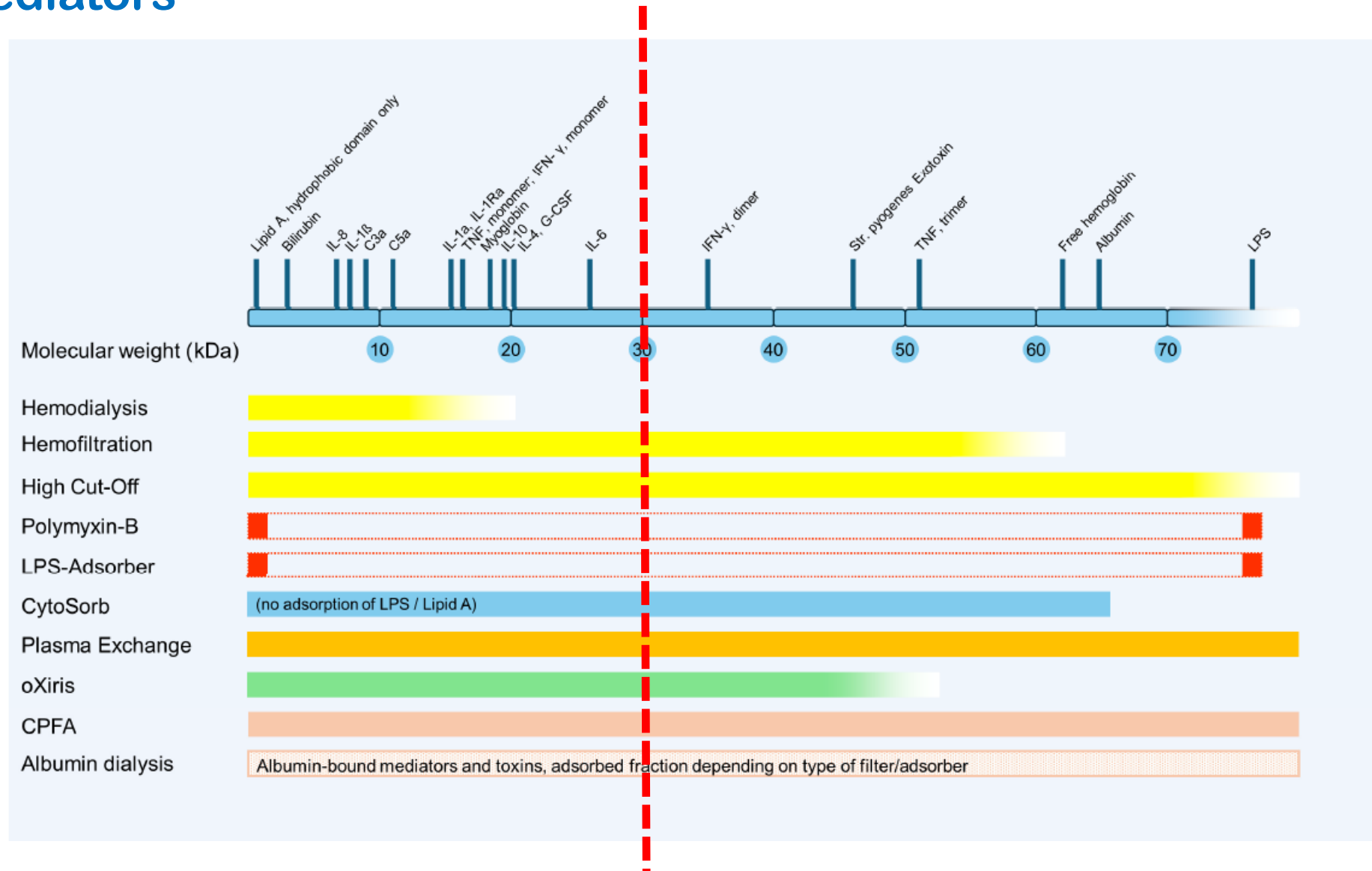
MELS®

AMC-BAL®

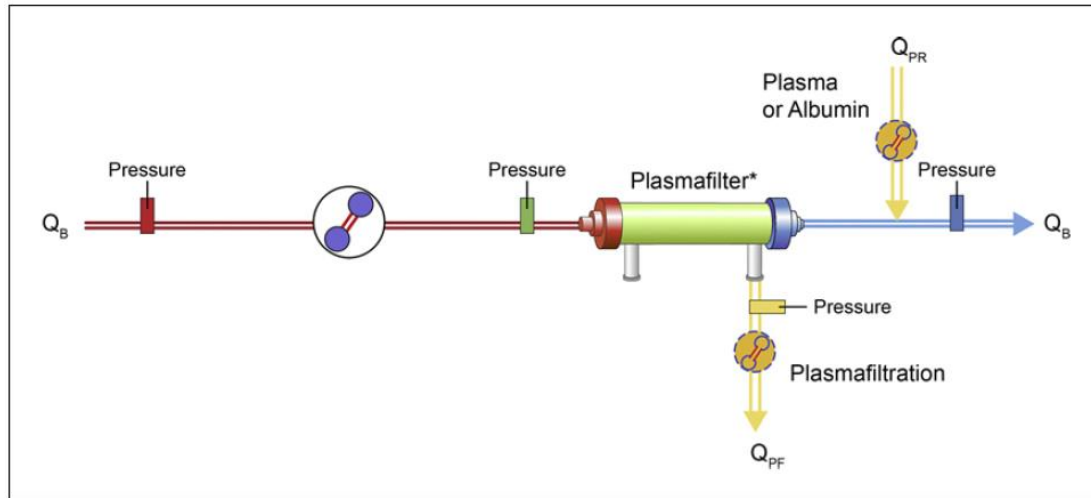
The molecular weight cut-off of the technique used determines the spectrum of purified mediators



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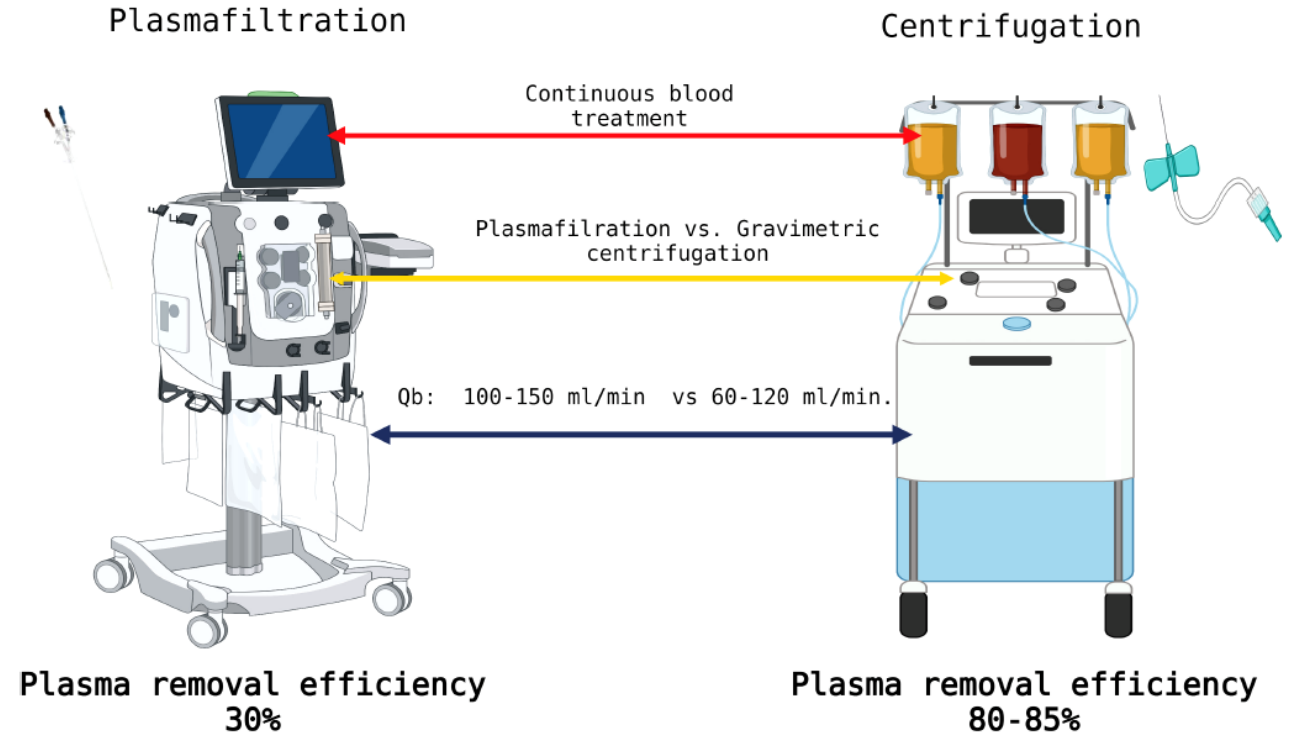
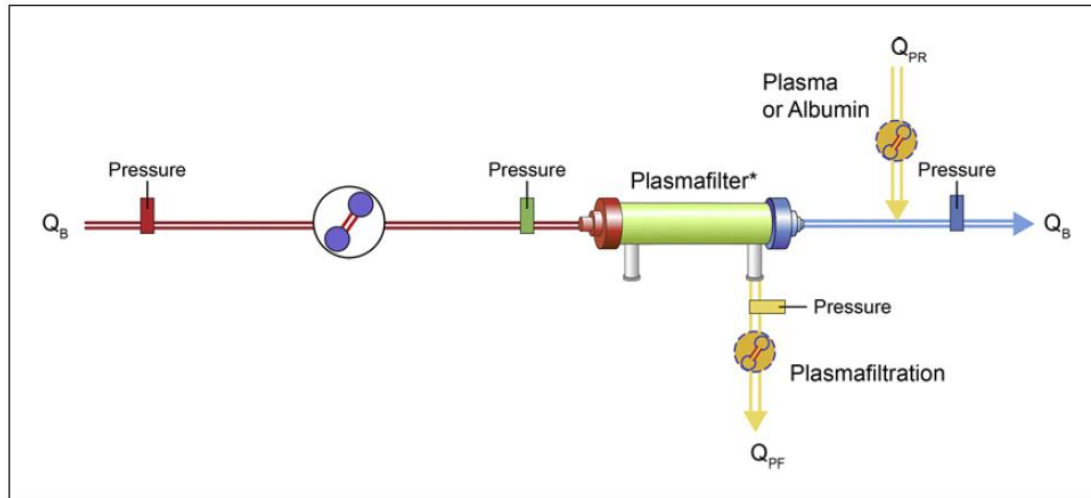


Plasma exchange: replacing circulating toxins with plasma « good » constituents





Plasma exchange: replacing circulating toxins with plasma « good » constituents

Therapeutic Plasma Exchange



Plasma exchange: HERCULEAN clinical trial in Acute Liver Failure

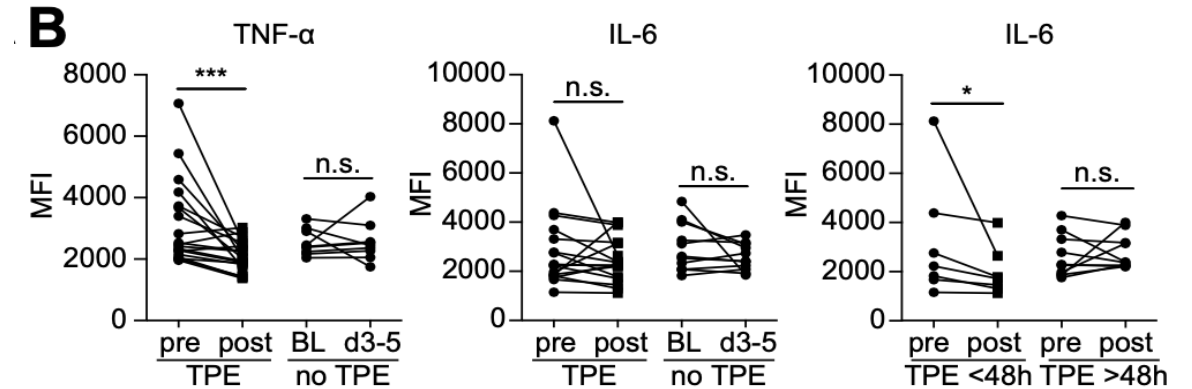
Research Article

  JOURNAL OF HEPATOLOGY
J Hepatol 2016; **64**: 69-78

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

Fin Stolze Larsen^{1,*}, Lars Ebbe Schmidt¹, Christine Bernsmeier², Allan Rasmussen³, Helena Isoniemi⁴, Vishal C. Patel², Evangelos Triantafyllou², William Bernal², Georg Auzinger², Debbie Shawcross², Martin Eefsen¹, Peter Nissen Bjerring¹, Jens Otto Clemmesen¹, Krister Hockerstedt⁴, Hans-Jørgen Frederiksen⁵, Bent Adel Hansen¹, Charalambos G. Antoniadou^{2,6,†}, Julia Wendon^{2,1}

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HERCULEAN

- RCT 180 patients, ALF
- 1998-2010
- **standard ttt vs standard ttt + HV-PE**
- London, Helsinki, Copenhagen



HV-PE:

- 9L treated plasma/session
- 1-2L/h
- Replacement : 100% FF plasma
- 2,4±0,8 HV-PE over 3 days

	Day	SMT (n = 90)		HVP (n = 92)		p value
		Median	IQR	Median	IQR	
MAP (mmHg)	0	75	[69-85]	75	[70-88]	0.66
	1	75	[69-84]	90**	[80-100]	<0.0001
	2	74	[68-80]	85**	[75-100]	<0.0001
	3	75	[65-85]	88#	[74-100]	<0.001
	7	80	[68-92]	80	[70-94]	0.51
NA (µg/kg/min) divided by 100	0	5	[0-10]	4	[0-10]	0.51
	1	5	[0-10]	0**	[0-3]	<0.0001
	2	5#	[0-16]	0**	[0-2]	<0.0001
	3	4	[0-14]	0**	[0-0]	<0.0001
	7	1	[0-14]	0#	[0-3]	0.06

Plasma exchange: HERCULEAN clinical trial in Acute Liver Failure

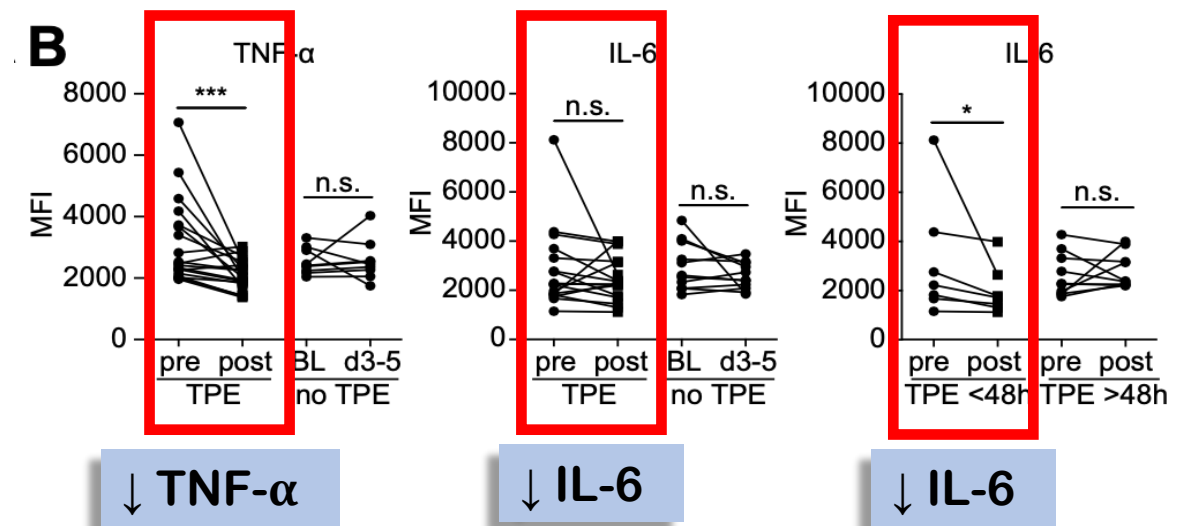
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	2	0**	[0-2]	0**	[0-2]	<0.0001
	3	0**	[0-0]	0**	[0-0]	<0.0001
	7	1	[0-14]	0#	[0-3]	0.06

