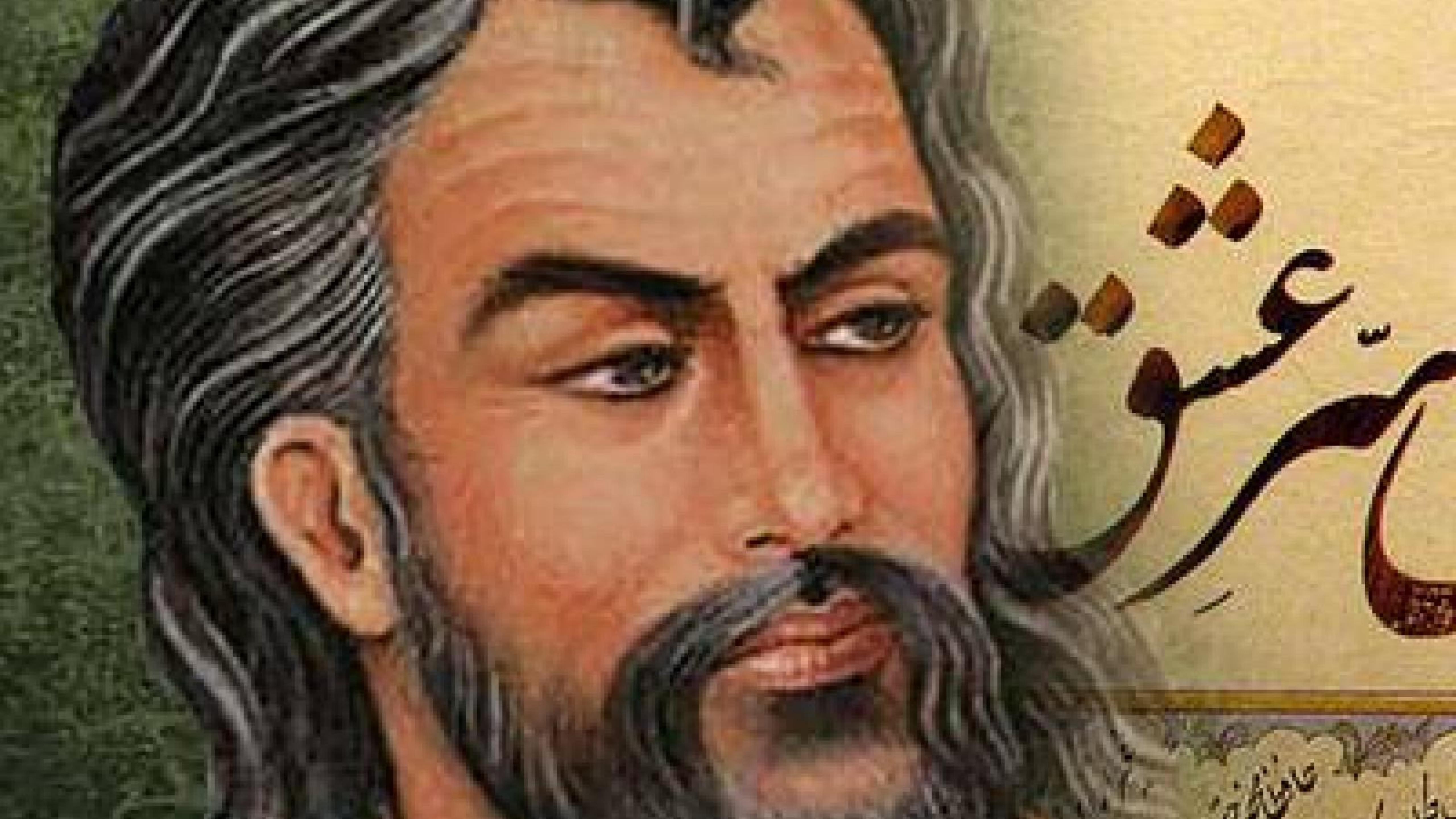
Advancing Renal Care
The role of Hemoadsorption in enhancing outcomes for kidney diseases in ICU

Amir A. Nassiri, MD, DIU
Zanjan
2024



دوش دیدم که ملایک در میخانه زدند

گل آدم بسرشتند و به پیمانه زدند

ساکنان حرم ستر و عفاف ملکوت

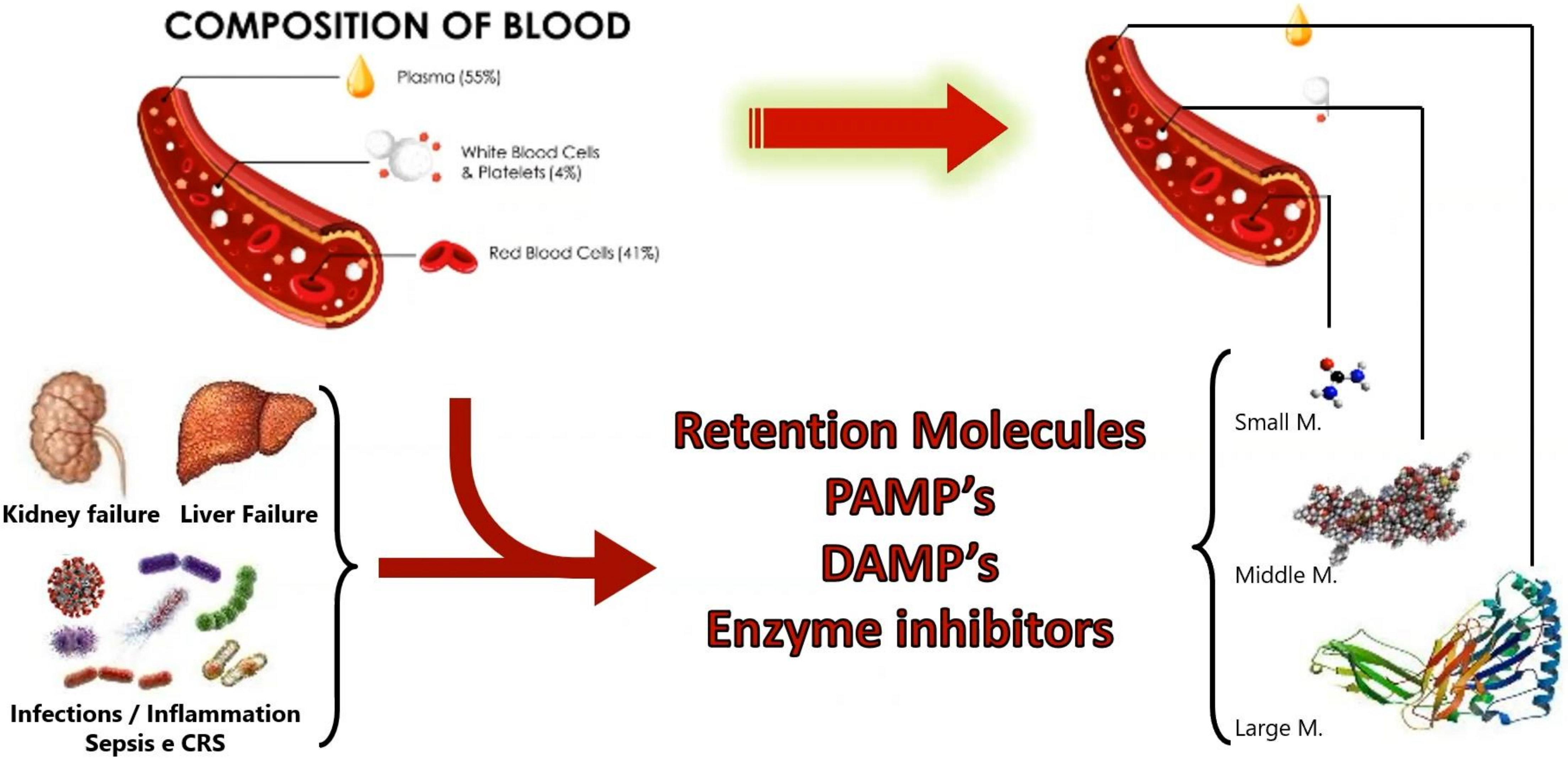
با من راه نشین باده مستانه زدند


Happy
Daughter's
Day

Disclosure Statement

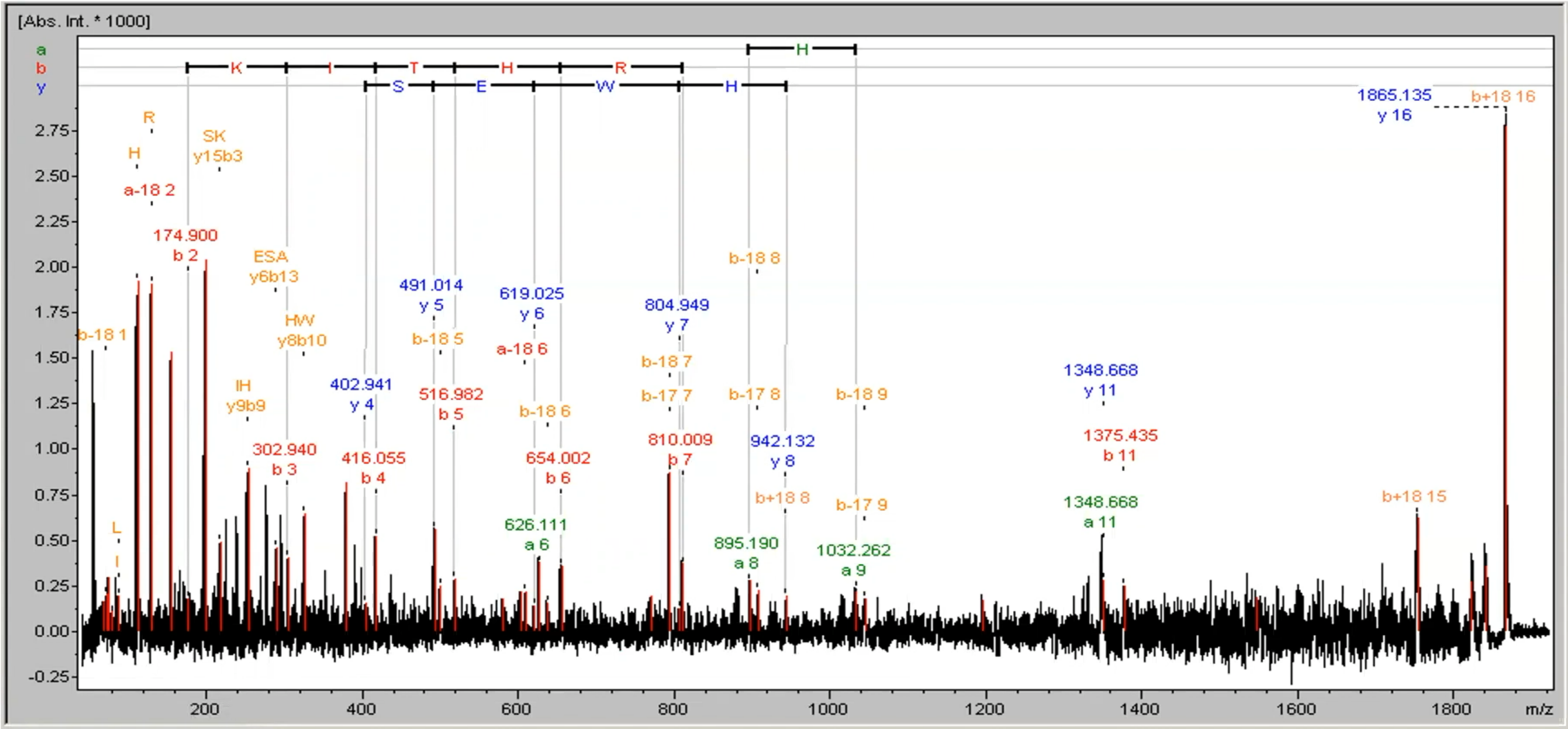
I have no financial disclosure or conflict of interest with this presentation

Acute Organ Failure



Uraemia Retention Molecule Profile

Proteomic assessment



CJASN ePress. Published on October 4, 2021 as doi: 10.2215/CJN.02660221

Classification of Uremic Toxins and Their Role in Kidney Failure

Clin J Am Soc Nephrol. 2021 Jul 7;16(12):1918–28. doi: 10.2215/CJN.02660221. Epub ahead of print. PMID: 34233920; PMCID: PMC8729494.