↑ MAP
↓ vasopressors

Plasma exchange: HERCULEAN clinical trial in Acute Liver Failure

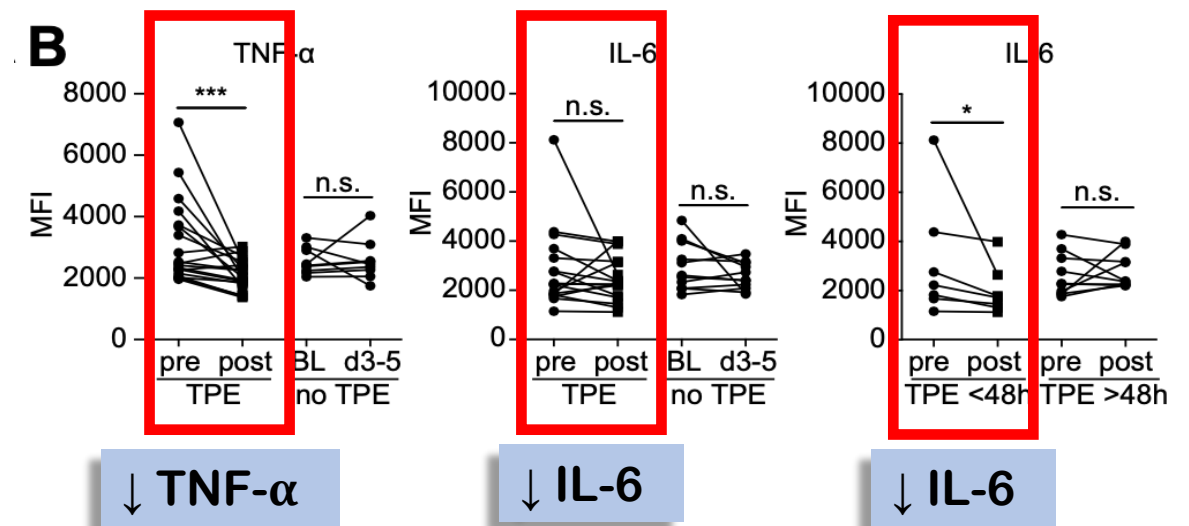
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	Day	SMT (n = 90)		HVP (n = 92)		p value
		Median	IQR	Median	IQR	
Bilirubin (μmol/L)	0	161	[84-359]	162	[100-387]	0.36
	1	176 [#]	[102-362]	127 ^{**}	[80-198]	<0.01
	2	195 [#]	[119-348]	123 [*]	[77-221]	<0.001
	3	257 [#]	[138-398]	135 [#]	[100-212]	<0.001
INR				183	[116-270]	<0.01
				5.5	[4.1-7.4]	0.11
				1.7 ^{**}	[1.3-2.3]	<0.0001
	3	3.7 [#]	[2.7-5.4]	1.7 ^{**}	[1.4-2.1]	<0.0001
	7	3.5 [#]	[2.7-4.4]	2.0 ^{**}	[1.7-2.6]	<0.0001

↓ bilirubin
↓ INR

Plasma exchange: HERCULEAN clinical trial in Acute Liver Failure

Research Article



EASL JOURNAL OF HEPATOLOGY

J Hepatol 2016; 64: 69-78

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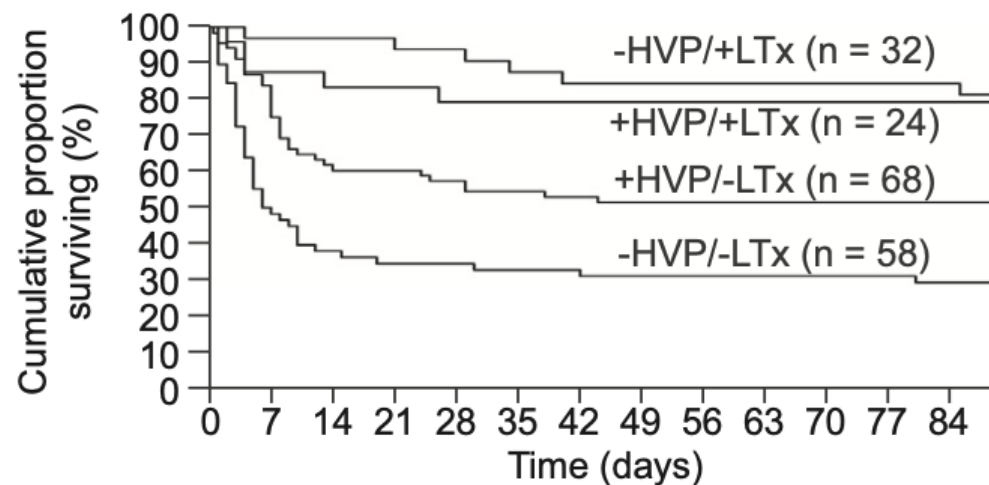
HERCULEAN

- RCT 180 patients, ALF
- 1998-2010
- **standard ttt vs standard ttt + HV-PE**
- London, Helsinki, Copenhagen

HV-PE:



- 9L treated plasma/session
- 1-2L/h
- Replacement : 100% FF plasma
- 2,4±0,8 HV-PE over 3 days

	Day	SMT (n = 90)		HVP (n = 92)		p value
		Median	IQR	Median	IQR	
SOFA-score	0	14	[11-18]	13	[11-18]	0.59
	1	15*	[13-19]	12 [#]	[10-16]	<0.01
	2	16 [#]	[14-19]	13	[10-16]	<0.001
	3	16 [#]	[14-19]	13	[11-16]	<0.0001
	7	17	[14-19]	13	[11-17]	0.05
CLIF-score	0	17	[14-20]	16	[14-19]	0.67
	1	18 [#]	[15-20]	13 ^{**}	[12-17]	<0.0001
	2	18 [#]	[15-20]	13 ^{**}	[12-16]	<0.0001
	3	18	[15-21]	13*	[12-16]	<0.0001
	7	18	[15-21]	13 [#]	[12-18]	0.01
SIRS-score	0	2	[1-3]	2	[2-3]	0.13
	1	2	[1-2]	1 ^{**}	[1-2]	0.24
	2	2	[1-3]	1 ^{**}	[0-2]	<0.001
	3	2	[1-3]	1*	[1-2]	0.01
	7	2	[1-3]	1*	[1-2]	0.06



Plasma exchange: HERCULEAN clinical trial in Acute Liver Failure

Research Article

  JOURNAL OF HEPATOLOGY
J Hepatol 2016; **64**: 69-78

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

Fin Stolze Larsen^{1,*}, Lars Ebbe Schmidt¹, Christine Bernsmeier², Allan Rasmussen³, Helena Isoniemi⁴, Vishal C. Patel², Evangelos Triantafyllou², William Bernal², Georg Auzinger², Debbie Shawcross², Martin Eefsen¹, Peter Nissen Bjerring¹, Jens Otto Clemmesen¹, Krister Hockerstedt⁴, Hans-Jørgen Frederiksen⁵, Bent Adel Hansen¹, Charalambos G. Antoniadis^{2,6,†}, Julia Wendon^{2,†}

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	1	2	[1-2]	1**	[1-2]	0.24
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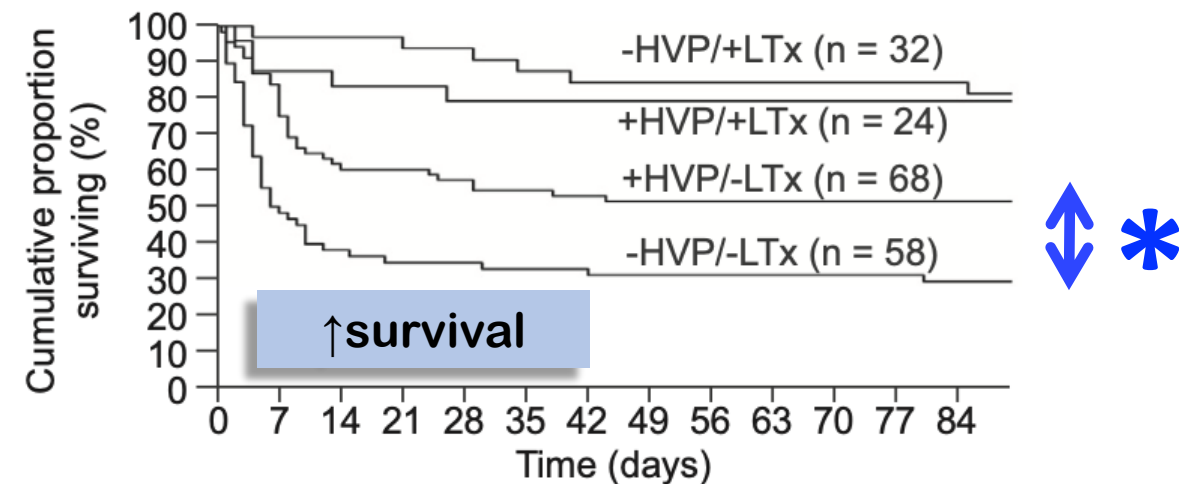
↓ SOFA
 ↓ CLIF
 ↓ SIRS

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HV-PE:

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- 1-2L/h
- Replacement : 100% FF plasma
- 2,4±0,8 HV-PE over 3 days



Plasma exchange: other trials in ALF and ACLF

ACUTE LIVER FAILURE

RESEARCH ARTICLE
J Clin Apher. 2021;1–11.
Initial experience with high-volume plasma exchange in patients with acute liver failure
Ji Eun Kim¹ | Sejong Chun² | Dong Hyun Sinn¹ | Nam Joong Kim³ | Semi Kim⁴ | Wonseok Kang¹ | Jong Man Kim⁵ | Gyu-Seong Choi⁵ | Yoo Man Juh⁵ | Duck Cho⁴

Transfusion and Apheresis Science 60 (2021) 103250
Contents lists available at ScienceDirect
Transfusion and Apheresis Science
journal homepage: www.elsevier.com/locate/transci
Original Article
Early therapeutic plasma exchange may improve treatment outcomes in severe acute toxic Hepatitis
Ilhami Berber^a, Yasir Furkan Cagin^{b,c}, Mehmet Ali Erdogan^b, Engin Ataman^b, Harika Gozukara^a, Mehmet Ali Erkurt^a, Oguzhan Yildirim^a, Irfan Kuku^a, Emin Kaya^a, Yilmaz Bilgic^a, Ahmet Sarici^a, Soykan Bicim^a, Alaadin Polat^a

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Wiersema et al. *BMC Anesthesiology* (2015) 15:30
DOI:10.1186/s12871-015-0017-9
RESEARCH ARTICLE
Open Access
Therapeutic plasma exchange does not reduce vasopressor requirement in severe acute liver failure: a retrospective case series
Ilkka E. Wiersema^{1*}, Susan W. Kim², David Drobnik³ and Andrew Hob¹

ACUTE ON CHRONIC LIVER FAILURE

J Artif Organs
DOI 10.1007/s10047-017-0986-1
ORIGINAL ARTICLE
Artificial Liver, Pancreas
A comparison among three different apheretic techniques for treatment of hyperbilirubinemia
Davide Viggiano² · Emanuela de Pascale¹ · Gaia Marinelli¹ · Corrado Pluvio¹

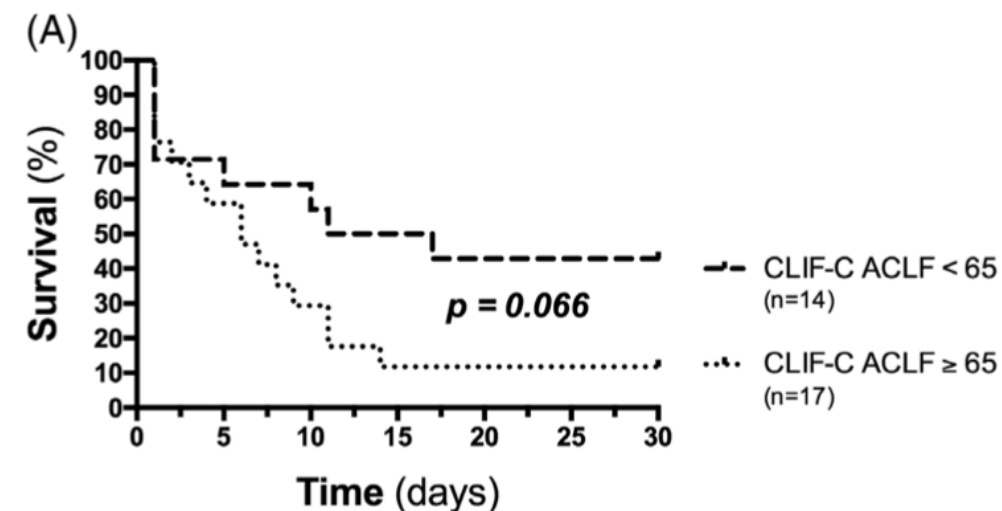
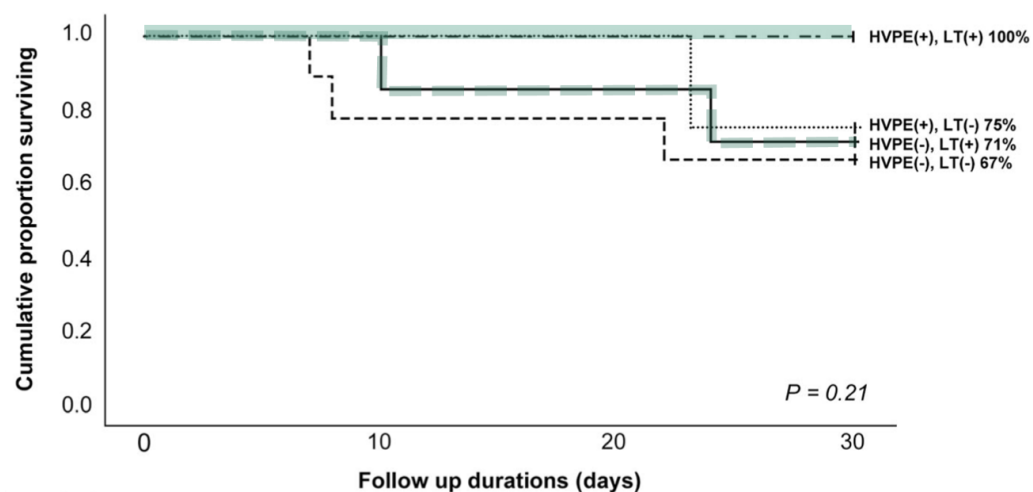
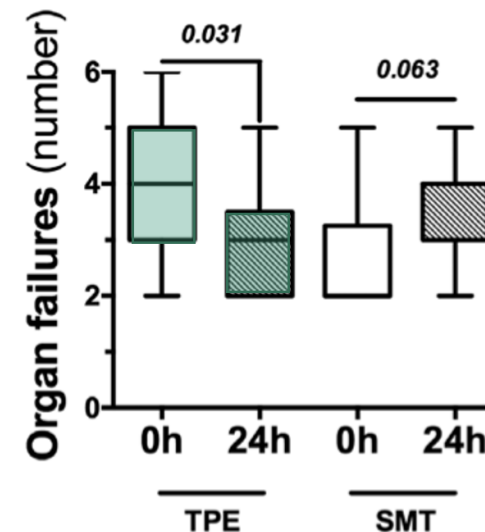
Received: 27 January 2020 | Revised: 26 May 2020 | Accepted: 27 May 2020
DOI: 10.1002/jca.21799
RESEARCH ARTICLE
Therapeutic plasma exchange in acute on chronic liver failure
Klaus Stahl^{1,2} | Markus Busch^{1,2} | Jan Fuge³ | Andrea Schneider^{1,2} | Michael P. Manns^{1,2} | Benjamin Seelizer³ | Julius J. Schmidt⁴ |

Received: 6 June 2020 | Revised: 24 December 2020 | Accepted: 23 January 2021
DOI: 10.1111/liv.14806
ORIGINAL ARTICLE
Liver INTERNATIONAL WILEY
Therapeutic plasma-exchange improves systemic inflammation and survival in acute-on-chronic liver failure: A propensity-score matched study from AARC
Rakhi Maiwall¹ | Meenu Bajpai² | Ashok K. Choudhury¹ | Anupam Kumar³ |

Plasma exchange: other trials in ALF and ACLF

Laboratory effects of TPE on patients with acute toxic hepatitis.

	Baseline, median (min-max)	After 48 h, median (min-max) [‡]	Last available, median (min-max) ^c	p-value
INR	1.5 (0.8–9.49) ^a	1.3 (0.8–3.3) ^b	1.1 (0.9–4.4) ^c	<0.001
AST, IU/L	920 (28–7491) ^a	251 (20–4948) ^b	89 (23–952) ^c	<0.001
ALT, IU/L	1076 (23–8156) ^a	392 (20–2368) ^b	170 (6–1195) ^c	<0.001
Total bilirubin, mg/dL	20.8 (10.1–46.7) ^a	12.5 (2.1–44.6) ^b	4.4 (0.5–20.3) ^c	<0.001
Ammonia, mcg/dL	125 (66–435)	–	97 (40–368)	<0.001
Lactate, mmol/L	13 (4–66)	–	11 (3–120)	0.028
MELD score	23 (16–39) ^a	20 (12–36) ^b	14 (6–40) ^c	<0.001



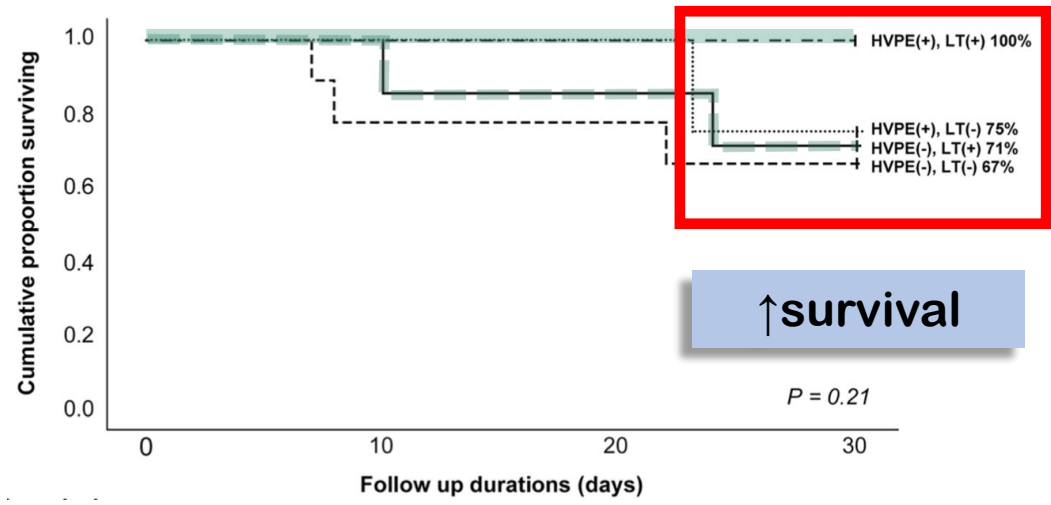
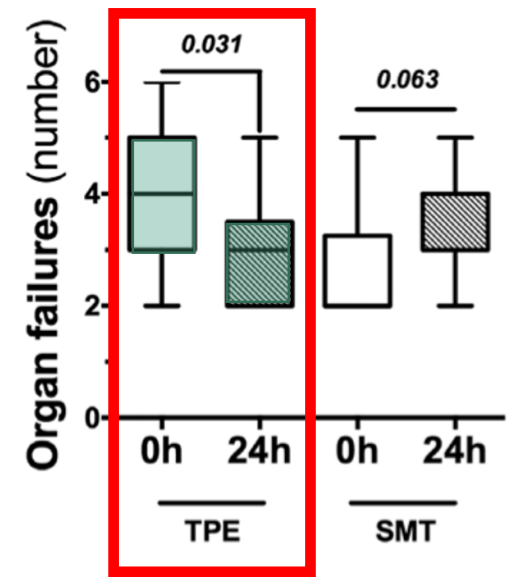
Plasma exchange: other trials in ALF and ACLF

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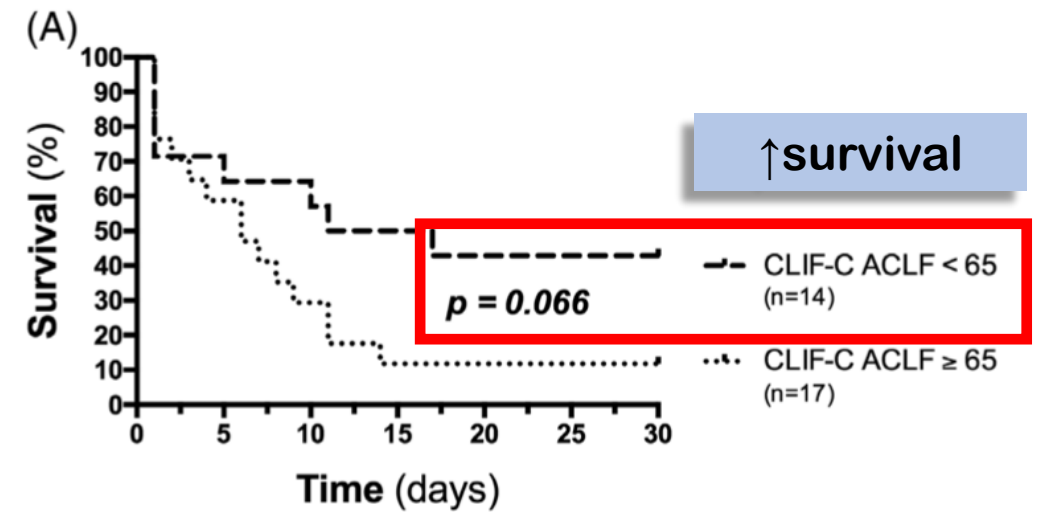
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↓ INR
 ↓ ALAT
 ↓ Ammonia
 ↓ lactates
 ↓ MELD
 ↓ bilirubin

↓ organ failures



↑ survival



↑ survival

Plasma exchange: what do the guidelines tell us?

J Clin Apheresis 2019

Journal of Clinical Apheresis ... ASEA WILEY

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

Anand Padmanabhan¹ | Laura Connelly-Smith² | Nicole Aquiri³ | Rasheed A. Balogun⁴ | Reinhard Klingel⁵ | Erin Meyer⁶ | Huy P. Pham⁷ | Jennifer Schneiderman⁸ | Volker Witt⁹ | Yanyun Wu¹⁰ | Nicole D. Zantek¹¹ | Nancy M. Dunbar¹² |

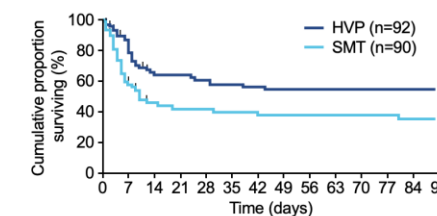
ACUTE LIVER FAILURE

Incidence: <10/1,000,000/yr		Procedure	Recommendation	Category
		TPE-HV*	Grade 1A	I
		TPE	Grade 2B	III
# reported patients: >300	RCT	CT	CS	CR
TPE-HV	1(183)	0	0	NA
TPE	1(120)	1(158)	40(878)	NA

*TPE-HV = TPE-high volume, not in routine use in US

Artificial and bioartificial liver devices

- Liver-assist devices are intended to provide a 'bridge' to LTx or recovery of liver function, reducing the need for transplant
 - Experience with 'liver support devices' to date has been disappointing
 - High-volume plasma exchange improved outcome in an RCT in ALF*



Recommendations	Grade of evidence	Grade of recommendation
Liver support systems (biological or adsorbent) should only be used in the context of RCTs	II-1	1
Plasma exchange in RCTs has been shown to improve transplant-free survival in patients with ALF and to modulate immune dysfunction	I	1
Plasma exchange may be of greater benefit in patients who are treated early and who will not ultimately undergo liver transplant	I	2

*HVP defined as exchange of 8–12 or 15% of ideal body weight with fresh frozen plasma, for 3 days was superior to SMT regarding transplant-free and overall hospital survival. Larsen FS, et al. *J Hepatol*. 2016;64:69–78; EASL CPG ALF. *J Hepatol* 2017;66:1047–81



J Hepatol 2017;66:1047–81

Guidelines support early and intensive PE in ALF !

Plasma exchange: what do the guidelines tell us?

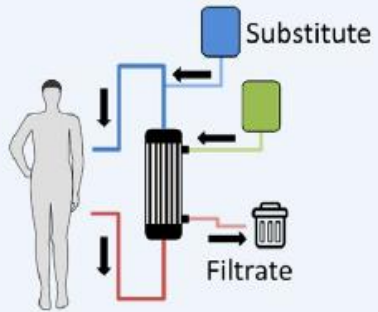
- 1 – 1.5 plasma mass (100-Hte x 0.7 x weight)
- *e.g.* for 70 kg adult: 3.5 L (50-55 mL/kg)
- HV-PE: 8-12 L
- replacement with albumin or FFP
- daily until recovery or OLT (> 3 HV-PE)



Guidelines support early and intensive PE in ALF !

Extracorporeal Artificial Liver Support: let's talk about techniques

Extracorporeal Blood Purification Techniques



Convection Therapies

High Cut-Off Membranes (HCO)

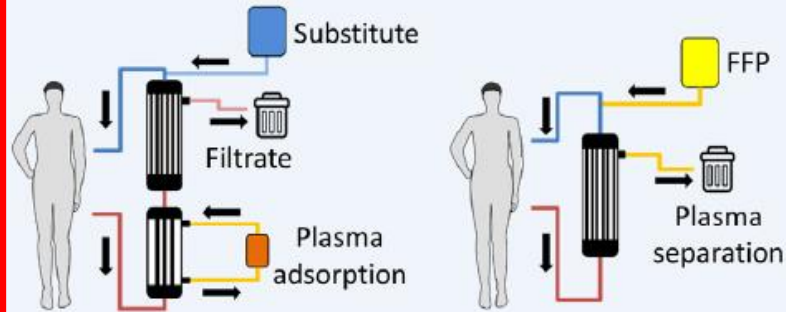
High Volume Hemofiltration (HVHF)



Adsorption Therapies

Specific Adsorption
Polymyxin B (PMX)
LPS Adsorber

Unspecific Adsorption
Hemoadsorption
(e.g. CytoSorb®)



Combination Therapies

Combined filtration and Adsorption (e.g. oXiris®)

Coupled Plasma Filtration Adsorption (CPFA)

Other Therapies

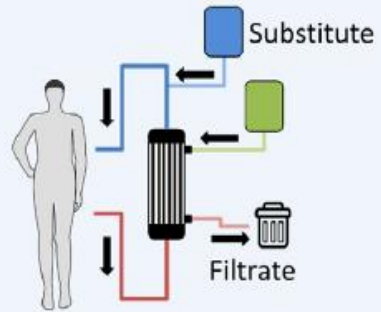
Plasma Exchange

RCTs

RCTs

Molecular Adsorbent Recirculating System: MARS®

Extracorporeal Blood Purification Techniques



Convection Therapies

High Cut-Off Membranes (HCO)

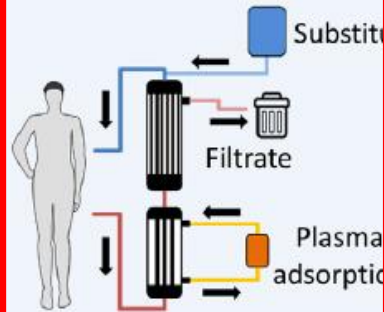
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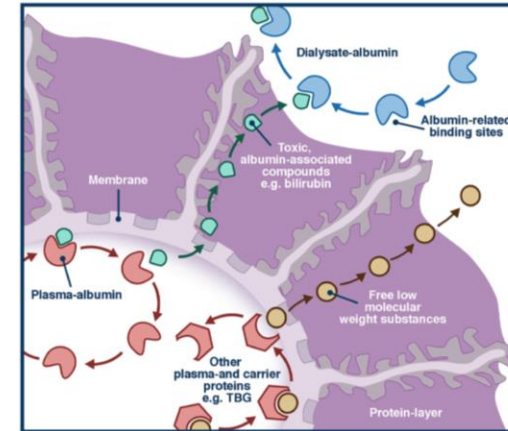


Combination Therapies

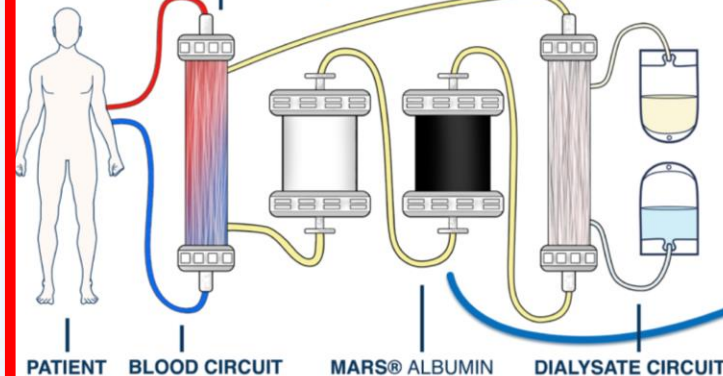
Combined filtration and Adsorption (e.g. oXiris®)

Coupled Plasma Filtration Adsorption (CPFA)

RC's



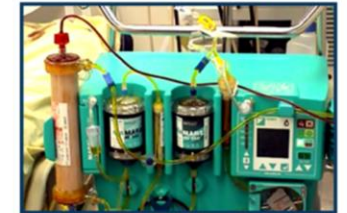
MARS® FLUX DIALYZER diaMARS® ADSORPTION COLUMNS MARS® FLUX DIALYZER