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Abstract

Advances in our understanding of uremic retention solutes, and improvements in hemodialysis membranes and other techniques designed to remove uremic retention solutes, offer opportunities to readdress the definition and classification of uremic toxins. A consensus conference was held to develop recommendations for an updated definition and classification scheme on the basis of a holistic approach that incorporates physicochemical characteristics and dialytic removal patterns of uremic retention solutes and their linkage to clinical symptoms and outcomes. The major focus is on the removal of uremic retention solutes by hemodialysis. The identification of representative biomarkers for different classes of uremic retention solutes and their correlation to clinical symptoms and outcomes may facilitate personalized and targeted dialysis prescriptions to improve quality of life, morbidity, and mortality. Recommendations for areas of future research were also formulated, aimed at improving understanding of uremic solutes and improving outcomes in patients with CKD.

CJASN 16: ●●●–●●●, 2021. doi: https://doi.org/10.2215/CJN.02660221

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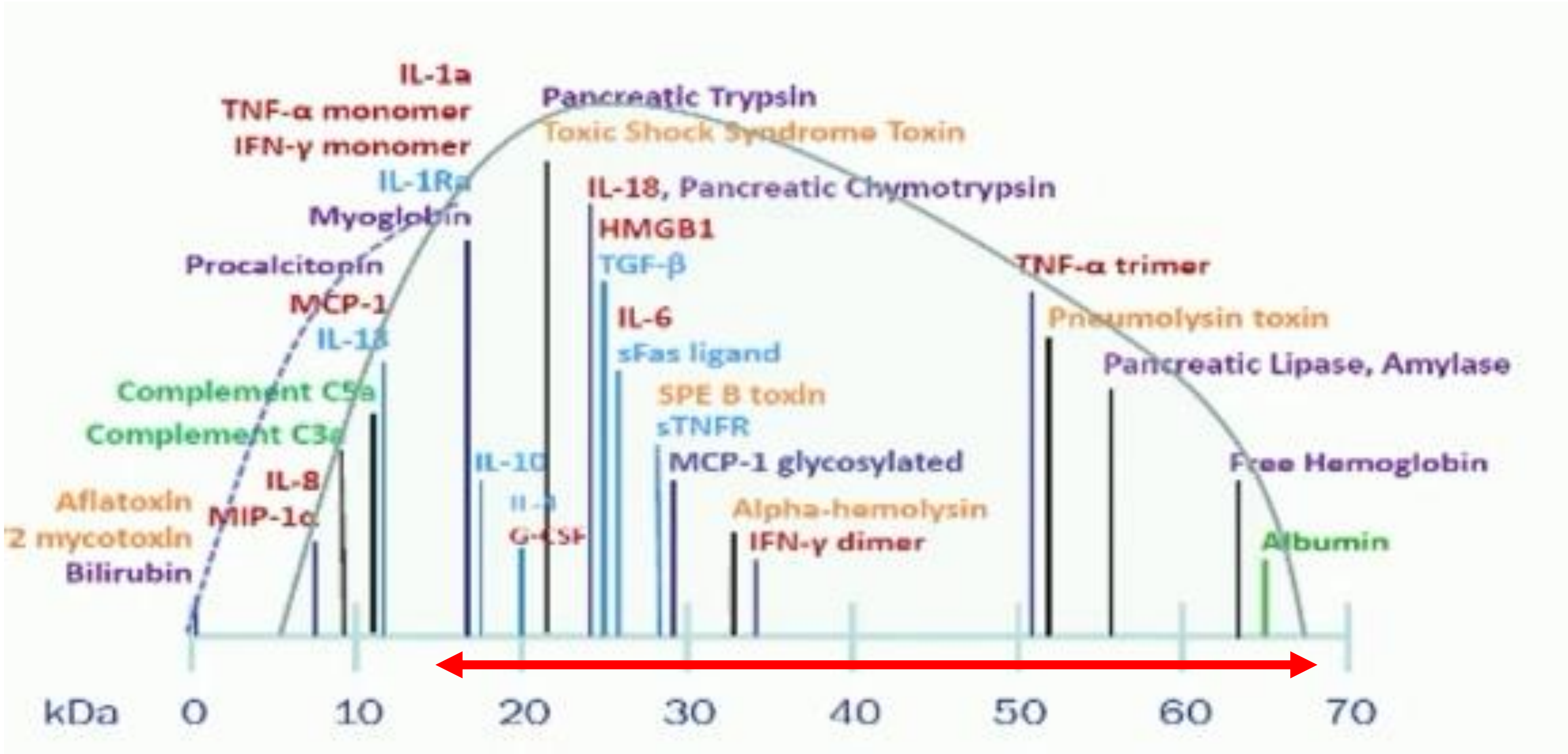
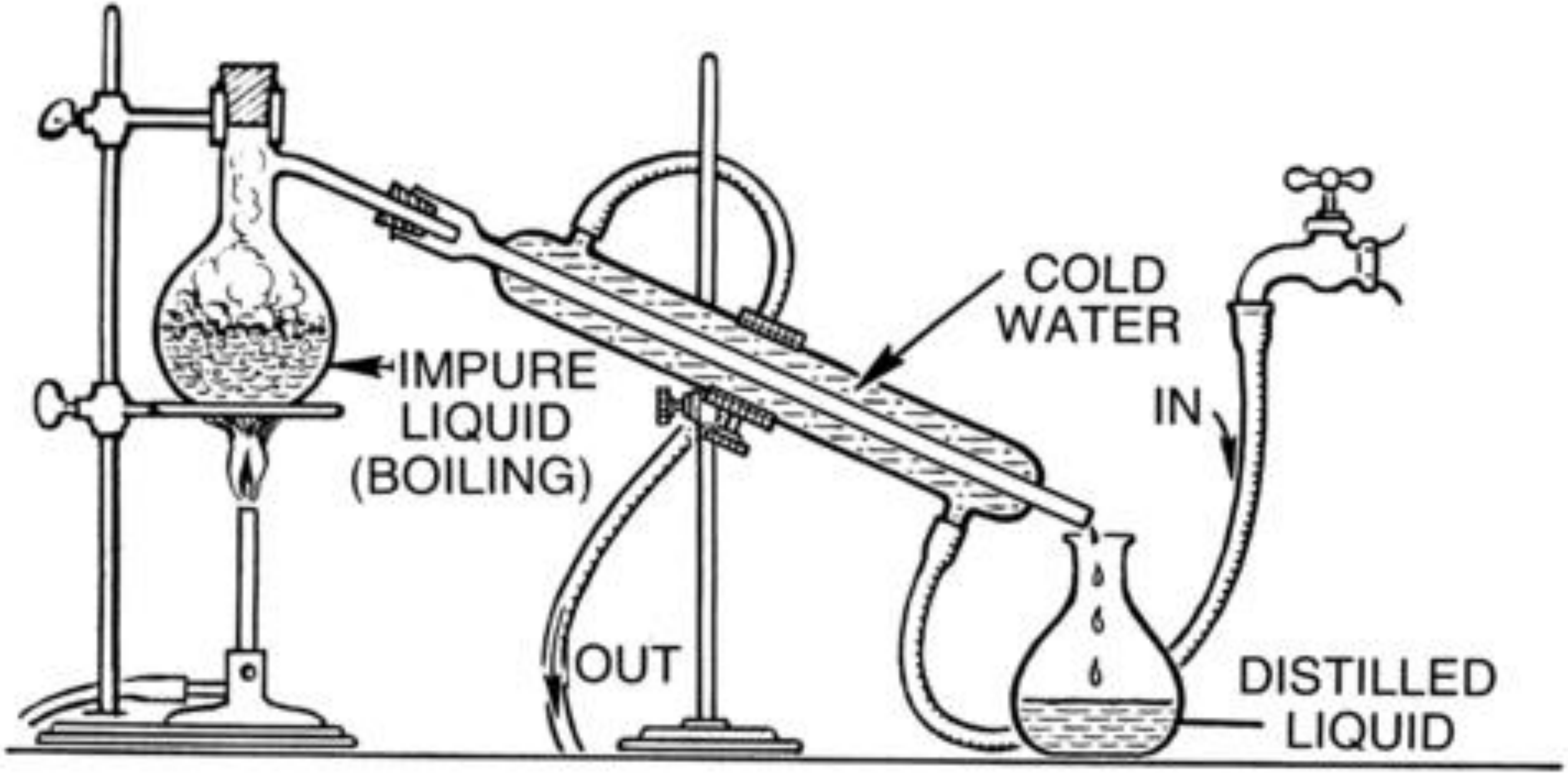
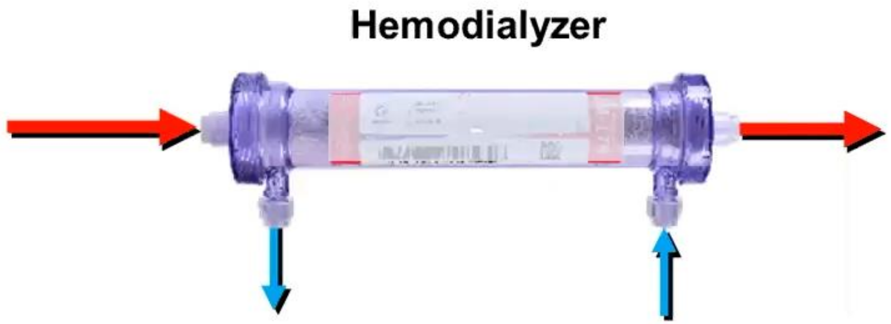
Most of the retained molecules are “middle/large”