Start of treatment



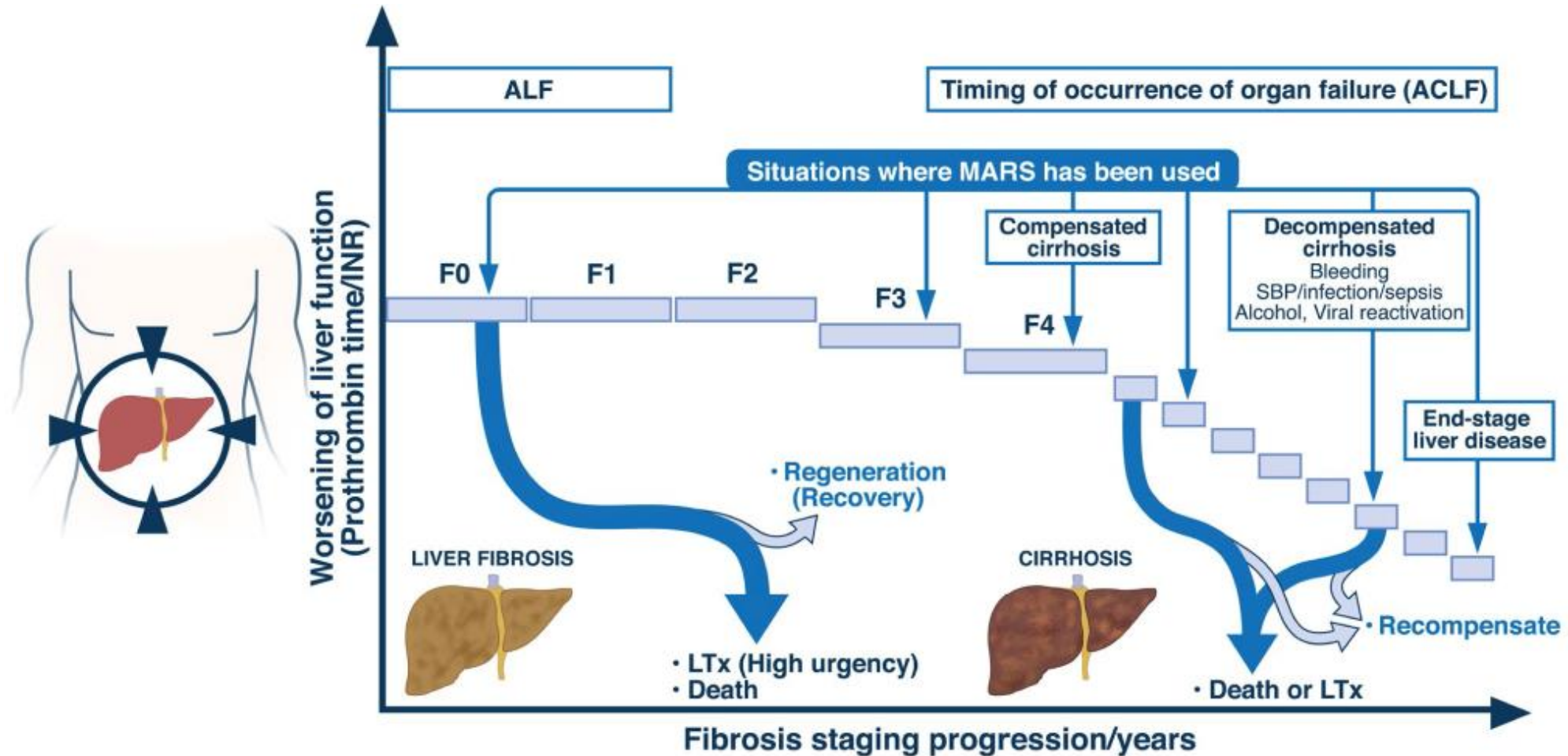
End of treatment



Toxic substances removed by MARS

- Bilirubin total and conjugated
- Bile acids
- Aromatic amino-acids
- Ammonia, Tryptophan, Thiols
- Short and medium chain fatty acids
- Indol/Phenol metabolites
- Paracetamol, Prostacyclines
- Urea, Creatinine, Lactate
- Copper, Digoxine, Nitric Oxide
- Benzodiazepines
- TFN-alpha, Cytokines

Molecular Adsorbent Recirculating System: MARS®



MARS® therapy leads to improved outcomes in several RCTs

First author, year	Design	Indication	No. of patients	Main results
Mitzner, 2000 [41]	RCTs	ACLF—HRS	13	Survival improvement at 28 days Increase urine output. Decrease creatinine levels Removal of albumin bound and water-soluble substances
Heemann, 2002 [40]	RCTs	ACLF—severe cholestasis	24	Survival improvement at 28 days Improvement of HE, hemodynamics, renal function, and reduction of bilirubin
Schmidt, 2003 [97]	RCTs	ALF	13	Improvement of systemic hemodynamics Reduction of MAP and SVRI Reduction of Cardiac Index and heart rate
Sen, 2004 [27]	RCTs	ACLF	18	Significant improvement of HE Significant decrease of NOx levels
Novelli, 2005 [98]	Retrospective	ALF, ACLF, PNF, PDF	116	Significant decrease of bilirubin, ammonia, lactates and creatinine Significant improvement of Glasgow coma scale
Laleman, 2006 [29]	RCTs	ACLF	18	MARS™ significantly attenuates the hyperdynamic circulation in ACLF Significantly reduces SVRI and MAP, associated to a decrease of NOx levels
Hassanein, 2007 [39]	RCTs	ACLF—HE	70	Significant improvement of 2 grades of HE Significant faster improvement of HE Not designed to assess survival improvement
El Banayosy, 2007 [9]	RCTs	ALF due to cardiogenic shock	40	Trend to higher survival at 28 days ($p < 0.061$) in the MARS treated group
Kantola, 2008 [22]	Comparative retrospective	ALF	159	No statistically significant difference in survival between the MARS™ and the control group patients at 28 days Trend to higher 6-months survival in the MARS™ group ($p = 0.07$) and in transplanted patients ($p = 0.06$) Survival without LTx was significantly higher in the MARS™ group ($p = 0.03$)
Parés, 2010 [53]	Pilot	Refractory pruritus in cholestatic liver	20	Important decrease in pruritus in 75% of the patients (72% in the VAS) Significant bile acids reduction (41% after treatment and 37% after 1 month)
Leckie, 2012 [54]	Pilot	Refractory pruritus in cholestatic liver diseases	15	Immediate and complete response in 11 patients (73.3%), partial response in 2 and no response in 2 patients Mean VAS and itchiness score improved significantly (both $p < 0.001$) with improvement in the patient's perception of their quality of life Duration of acceptable relief in responders was 3.3 months (range 2–5)
Saliba, 2013 [19]	RCTs	ALF	102	No significant improvement in 6- and 12-months survival Significant improvement of transplant free survival in patients that received ≥ 3 MARS™ sessions Significant improvement in the probability to be transplanted
Banares, 2013 [38]	RCTs	ACLF	187	No significant improvement in 28- and 90-days survival Significant decrease of bilirubin and creatinine levels Short term beneficial effects in hepatic encephalopathy and HRS
Gerth, 2017 [100]	Comparative Non-randomized	ACLF	101	Significant reduction of 14-days mortality rate in the MARS™ group ($p = 0.004$), especially in patients with ACLF grades 2 and 3) Significant decrease of bilirubin and creatinine
Banares, 2019 [32]	Meta-analysis of individual patient data from 3 RCTs	ACLF	285	Significant survival improvement in patients receiving HIT both in the entire cohort (10-day survival: 98.6% vs. 82.8%, $p = 0.001$; 30-day survival: 73.9% vs. 64.3%, $p = 0.032$), and within the ACLF patients (10-day survival: 97.8% vs. 78.6%, $p = 0.001$; 30-day survival: 73.3% vs. 58.5%, $p = 0.041$) HIT increased survival independently of ACLF grade Independent predictors of survival were age, MELD score, ACLF grade, number of MARS™ sessions received and intensity of MARS™ therapy
MacDonald, 2021 [25]	Propensity-score matched controls 1:4	ALF	520	Significant 21-day transplant-free survival improvement in patients receiving MARS™. Significant improvement (pre vs. post MARS™) in mean arterial pressure, creatinine, lactate, and ammonia for all. In non-acetaminophen ALF ($n = 53$), MARS™ significantly improved bilirubin, creatinine and ammonia

↑ survival

↑ survival

↑ HE

↑ hemodynamics

↑ survival

↑ renal failure

↑ survival

↑ HE and HRS

↑ survival

MARS® therapy leads to improved outcomes in several RCTs

Meta-analysis of individual patient data of albumin dialysis in acute-on-chronic liver failure: focus on treatment intensity

Rafael Bañares, Luis Ibáñez-Samaniego ^{ID}, Josep María Torner, Marco Pavesi, Carmen Olmedo, María Vega Catalina, Agustín Albillos, Fin Stolze Larsen, Frederik Nevens, Tarek Hassanein, Harmuth Schmidt, Uwe Heeman, Rajiv Jalan, Richard Moreau and Vicente Arroyo

- 285 patients with 165 ACLF
- Day 30 survival > group « **INTENSE THERAPY** »
- **Nb of MARS®** sessions = **survival benefit**
- HR 0,9 CI 95% 0,83-0,98

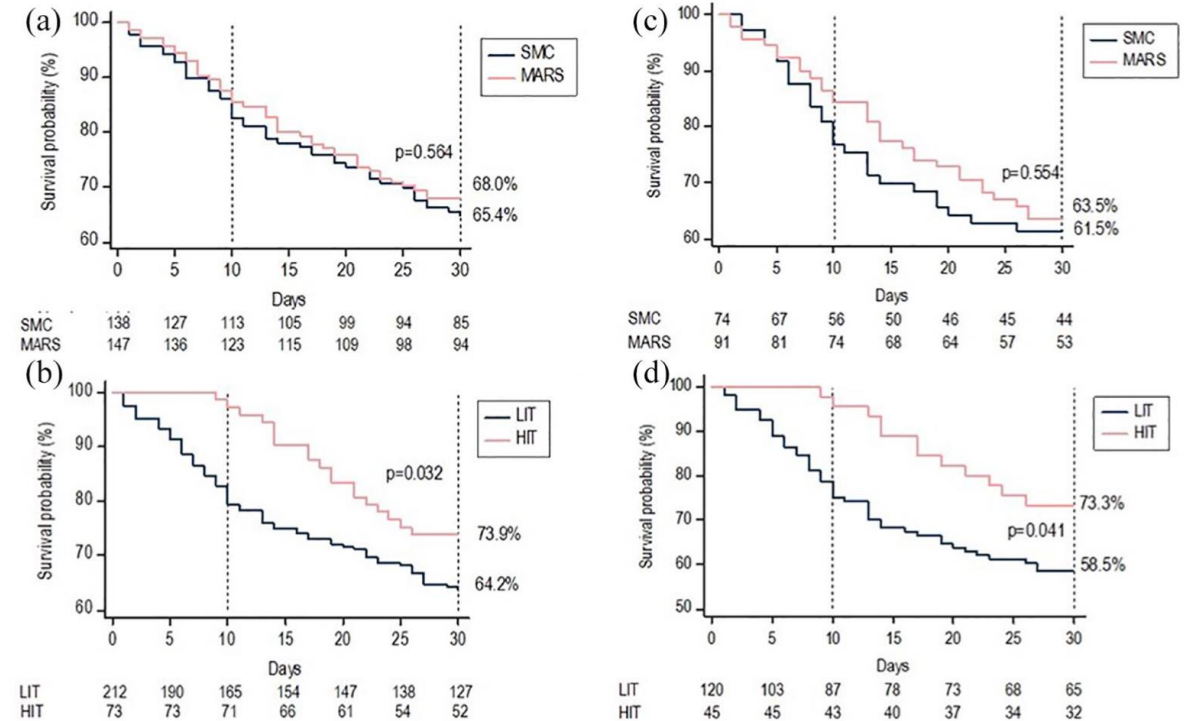


Figure 2. (a) 30-day survival according to allocation to SMC or MARS. (b) 30-day survival according to allocation to LIT or HIT. (c) 30-day survival according to allocation to MARS-SMC or SMC in ACLF patients. (d) 30-day survival according to allocation to LIT or HIT in ACLF patients.

Lower intensity **MARS®** therapy ≤ 4 MARS
 High intensity **MARS®** therapy > 4 MARS

MARS® therapy leads to improved outcomes in several RCTs

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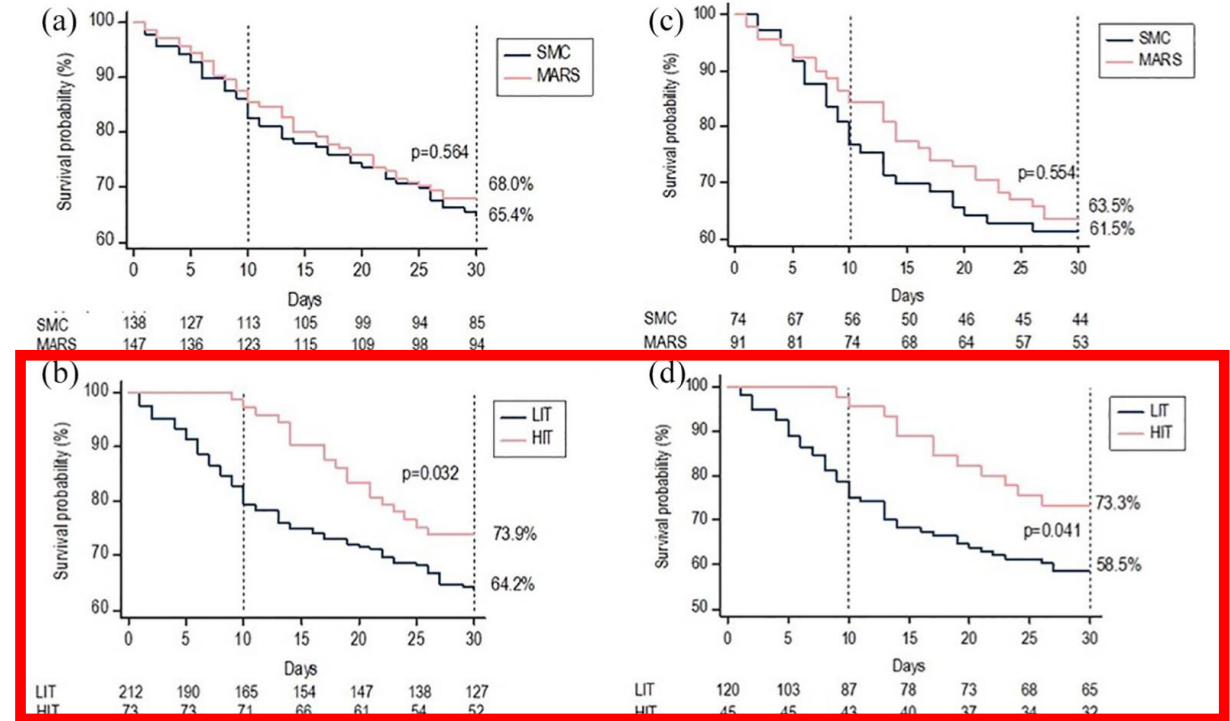
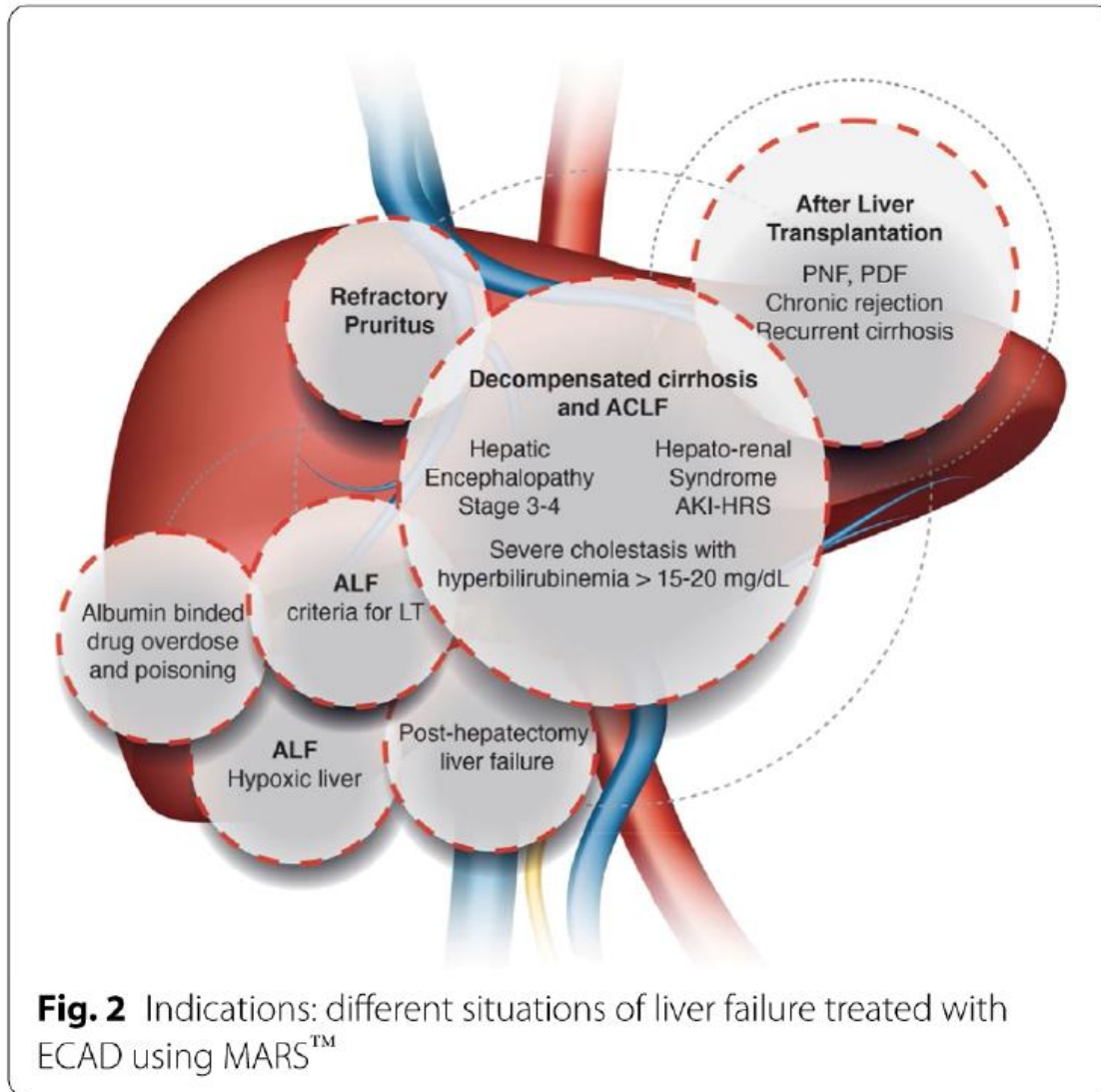