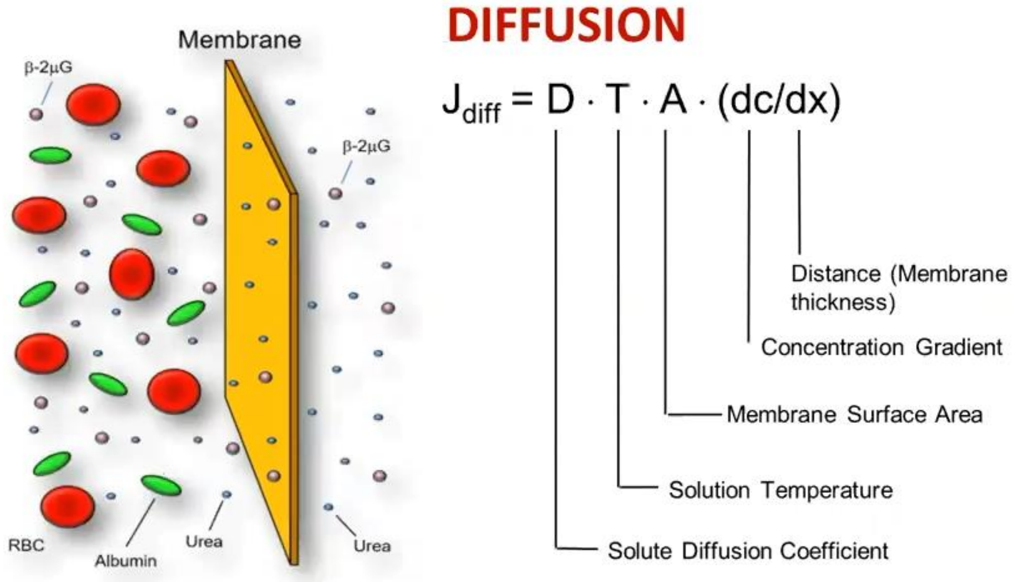


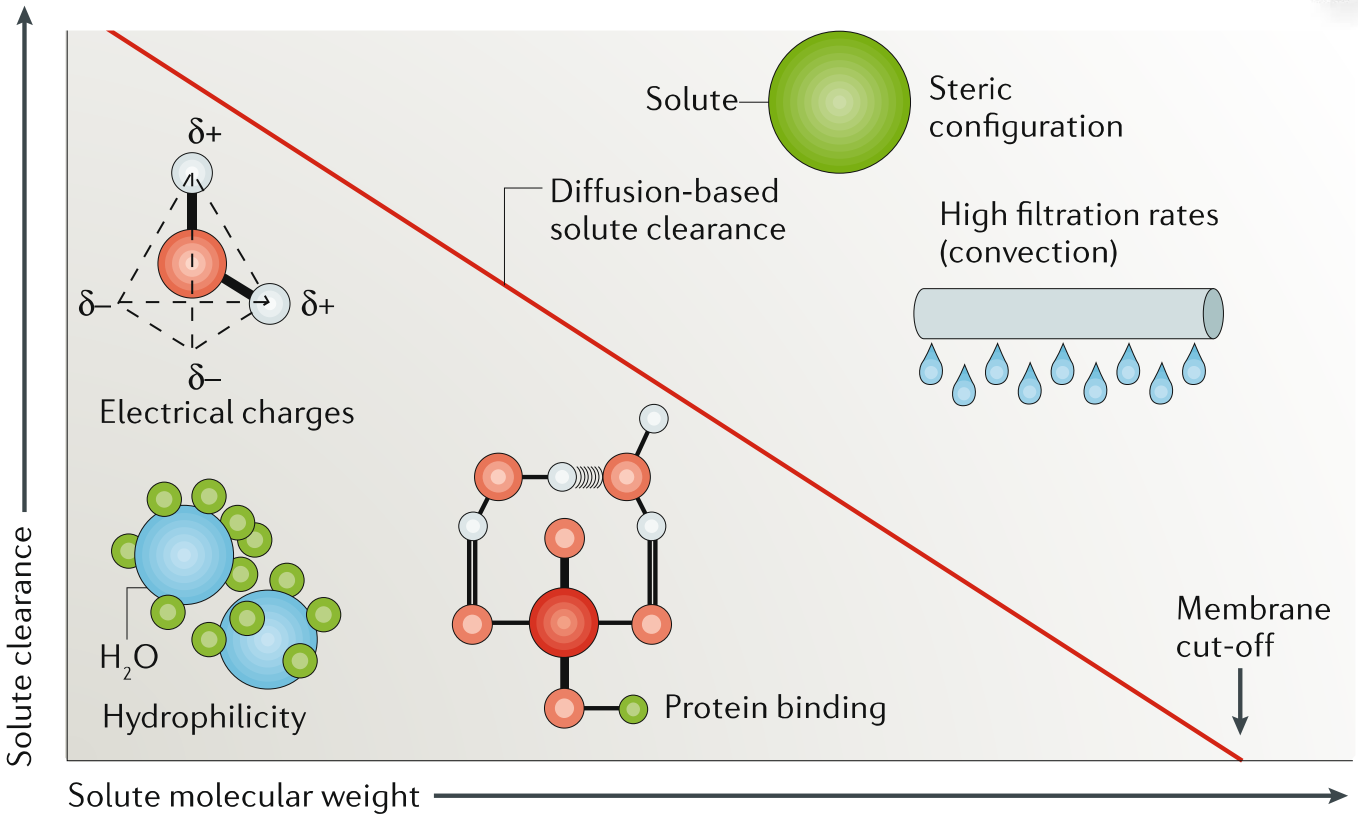

Middle
Molecules
THE
UNFOLDING
STORY
THE
UNFOLDING
STORY

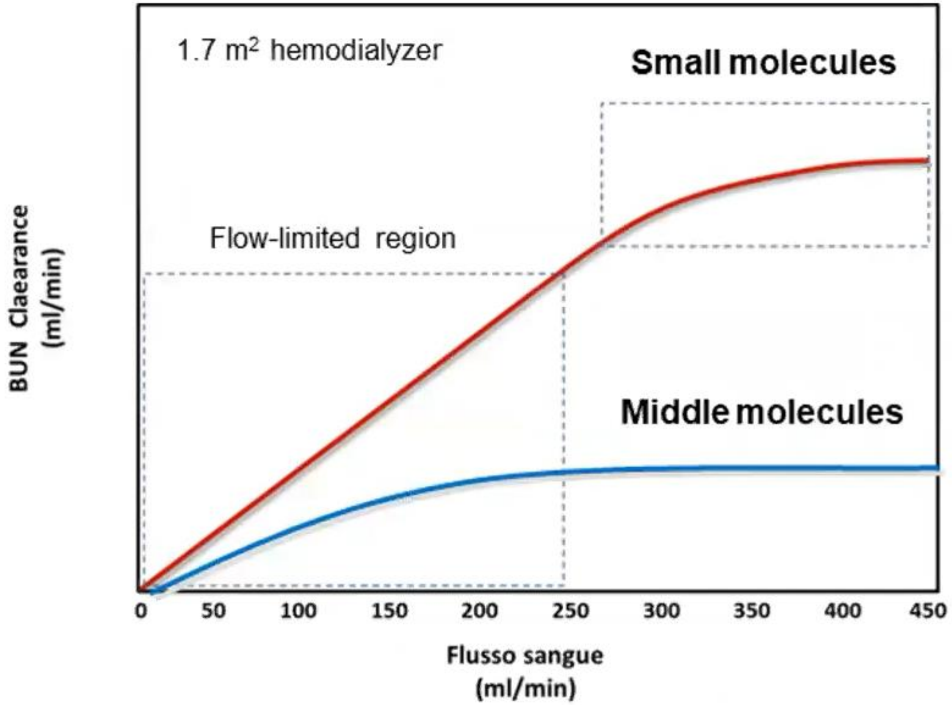
Mass Separation



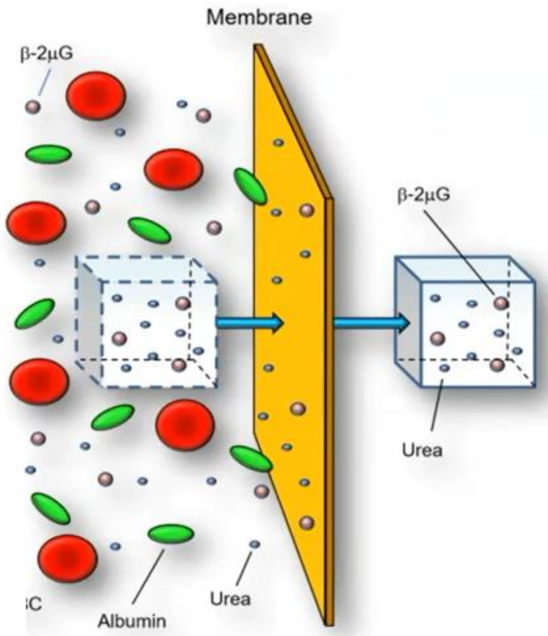

Hemodialyzer


DIFFUSION
Membrane
β-2μG
β-2μG
RBC
Albumin
Urea
Urea
$J_{diff} = D \cdot T \cdot A \cdot (dc/dx)$
Distance (Membrane thickness)
Concentration Gradient
Membrane Surface Area
Solution Temperature
Solute Diffusion Coefficient


Solute clearance
Solute molecular weight
Solute
Steric configuration
Diffusion-based solute clearance
High filtration rates (convection)
δ+
δ+
δ–
δ–
Electrical charges
H_2O
Hydrophilicity
Protein binding
Membrane cut-off


1.7 m² hemodialyzer
Small molecules
Flow-limited region
Middle molecules
BUN Clearance (ml/min)
0
50
100
150
200
250
300
350
400
450
Flusso sangue (ml/min)

Hemodialyzer



CONVECTION

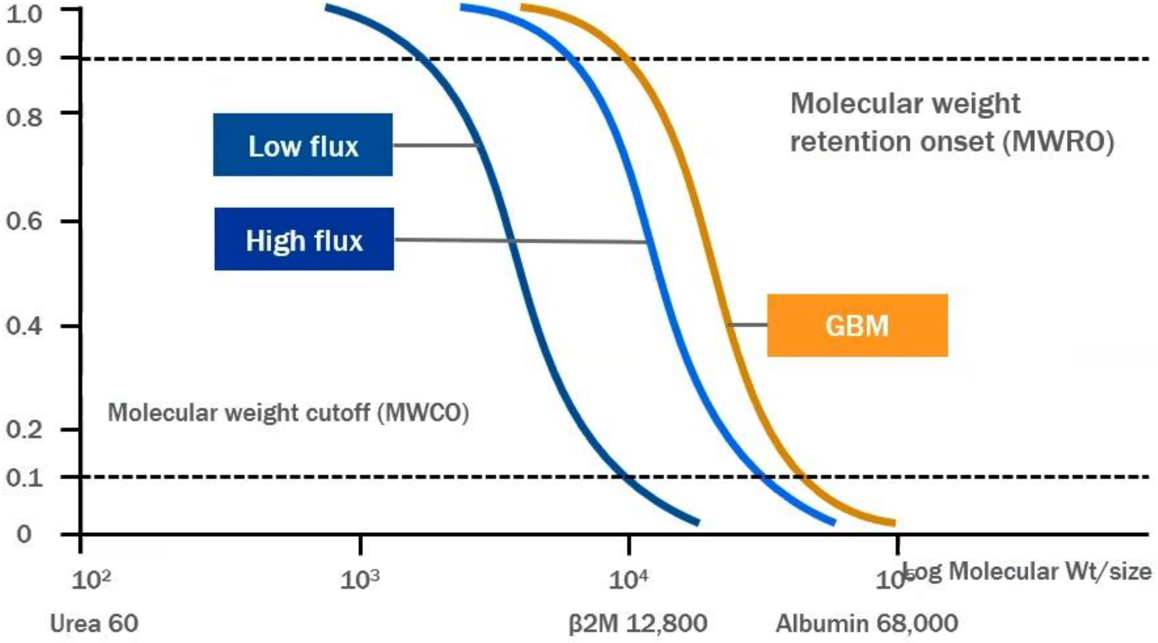
$$J_{conv} = Qf \cdot [uf]/[p]$$

$[uf]/[p] = S$

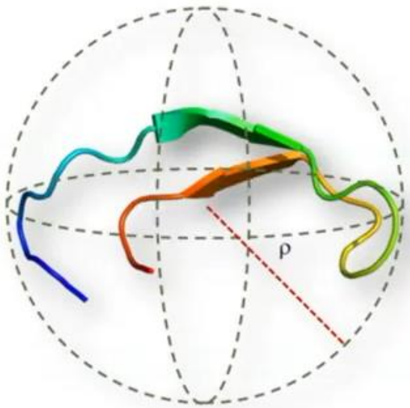
Solute concentration in plasma

Solute concentration in the ultrafiltrate

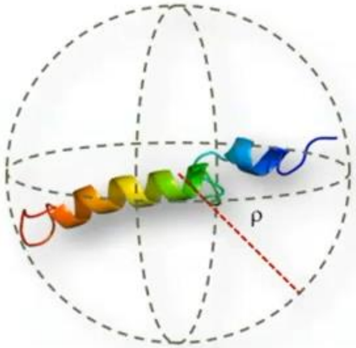
Ultrafiltration rate



Hepcidin Anti Microbial Peptide
MW: 27000 Da



Parathiroid Hormon
MW: 9300 Da



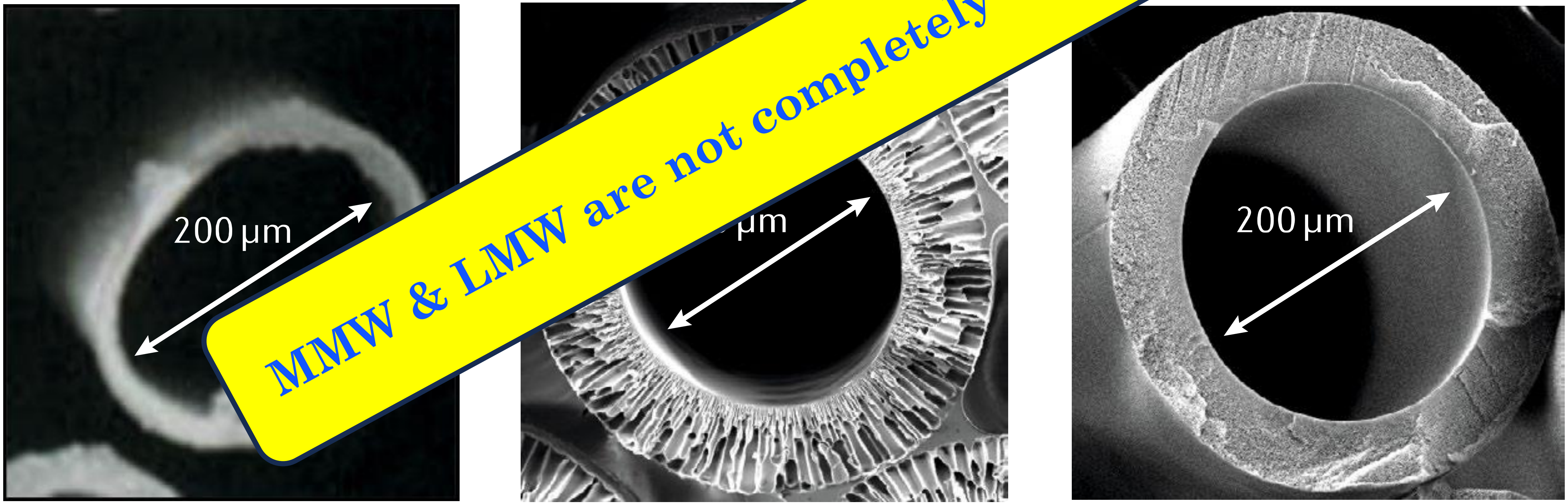
Membranes
Diffusion/Convection

High Flux, HCOM
High ... ficiency

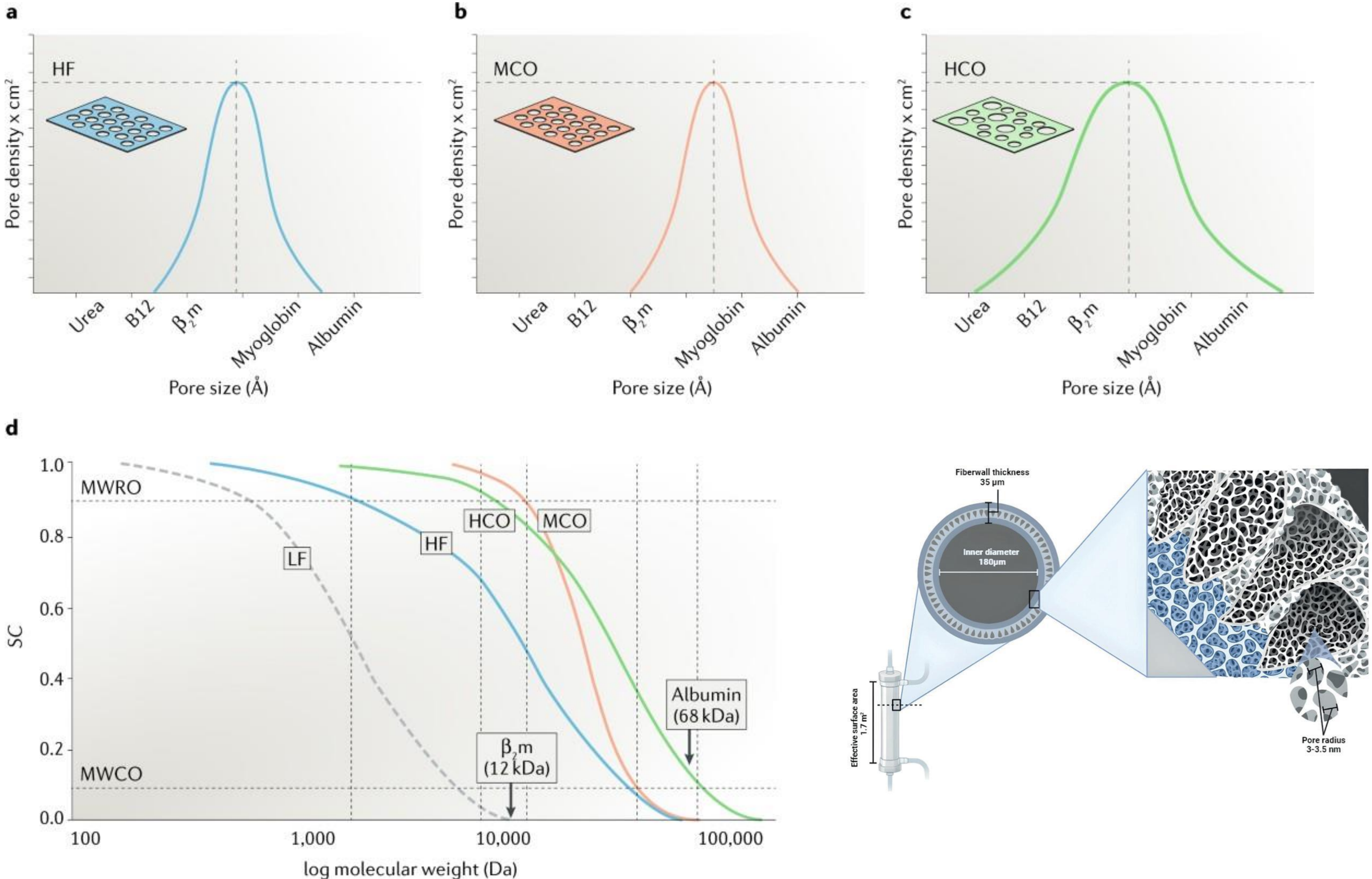
a Cuprophan (cellulose)
Wall thickness 5–15 µm

Polysulfone
Wall thickness 75–10...