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MARS® therapy in ALF and ACLF: what do the guidelines tell us ?



early ALF (acetaminophen +++)



ALF with HE (II-III)



bridge to transplant



early ACLF with refractory HE



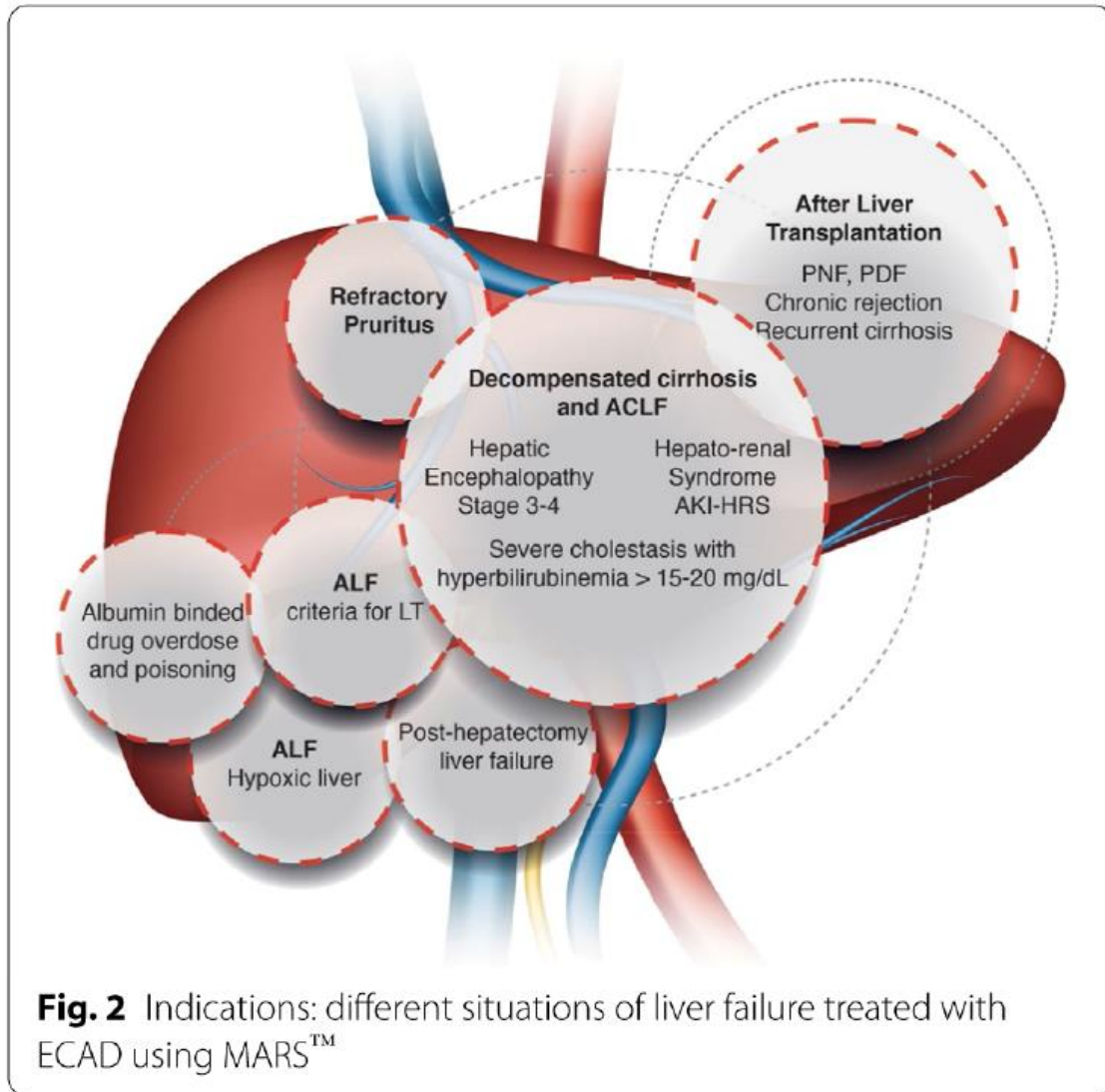
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bridge to transplant



MARS® therapy in ALF and ACLF: what do the guidelines tell us ?



early ALF (acetaminophen +++)



ALF with HE (II-III)



bridge to transplant



early ACLF with refractory HE



early ACLF with refractory HRS



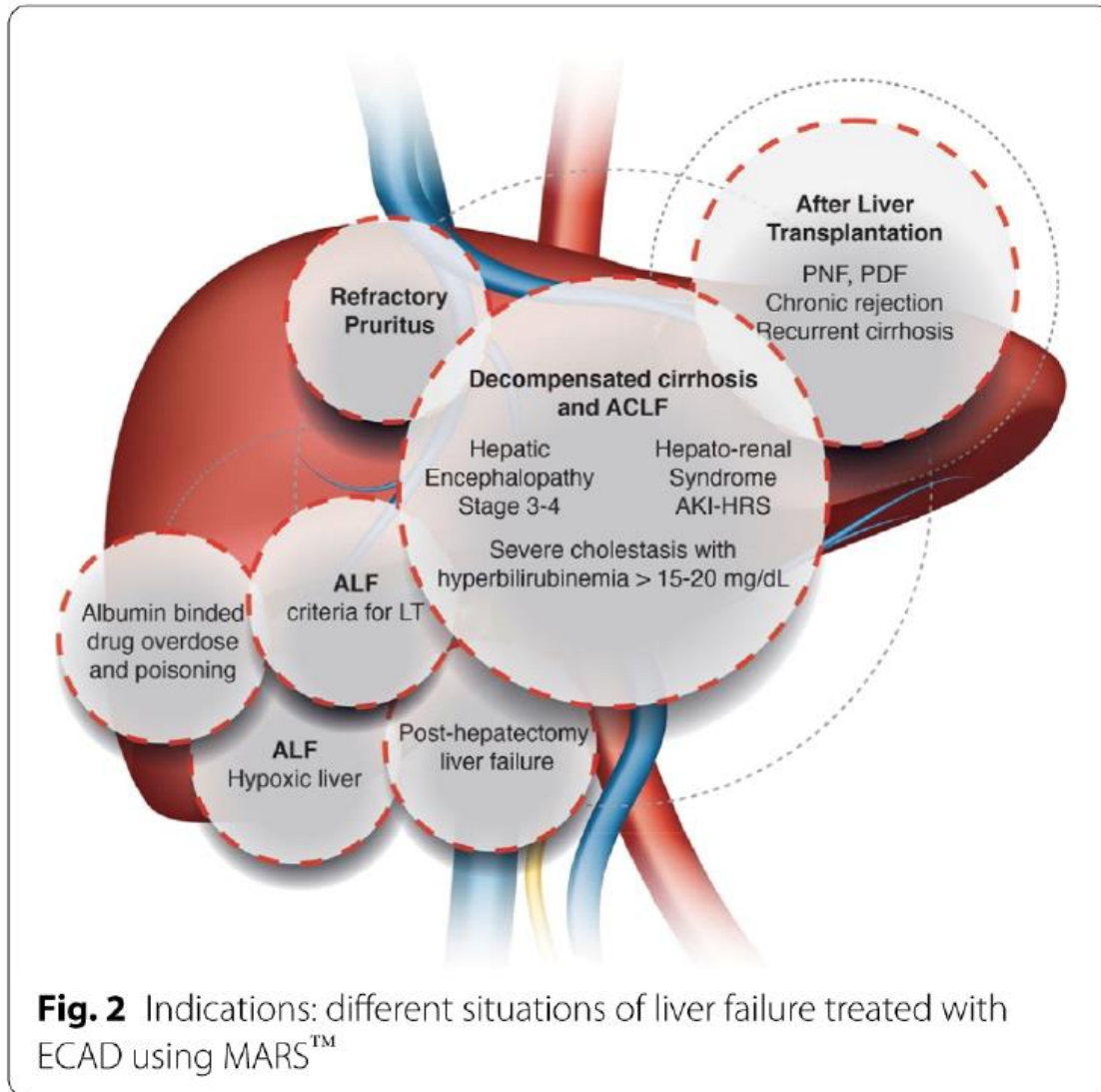
bridge to transplant



- **6-8 hours session +++**
- **5 sessions in 7-10 days**
- **3 first sessions: D1-D2-D3**

↳ **Early and intensive MARS® Therapy**

MARS® therapy in ALF and ACLF: what do the guidelines tell us ?



early ALF (acetaminophen +++)



ALF with HE (II-III)



bridge to transplant



early ACLF with refractory HE



early ACLF with refractory HRS



bridge to transplant



ALF with multiple organ failures



uncontrolled sepsis or septic shock



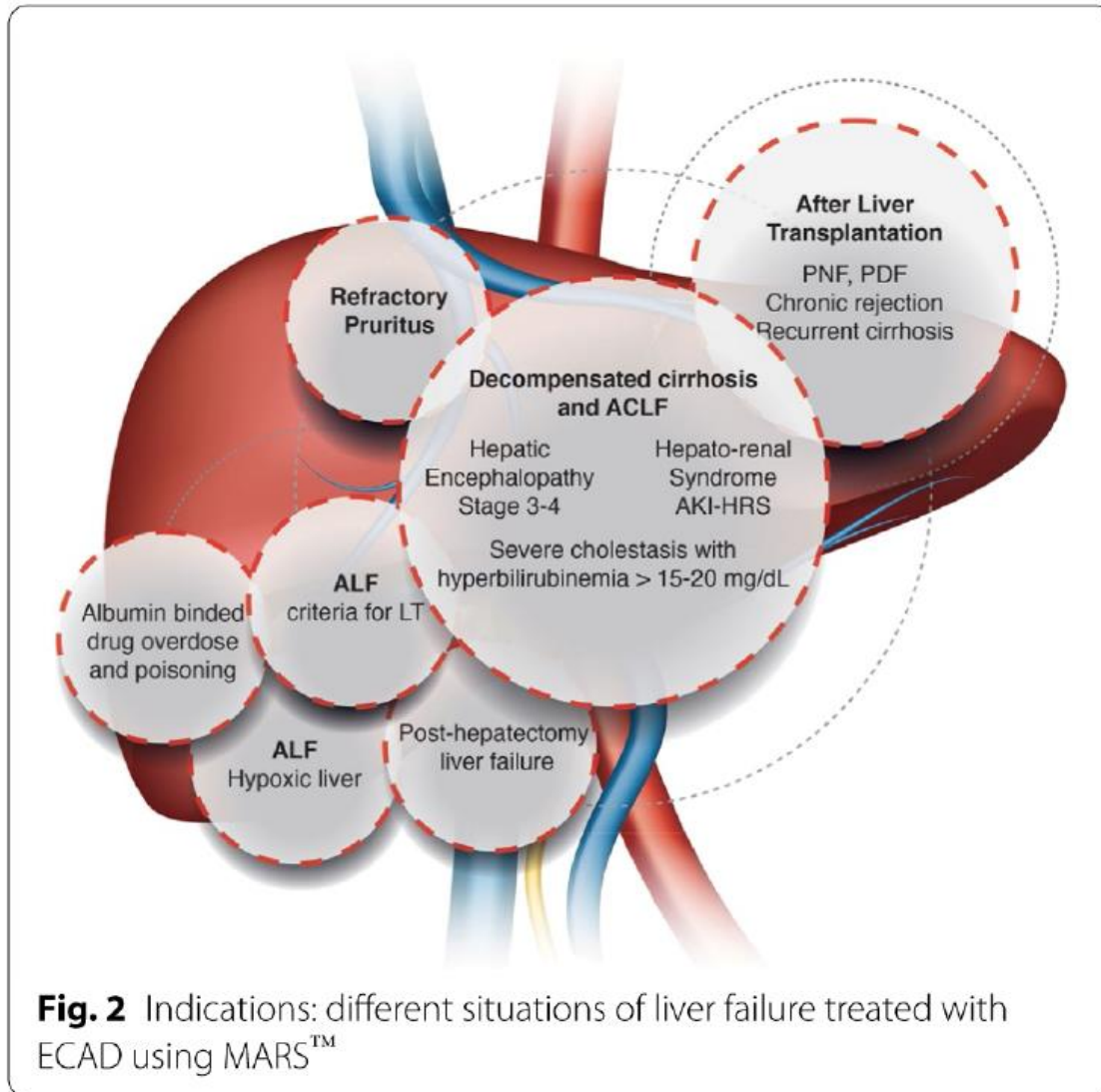
ARDS



ACLF – OF grade > III



MARS® therapy in ALF and ACLF: what do the guidelines tell us ?



early ALF (acetaminophen +++)