...lfone
...ckness 30 µm



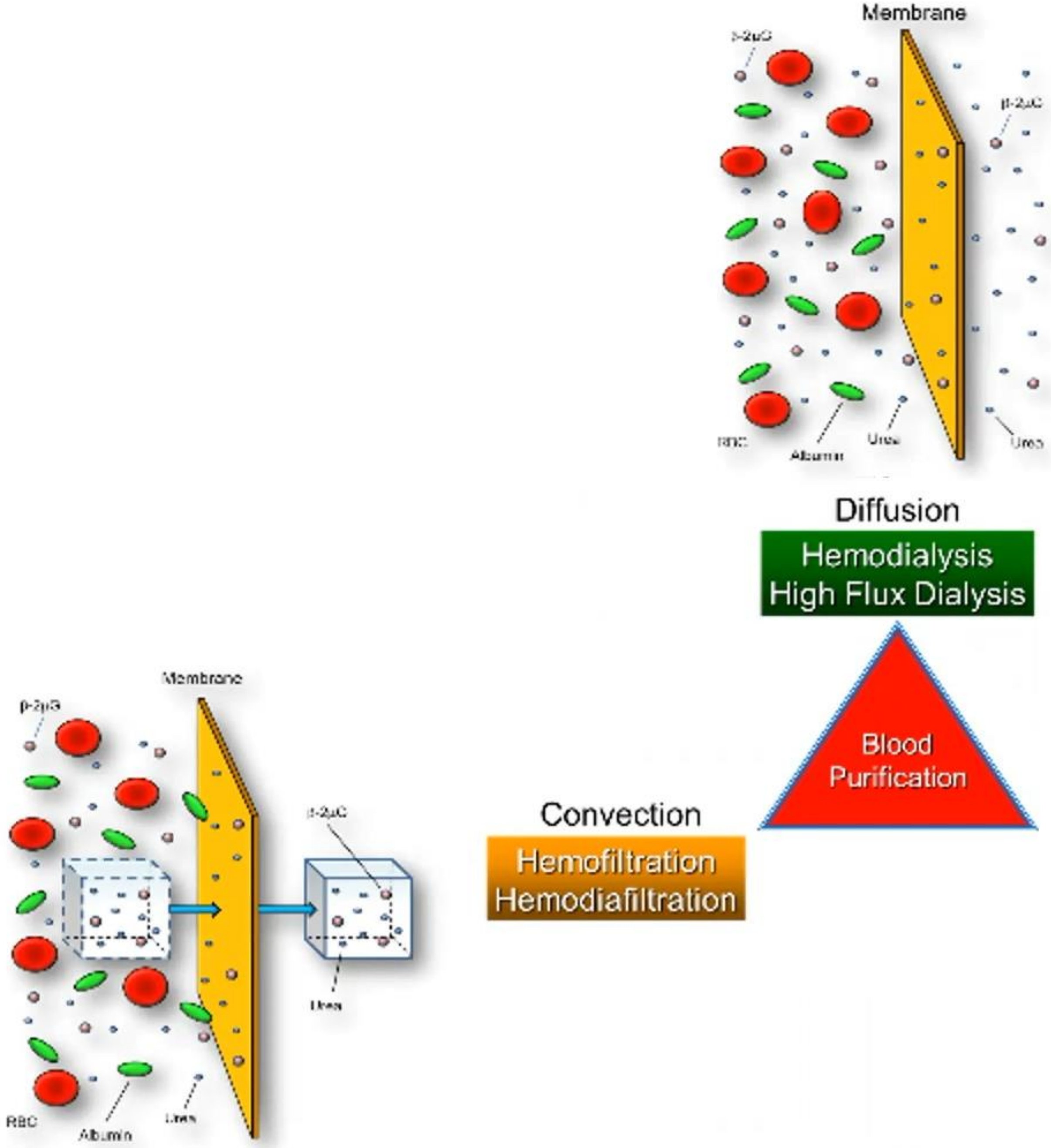
MMW & LMW are not completely removed


a
HF
Pore density x cm²
Urea
B12
β₂m
Myoglobin
Albumin
Pore size (Å)
b
MCO
Pore density x cm²
Urea
B12
β₂m
Myoglobin
Albumin
Pore size (Å)
c
HCO
Pore density x cm²
Urea
B12
β₂m
Myoglobin
Albumin
Pore size (Å)
d
1.0
0.8
0.6
0.4
0.2
0.0
SC
MWRO
MWCO
LF
HF
HCO
MCO
β₂m (12 kDa)
Albumin (68 kDa)
100
1,000
10,000
100,000
log molecular weight (Da)
Fiberwall thickness 35 µm
Inner diameter 180µm
Effective surface area 1.7 m²
Pore radius 3-3.5 nm

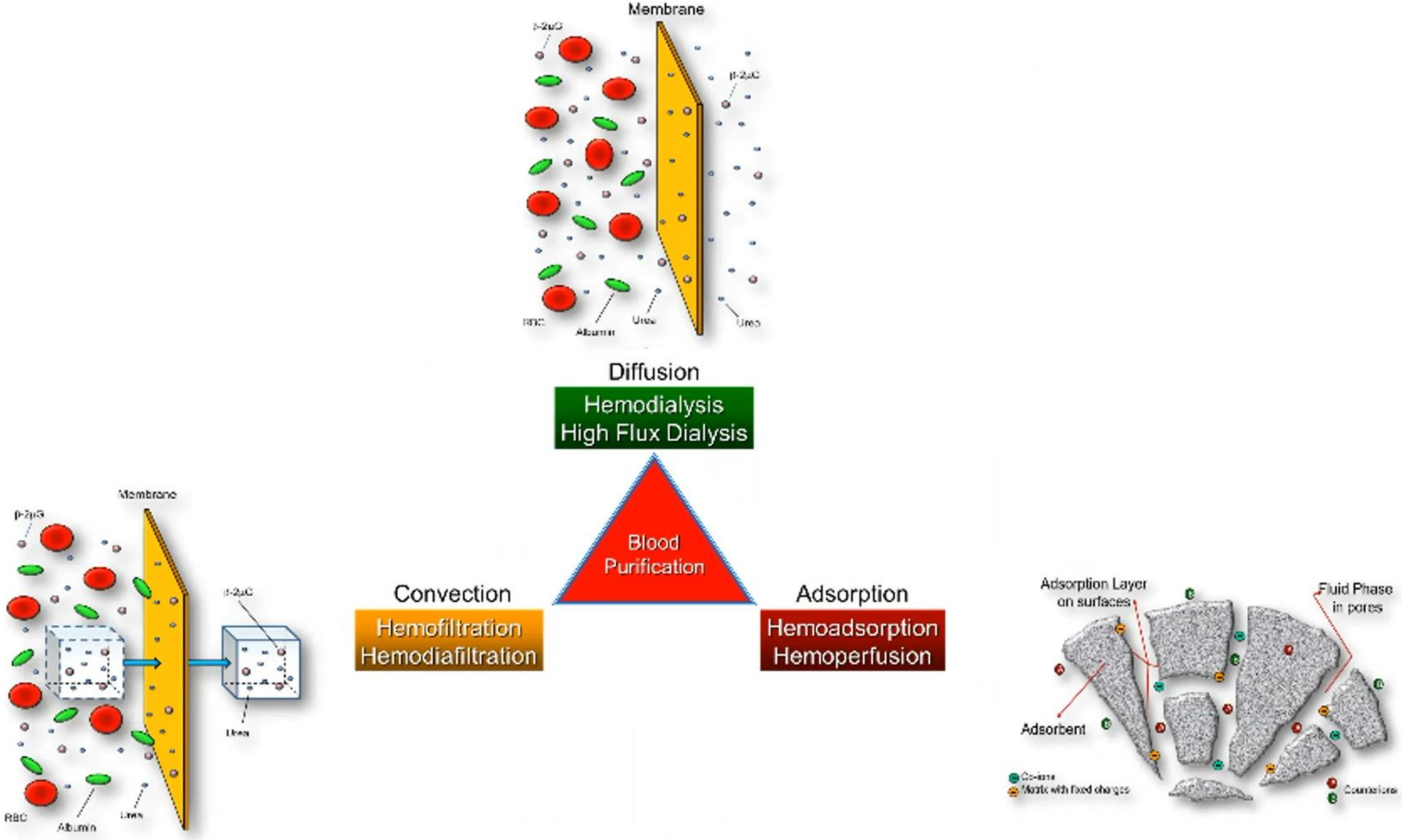
Class	SOLUTE	MW (Da)	Action/Effect
Small	Urea	60	General toxicity
	Creatinine	125	
	Vitamin B12	1250	
Middle	β 2 M	12000	Amiloidosis CTS
	Leptin	16000	Malnutrition
	Myoglobin	17000	Organ damage
Large	κ-FLC	23000	Toxicity
	Prolactin	23000	Infertility
	Interleukin-6	25000	Inflammation
	Hepcidin	27000	Anemia
	Bound P-Cresol	33500	CV Toxicity
	Pentraxin-3	43000	Acute Phase Prot.
	λ-FLC	45000	CV Toxicity
	TNF-α (Trim)	51000	Inflammation
Essential protein	Albumin	68000	Toxin binding capacity

Innovation is mandatory…

“unmet clinical needs”



Membrane
RBC
Albumin
Urea
Urea
Diffusion
Hemodialysis
High Flux Dialysis
Blood
Purification
Membrane
RBC
Albumin
Urea
Urea
Convection
Hemofiltration
Hemodiafiltration



Membrane
β-2μG
RBC
Albumin
Urea
Diffusion
Hemodialysis
High Flux Dialysis
Blood Purification
Convection
Hemofiltration
Hemodiafiltration
Adsorption
Hemoadsorption
Hemoperfusion
Adsorption Layer on surfaces
Fluid Phase in pores
Adsorbent
Co-ions
Matrix with fixed charges
Counterions

If we want to use <u>adsorption</u>, we should use "<u>sorbents</u>"

Sorbents Hx

- **1850**: first inorganic allumino-silicates (zeolites) used to exchange NH_4 & Ca
- **1910**: (we used it for) **Water softeners** using zeolites
- **1935**: Adams & Homes synthetize the <u>first organic ion exchange resin</u>
- **1940-50**: synthetic porous polymers (stytrene ot acrylic acid based) to create >>> (trade names of) Amberlyte, Duolite, Dowex, Purolite
- **1960**: these polymers were ***used in BP tech*** >>>> sorbent-based BP tech (<u>**HP**</u>)
- **1980-2000**: improved design & coating for better hemo-compatibility
- **2020**: we have spectrum of devices & sorbent biomaterials for clinical application

Sorbent Materials

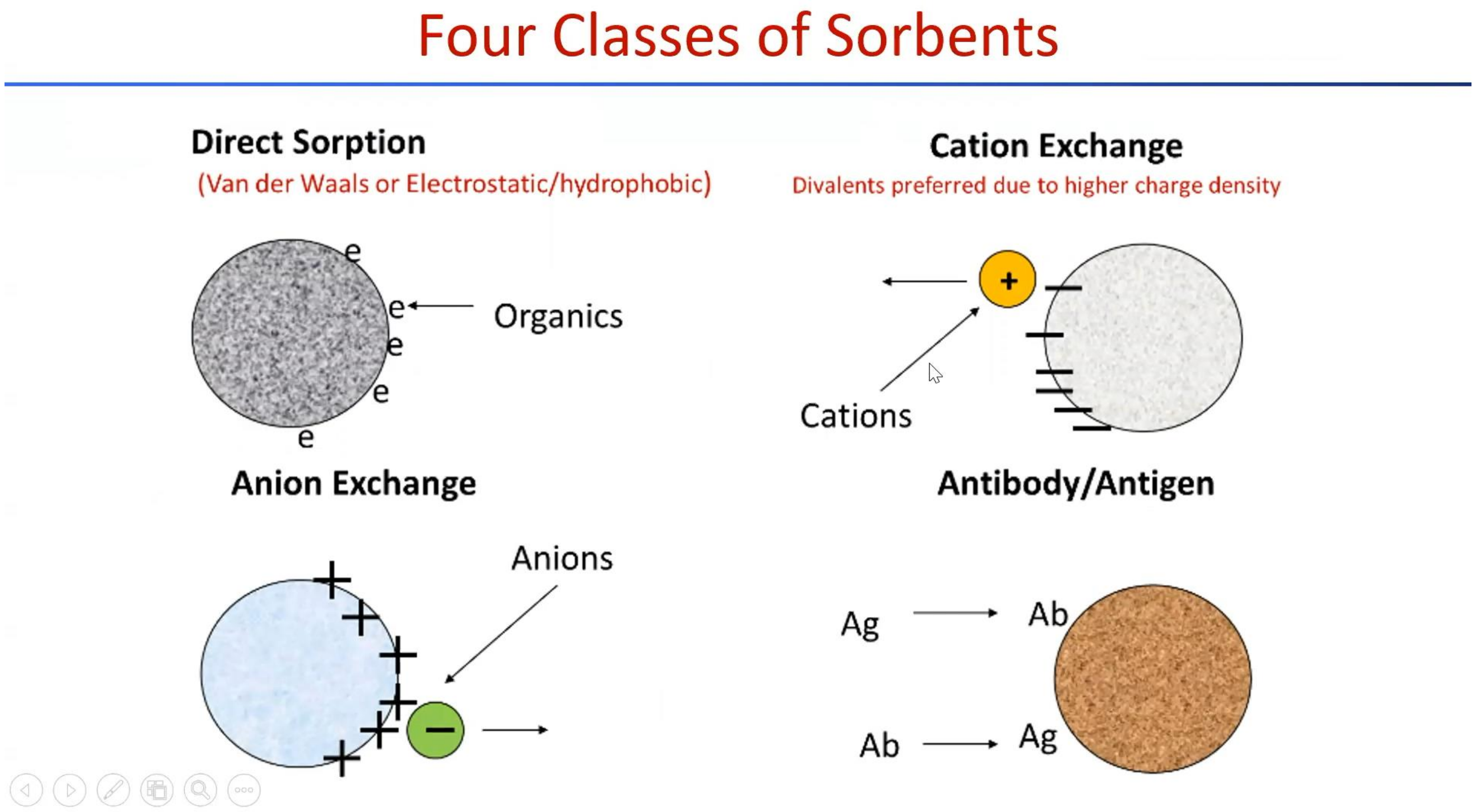
- **Natural**,
- **Synthetic** (mostly used todays): high S/V ratio (1000 m2/gr)

- The sorbents are in different "**Formats**"
- Mostly we have seen recently in "**beads**", but also in the form of fibers, granules, powder, cylindrical pellets, Flakes,…

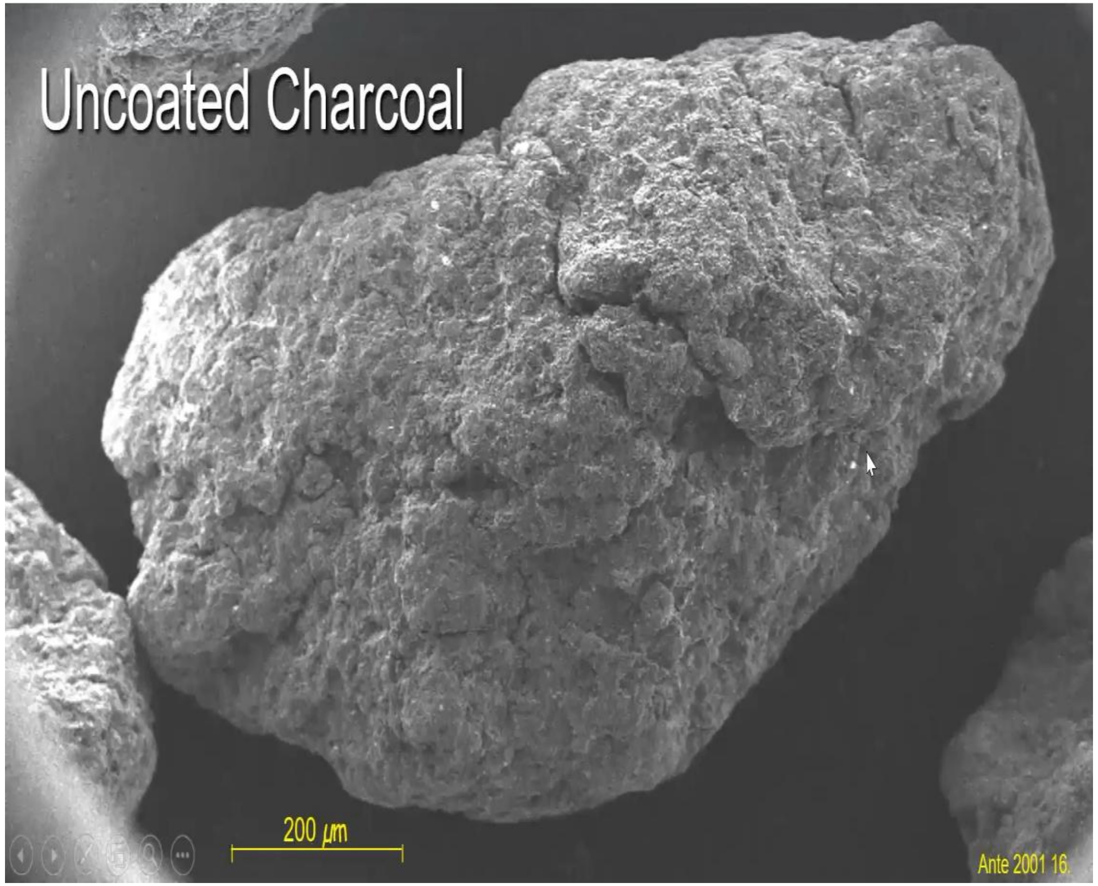
- The "**structure**" can be Macro-/Meso-/Micro-porous,

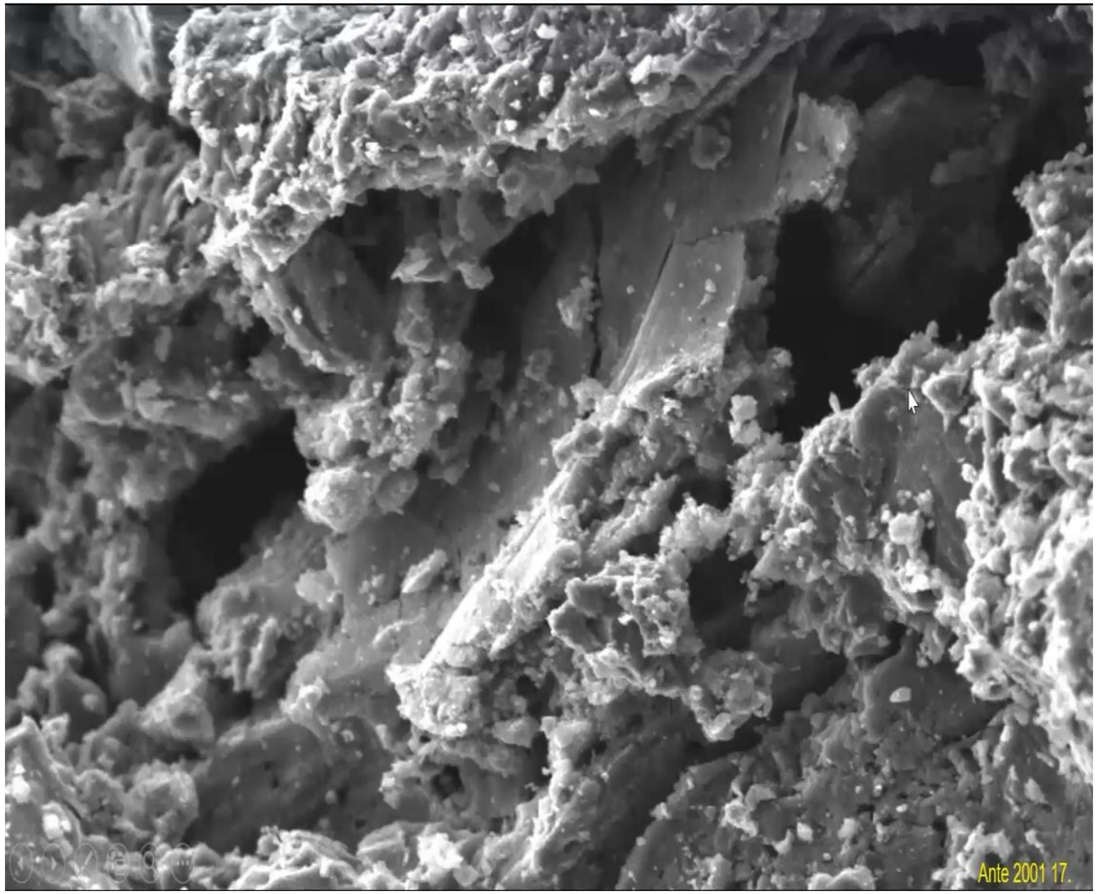
- **Mechanism** : directs ads, Anion or Cation exchange< Immuno-ads.

We have 4 classes of sorbent (natural, synthetic)



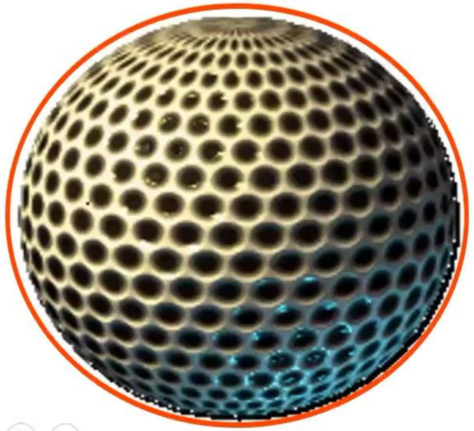
Sorbent material can be *rough* & cannot be placed in contact with the blood

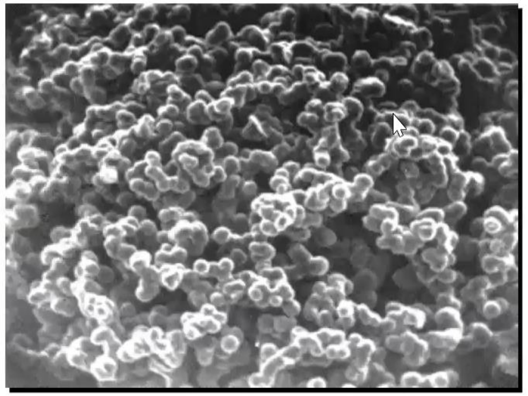




Surface can be coated, Bio-compatible, & thus, Performant

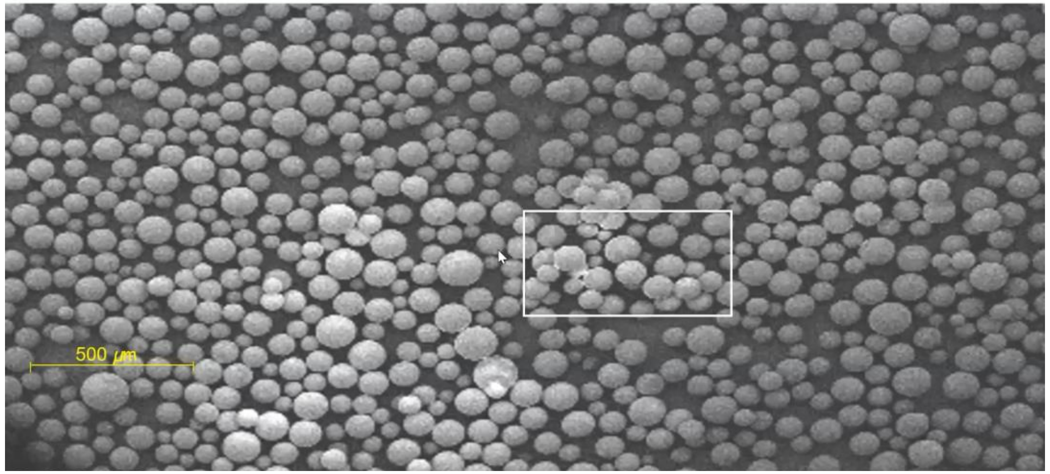
Schematic representation of a sorbent bead