ALF with HE (II-III)



bridge to transplant



early ACLF with refractory HE



early ACLF with refractory HRS



bridge to transplant



Platelets < 40 000 / mm³

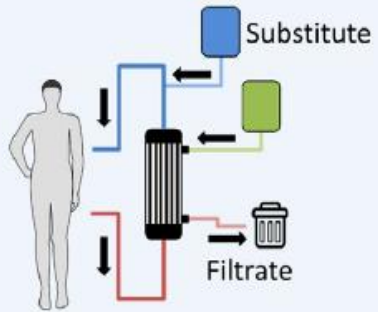
INR > 2.5

FN < 1g/L



Extracorporeal Artificial Liver Support: let's talk about techniques

Extracorporeal Blood Purification Techniques



Convection Therapies

High Cut-Off Membranes (HCO)

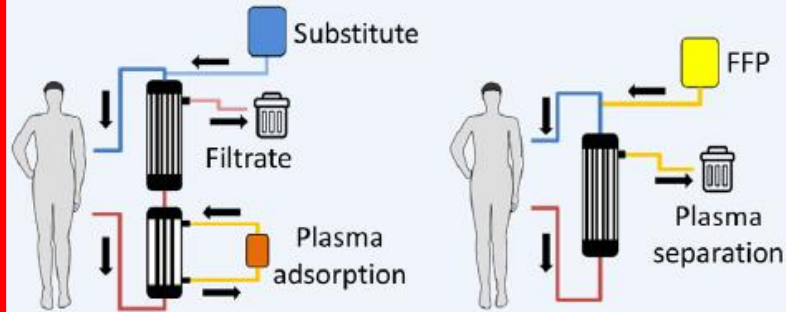
High Volume Hemofiltration (HVHF)



Adsorption Therapies

Specific Adsorption
Polymyxin B (PMX)
LPS Adsorber

Unspecific Adsorption
Hemoadsorption
(e.g. CytoSorb®)



Combination Therapies

Combined filtration and Adsorption
(e.g. oXiris®)

Coupled Plasma Filtration Adsorption (CPFA)

Other Therapies

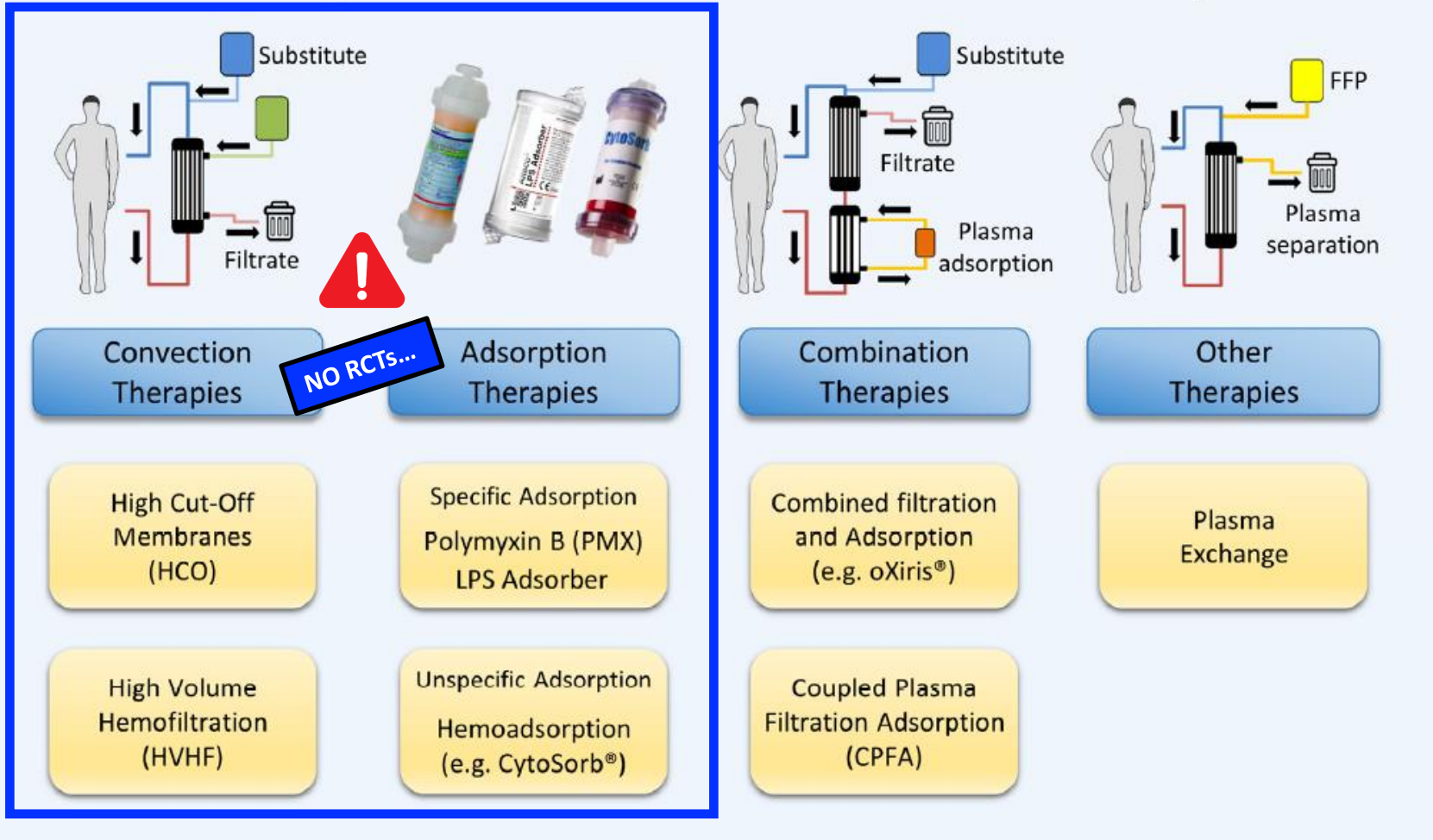
Plasma Exchange

RCTs

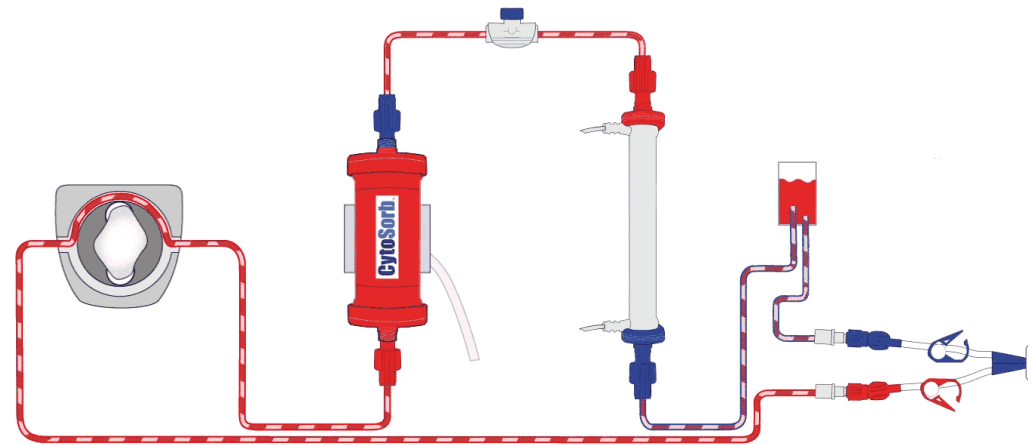
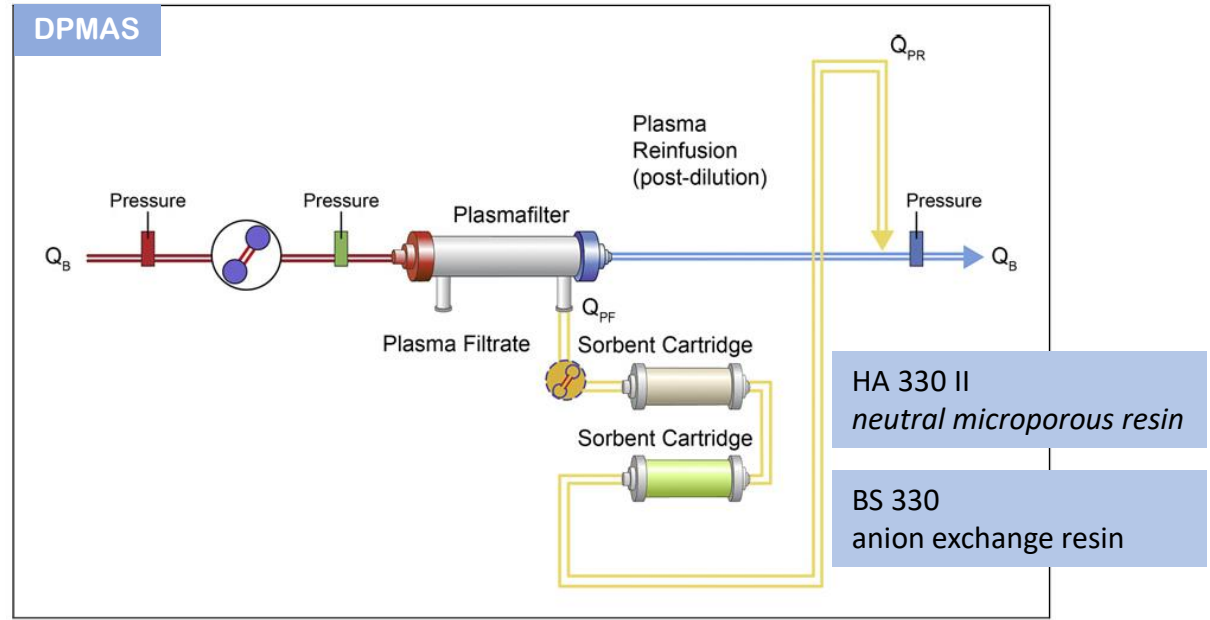
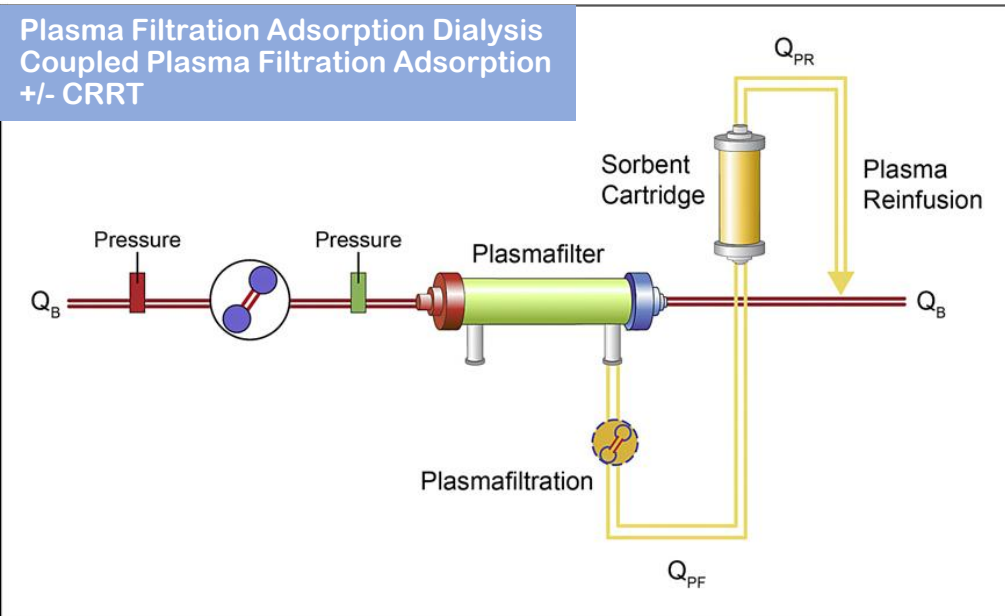
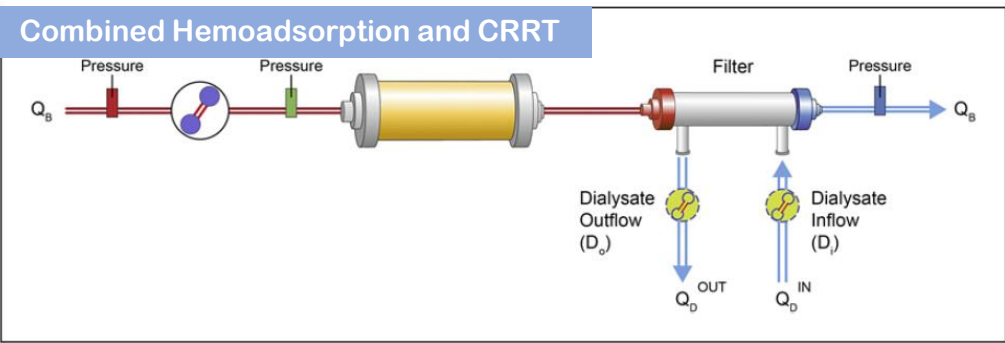
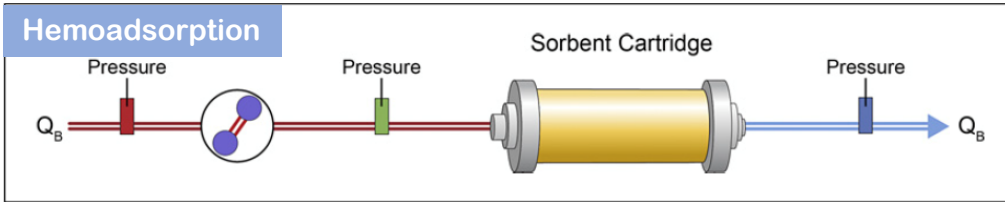
RCTs