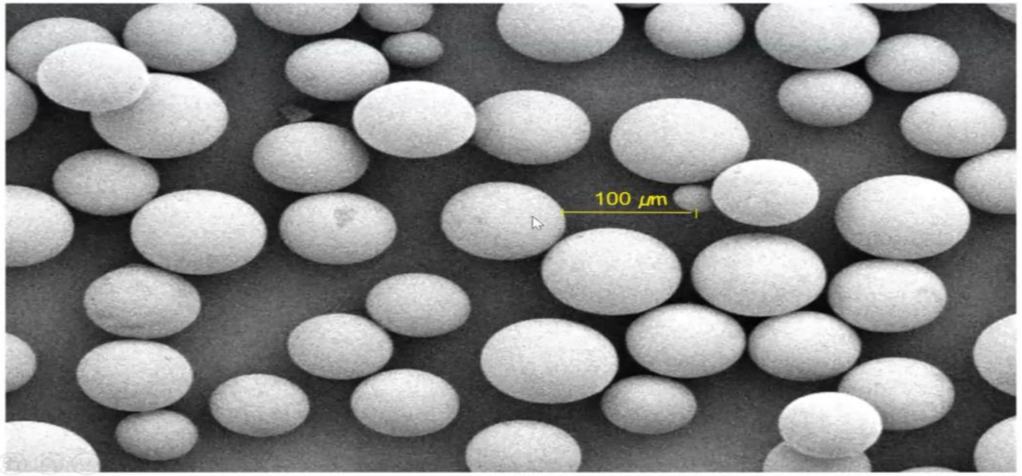


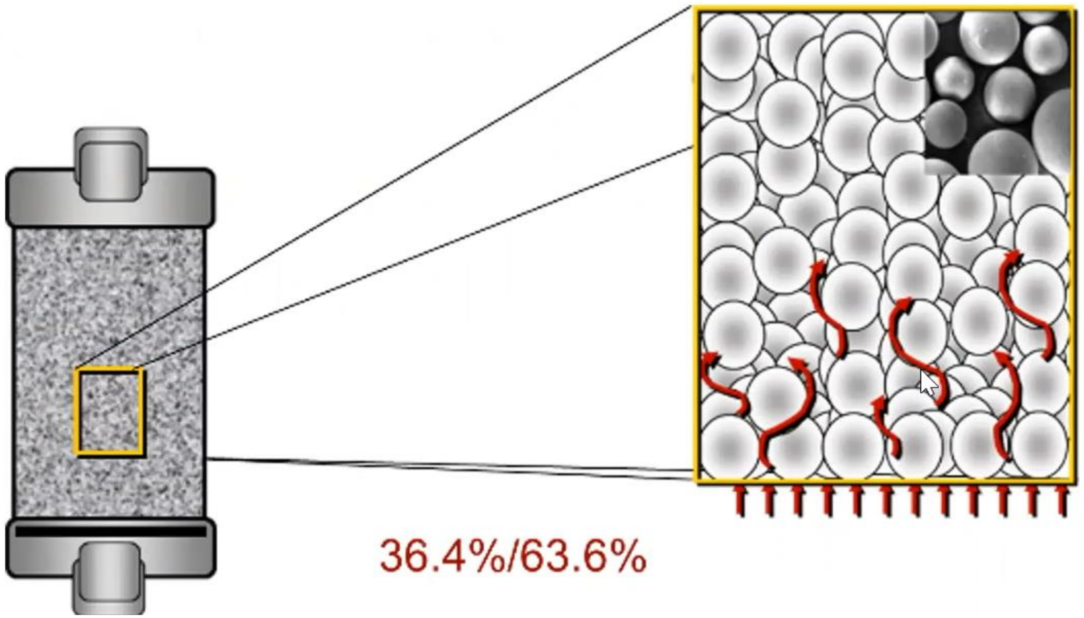
8-50Å
Pore structure

Hydrophobic Resin (Scanning Electron Microscopy)



Hydrophobic Resin (Scanning Electron Microscopy)



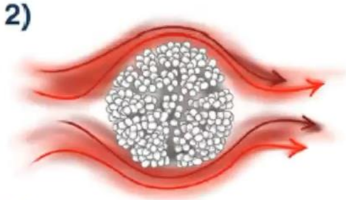


36.4%/63.6%

1)

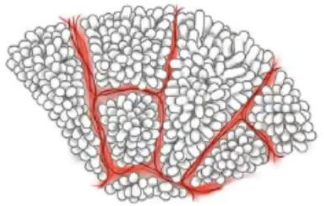
Interparticle (Packing density)

2)

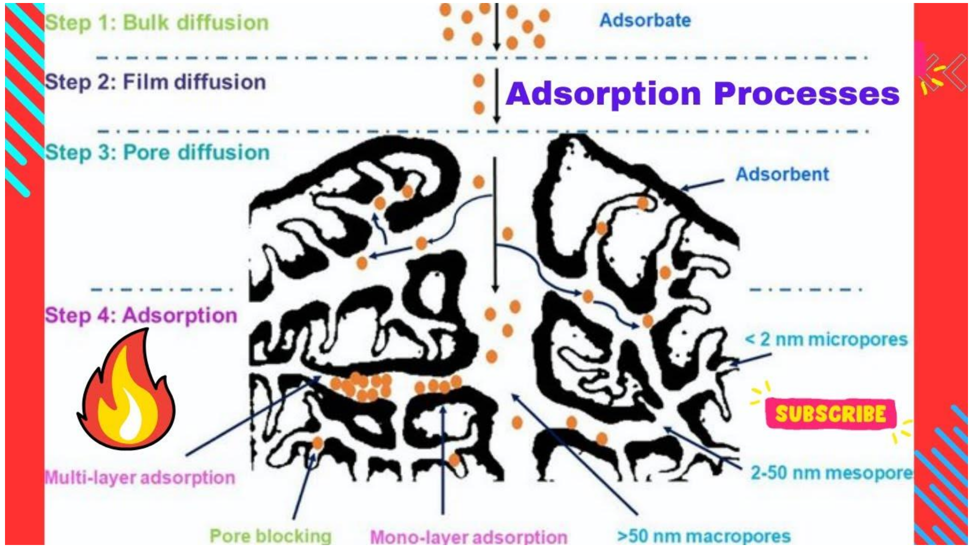


Extraparticle (Bead design)

3)



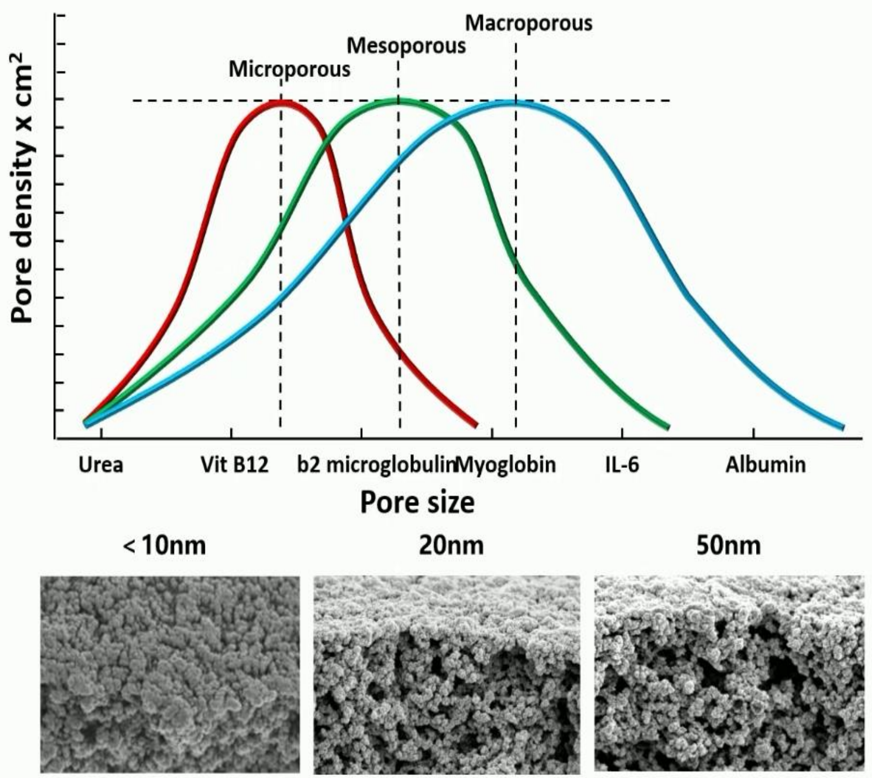
Intraparticle (Bead Porosity)