Extracorporeal Artificial Liver Support: let's talk about techniques

Extracorporeal Blood Purification Techniques

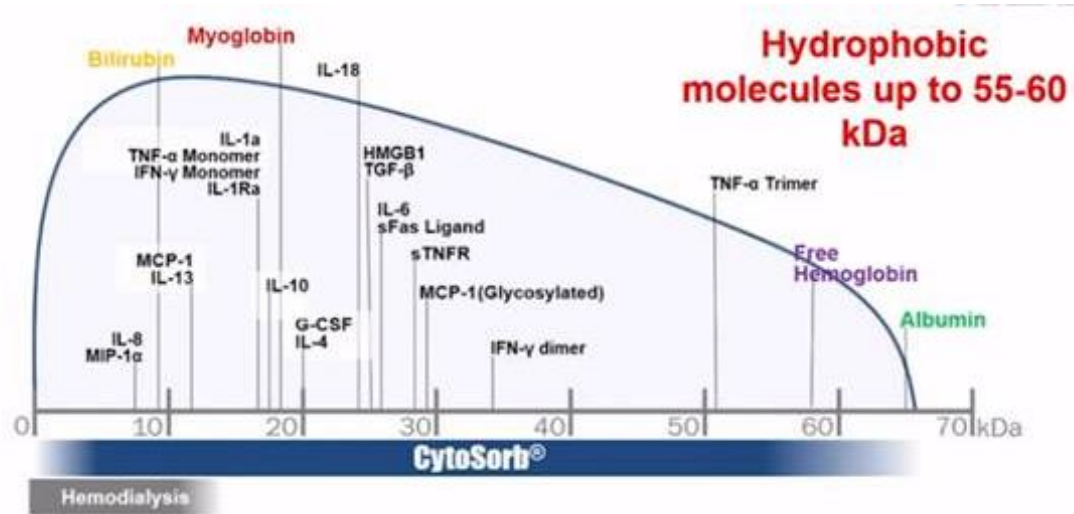


Hemoadsorption

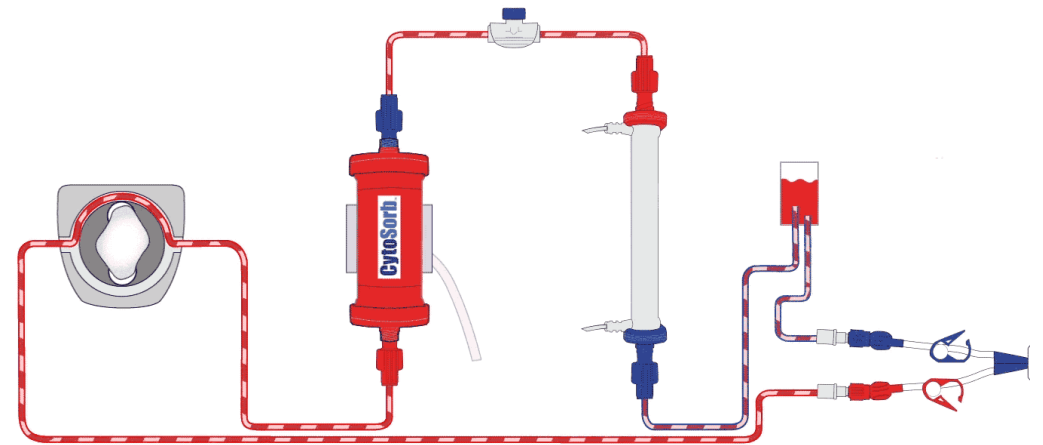
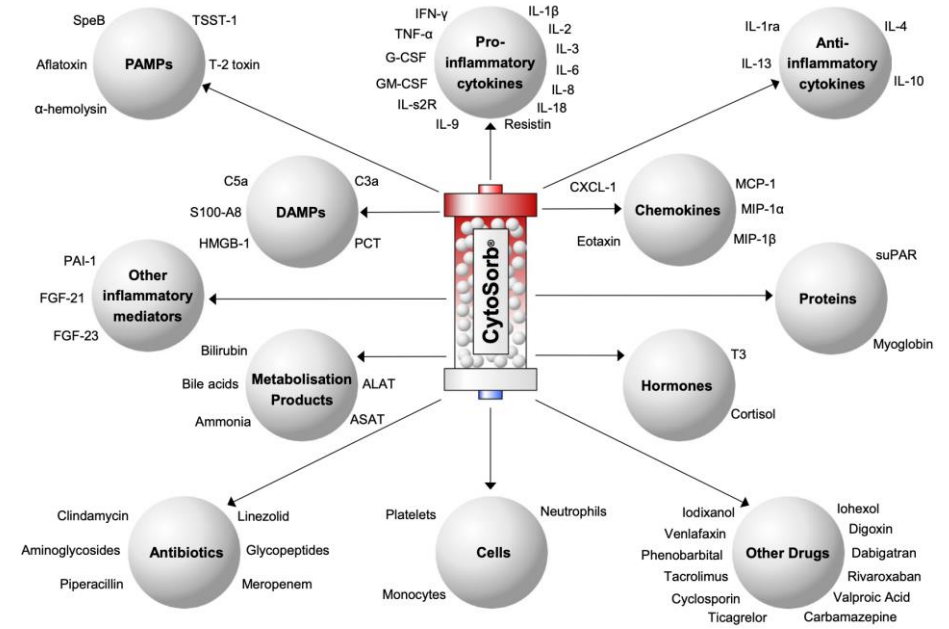


CYTOSORB®

Hémo-adsorption



Biocompatible porous polymer microbeads
 Adsorption in pores and surface adsorption
 Surface membrane about 45.000 m²

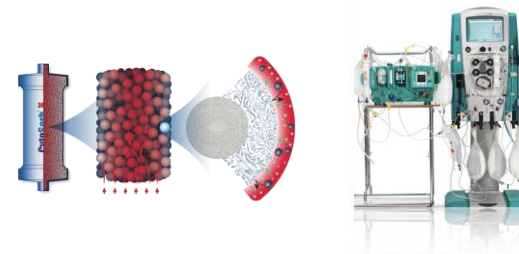


Hémo-adsorption: biological efficacy

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

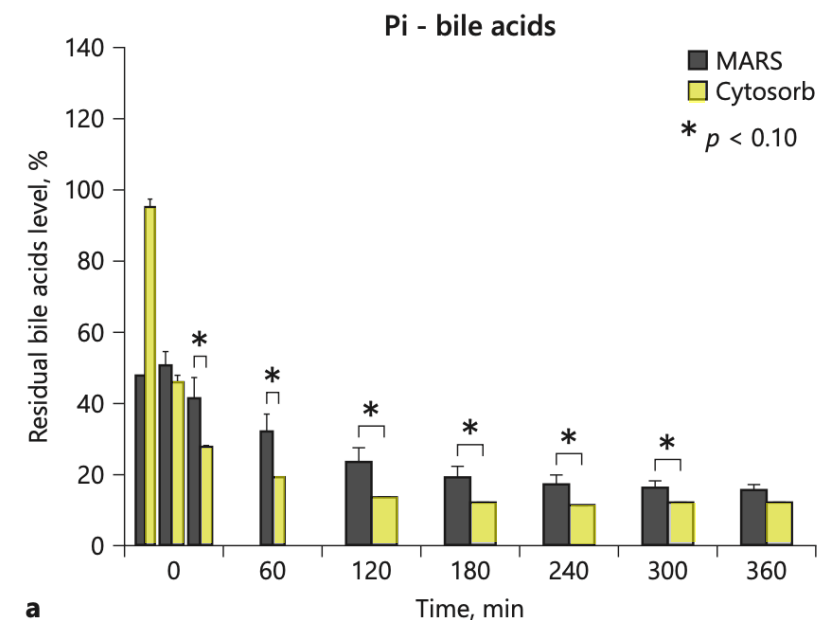
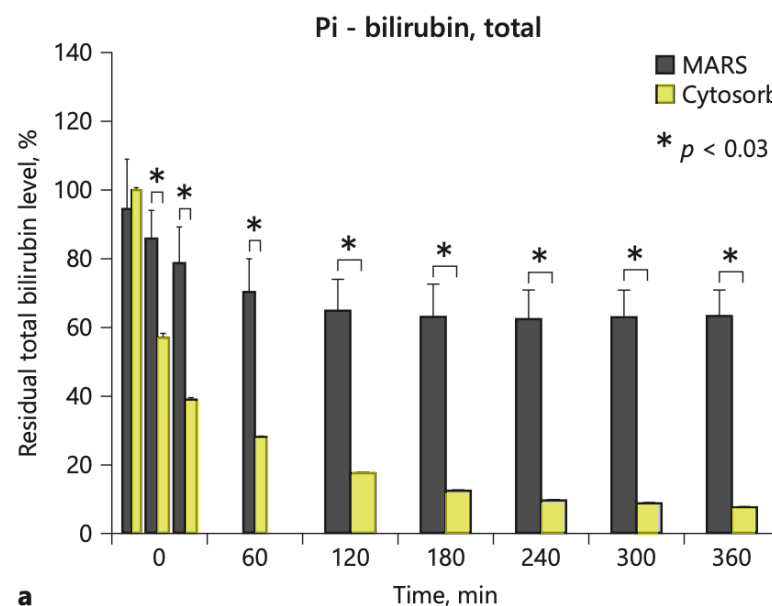
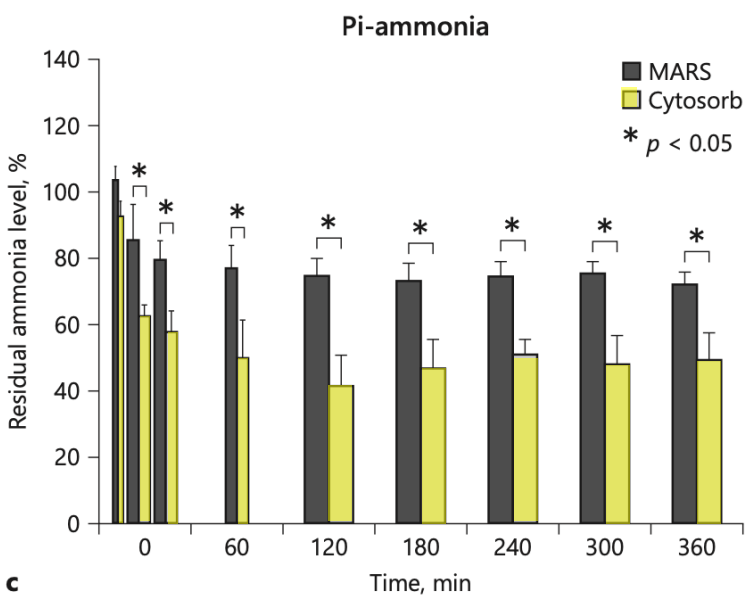
Adrian Dominik Jan Stanca

Blood Purif 2021;50:119–128



In Vitro

→ **CYTOSORB**® > **MARS**® for bilirubin and ammonia clearance

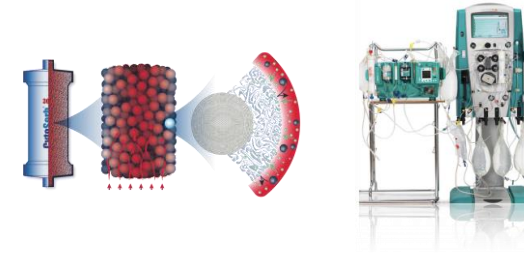


Hémo-adsorption: biological efficacy

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

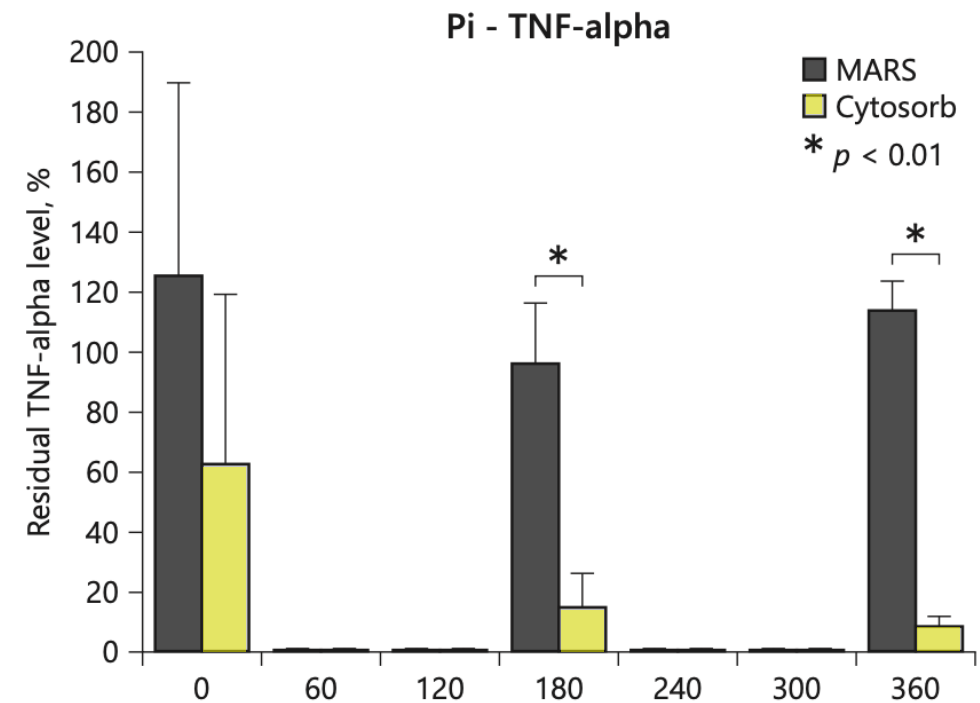
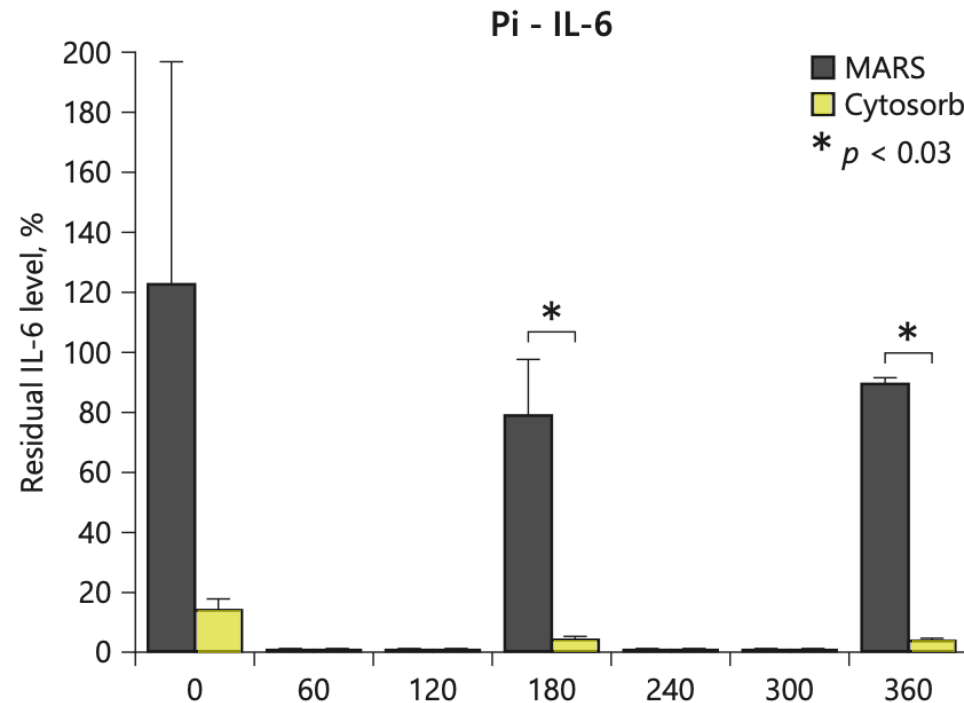
Adrian Dominik Jan Stanca

Blood Purif 2021;50:119–128

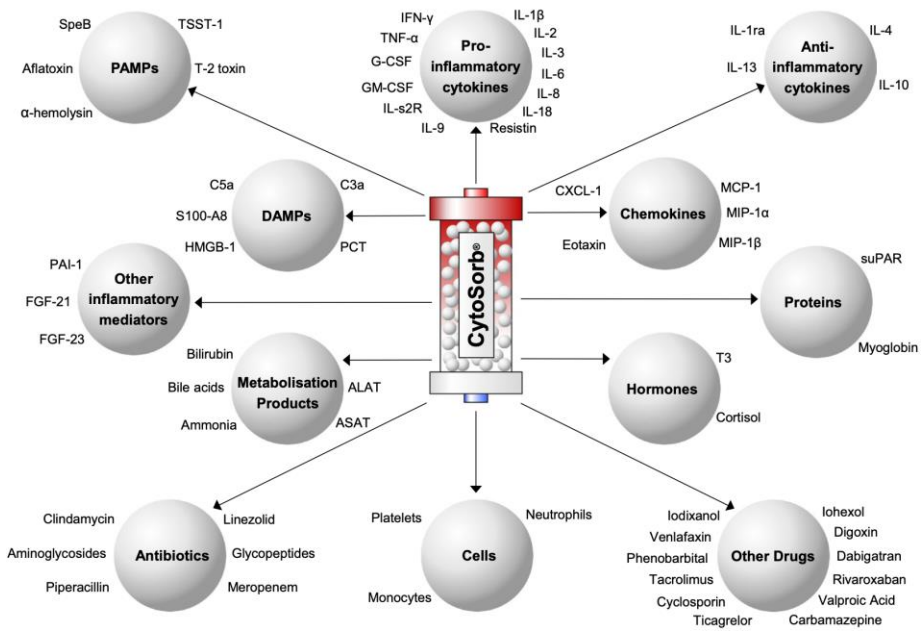


In Vitro

→ **CYTOSORB**® >>> **MARS**® for IL-6 and TNF- α clearance

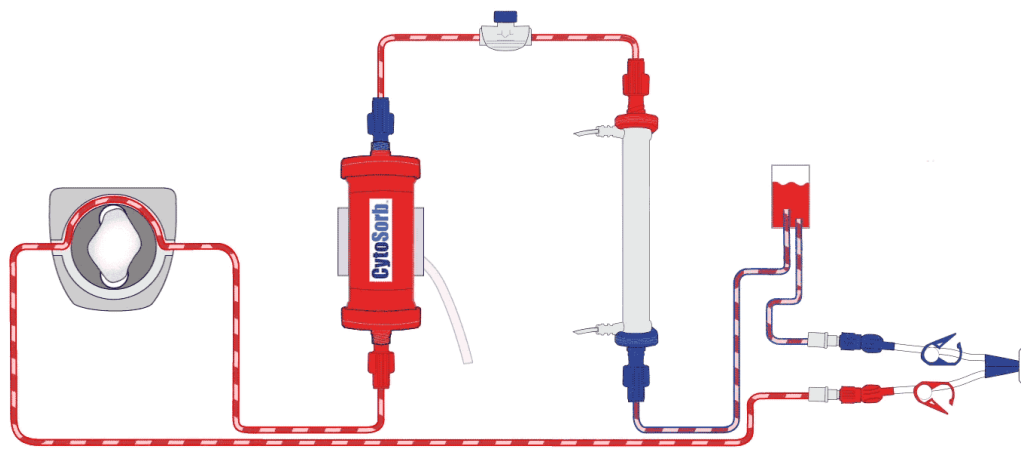


Hémo-adsorption: clinical efficacy ?

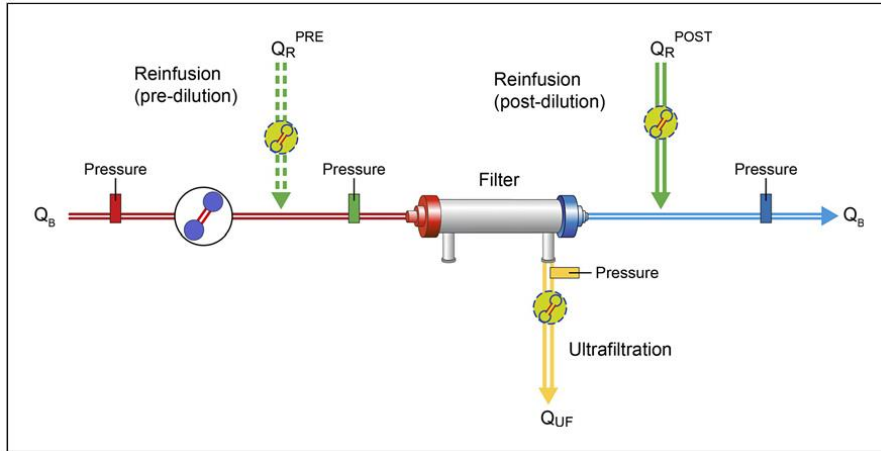


We do not know yet...

No RCTs



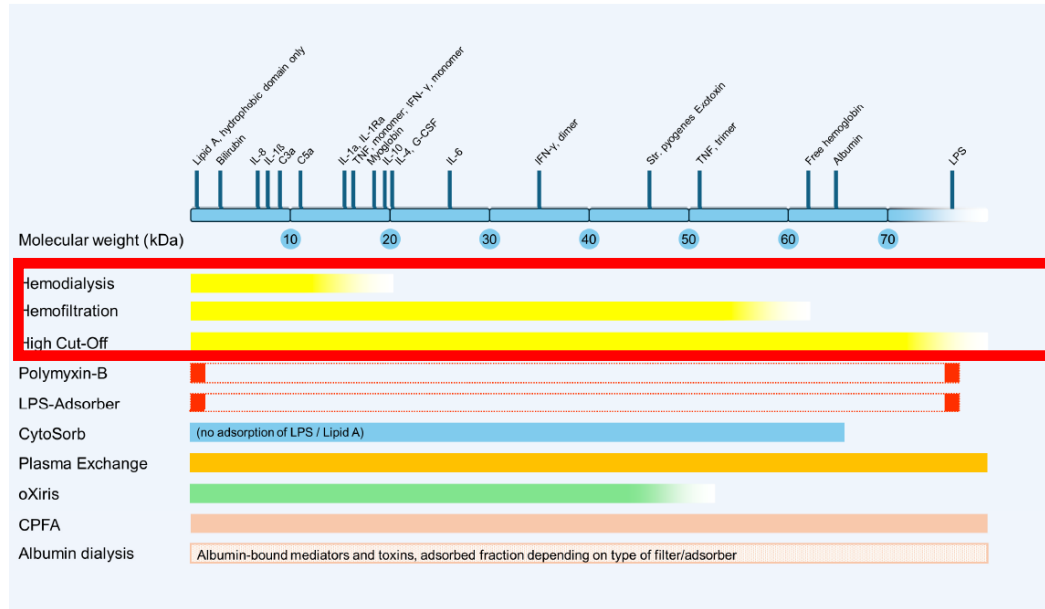
Continuous Renal Replacement Therapy



High Volume
 $> 35 \text{ mL/kg/h}$

Very High Volume
 $> 45 \text{ mL/kg/h}$

High cut-off membrane
 Pores size 20 nm (*versus* 10nm)
 Standard Volume CRRT - 25 – 35 mL/kg/h



↑ clearance of higher MW molecules with HV and HCO membranes but only for water-soluble molecules (cytokines), and still not for albumin-bound toxins...

High Volume CRRT + Albumin dialysis device

CRRT and ammonia clearance

Characteristics and outcomes of patients with acute liver failure admitted to Australian and New Zealand intensive care units

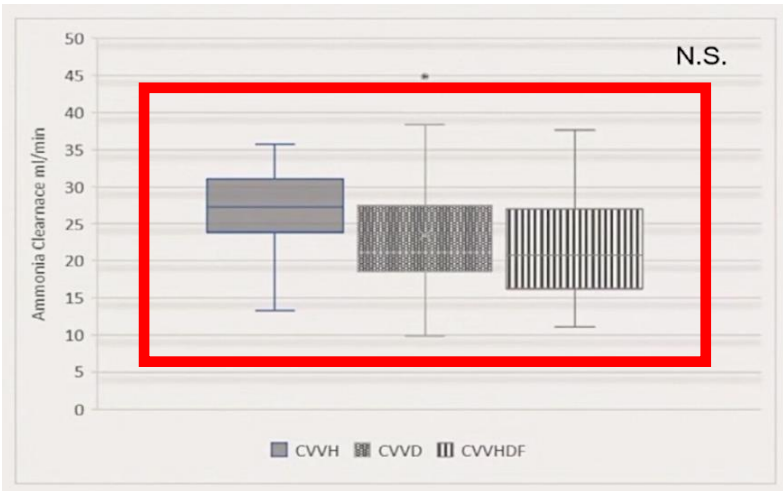
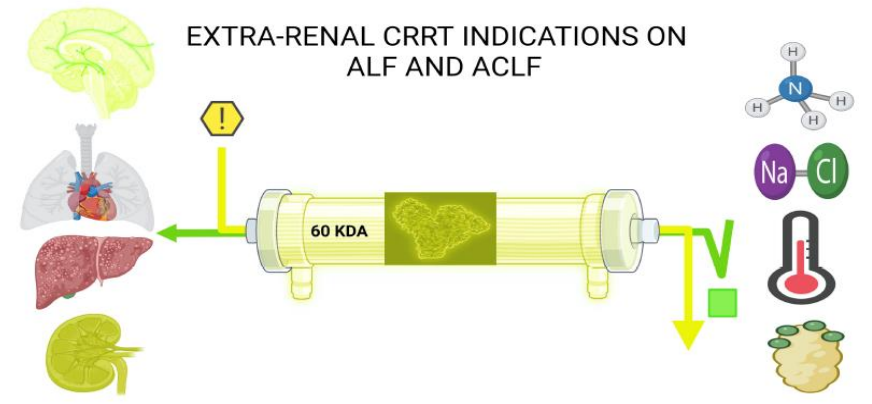
Stephen Warrillow ✉, Michael Bailey, David Pilcher, Alex Kazemi, Colin McArthur, Paul Young, Rinaldo Bellomo,

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

Stephen Warrillow ^{1 2 3}, Caleb Fisher ¹, Rinaldo Bellomo ^{1 3 4 5}

Affiliations + expand
 PMID: 31939790 DOI: 10.1097/CCM.0000000000004153

- Australia, New Zealand
- 723 patients with ALF
- **EARLY and INTENSE CRRT decreases Ammonia levels**
- CVVHF=CVVHD=CVVHDF



↓ ammonia levels
20 mL /min

Details of CRRT Management	Characteristic	Patients (n = 54)
Timing of CRRT, hr, median (IQR)	Time from admission to CRRT	4.0 (2.0–4.5)
	Cumulative duration of CRRT ^a	75 (57–78)
CRRT dosing, mL/kg/hr, median (IQR)	CRRT hourly rate	43 (37–61)

Conclusion (1)

Bayesian Network Meta-analyses identified MARS and PE as best strategy in ALF and ACLF

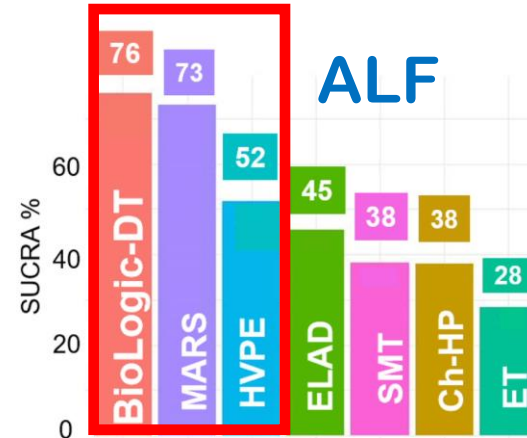
scientific reports

OPEN

Efficacy and safety of liver support devices in acute and hyperacute liver failure: a systematic review and network meta-analysis

Anna Kanjo^{1,2,3}, Klementina Ocskay¹, Noémi Gede¹, Szabolcs Kiss^{1,3}, Zsolt Szakács^{1,4}, Andrea Pámiczky^{1,2,3}, Steffen Mitzner⁵, Jan Stange⁵, Péter Hegyi^{1,3,4} & Zsolt Molnár^{1,3,6}

Check for updates



REVIEW

Open Access

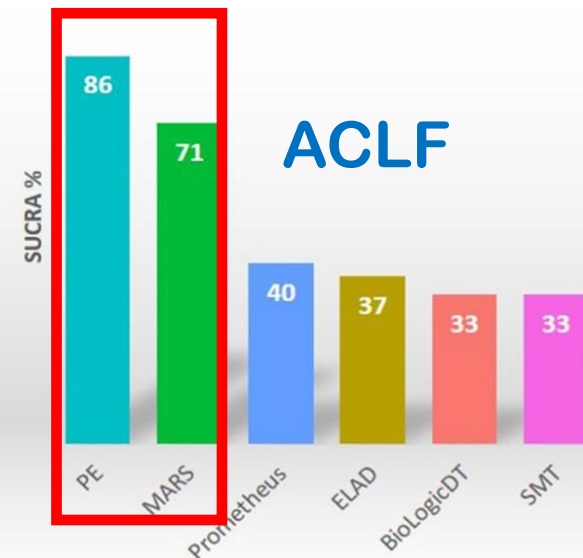
Uncertainty in the impact of liver support systems in acute-on-chronic liver failure: a systematic review and network meta-analysis

Klementina Ocskay¹, Anna Kanjo^{1,2}, Noémi Gede^{1,3}, Zsolt Szakács¹, Gabriella Pár⁴, Bálint Eröss¹, Jan Stange⁵, Steffen Mitzner⁵, Péter Hegyi^{1,6,7} and Zsolt Molnár^{1,8*}

Check for updates

Ocskay et al. *Ann. Intensive Care* (2021) 11:10
<https://doi.org/10.1186/s13613-020-00795-0>

Annals of Intensive Care



Conclusion (2)

Extracorporeal Artificial Liver Support in ALF and ACLF: WHEN ? For WHOM ?

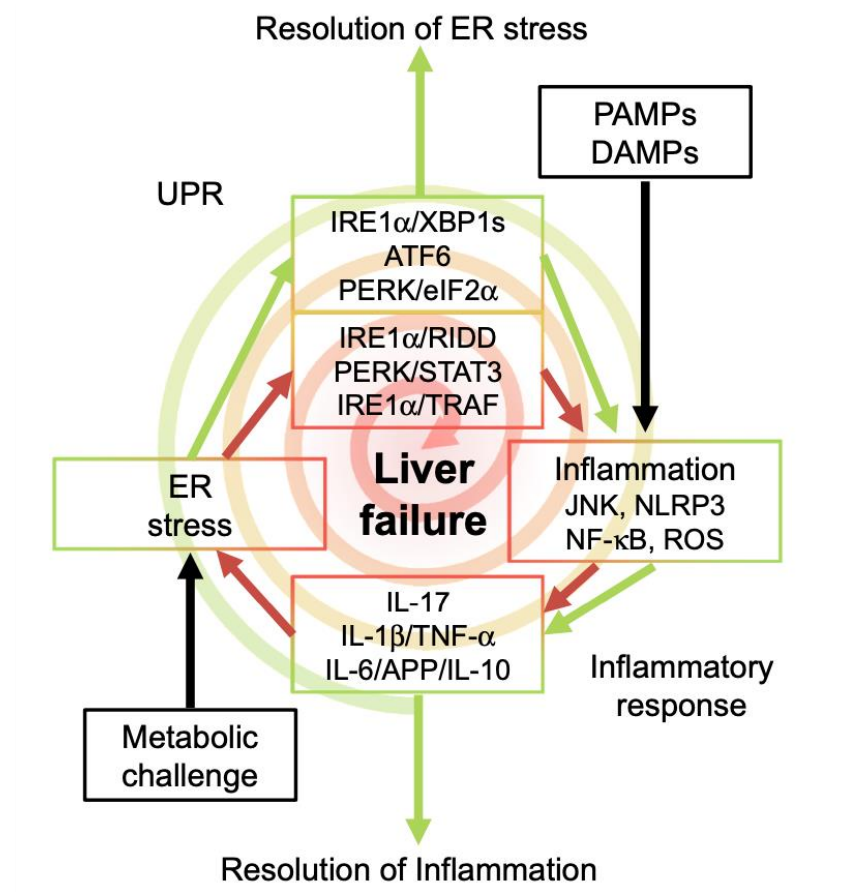


Plasma Exchanges



MARS / SPAD / Prometheus®

- Early course
- Intensively
- Before refractory multiple organ failure
- Bridge to (potential) transplantation
- Bridge to decision
- New studies are eagerly awaited and needed.



ECOS-TCS

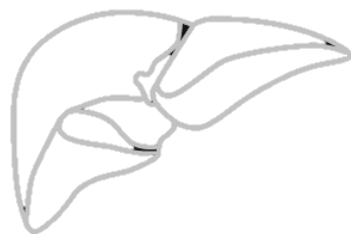
INTERNATIONAL CONGRESS

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Thank you for your attention.
Any questions ?

Pr Antoine Monsel

Réanimation Chirurgicale Hépato-Digestive Polyvalente
Département d'Anesthésie Réanimation Pitié-Salpêtrière



AP-HP.Sorbonne Université



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