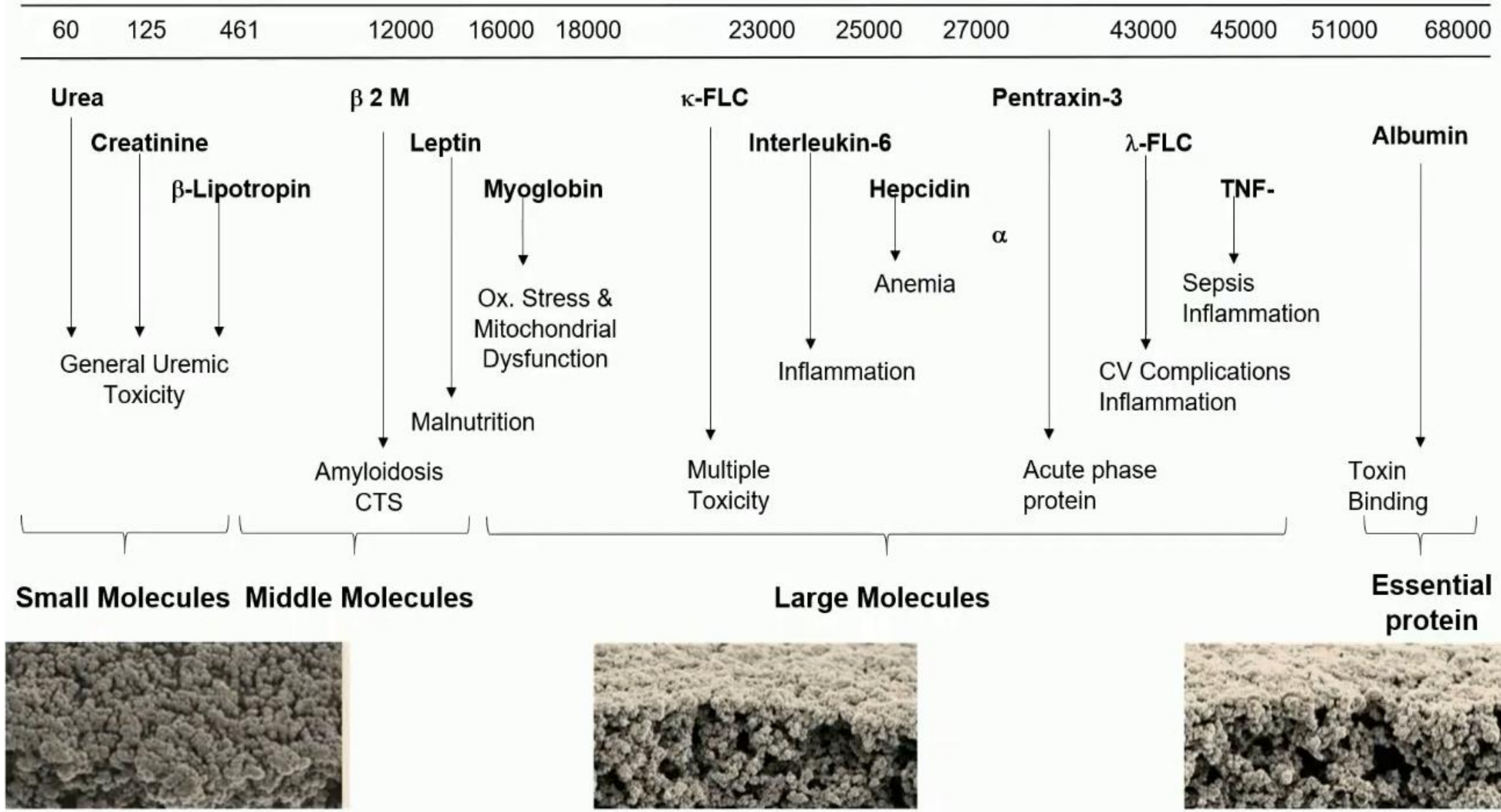


Sorbents

Structure

- Macroporous = Pore size > 500 Å (50 nm)
- Mesoporous = Pore size 20-500 Å
- Microporous = Pore size < 20 Å



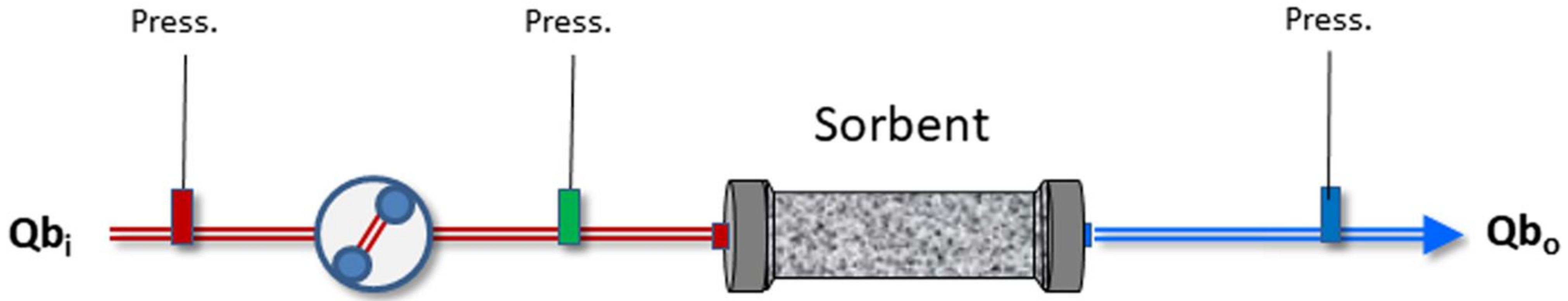


Use of Sorbent (HA) in Acute Medicine

How do we use sorbents ?

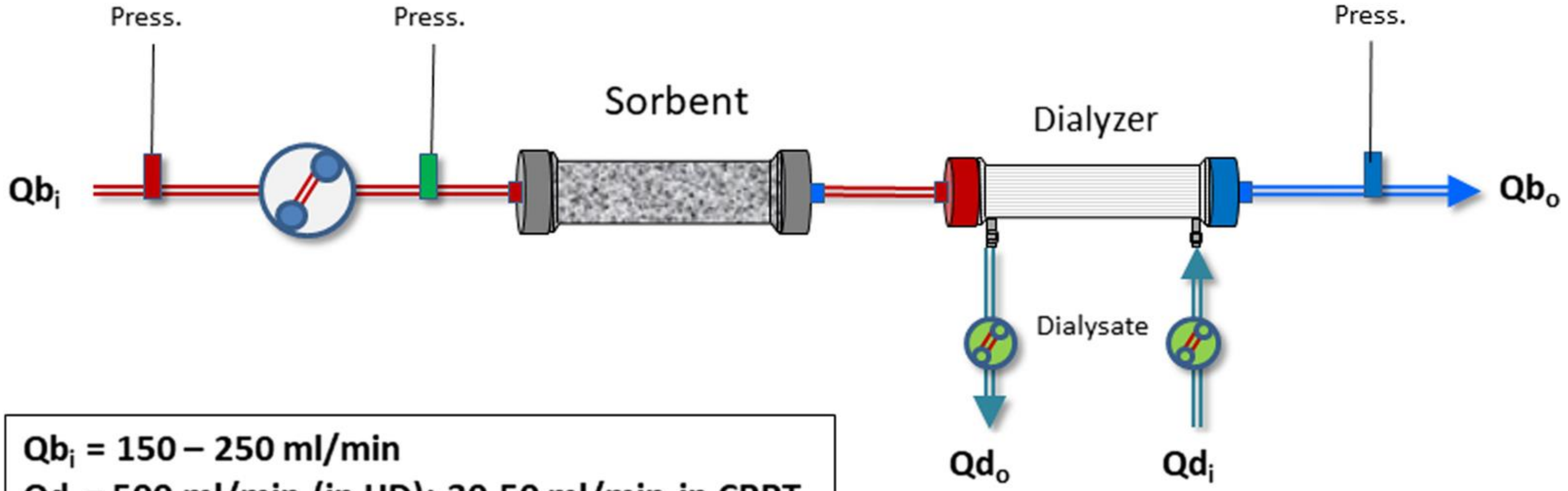
Once we have a good sorbent…

HA



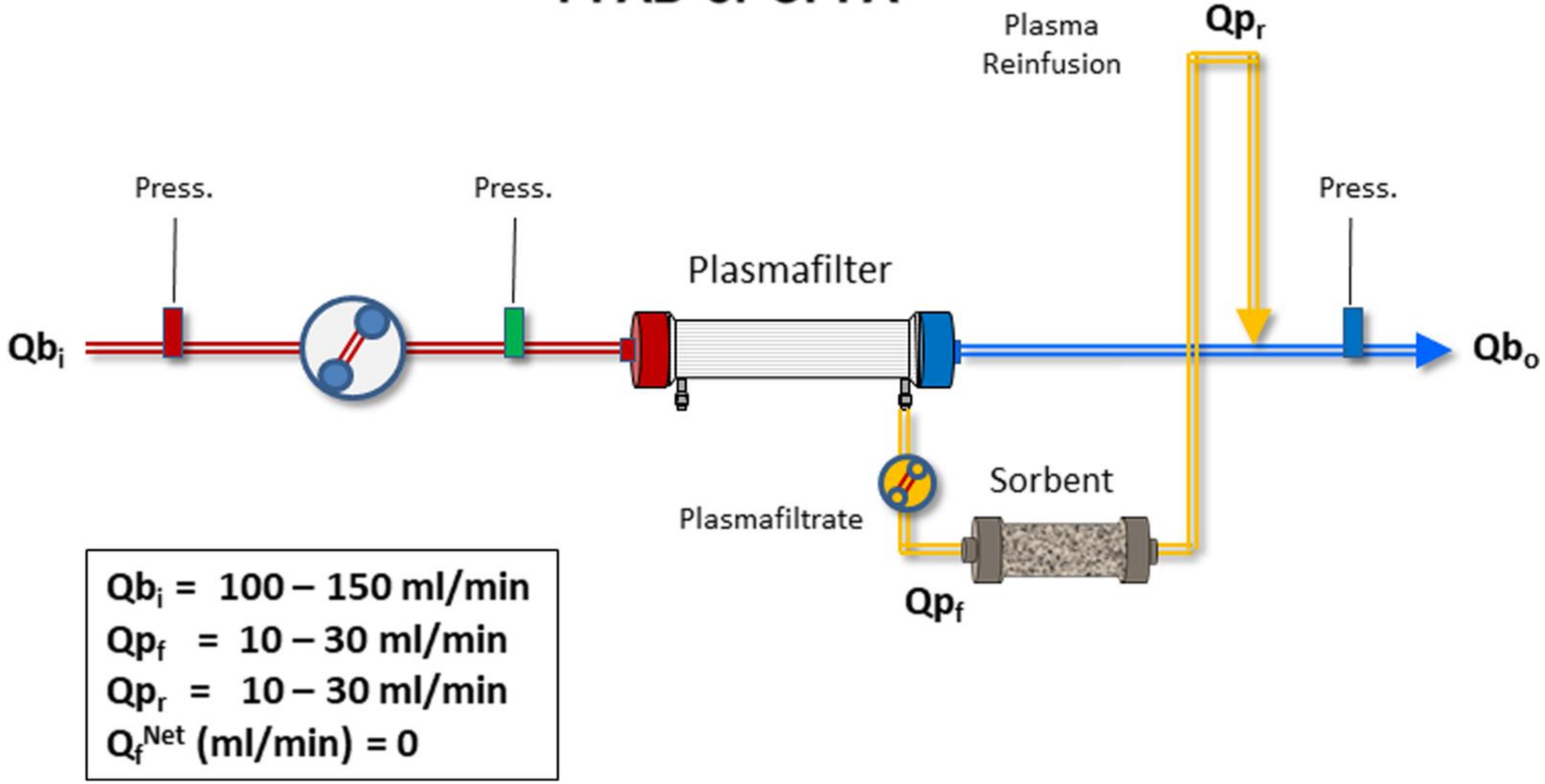
Qb_i = 100 – 250 ml/min
Q_f^{Net} (ml/min) = 0 ml/min

HP-HD or HP-CRRT

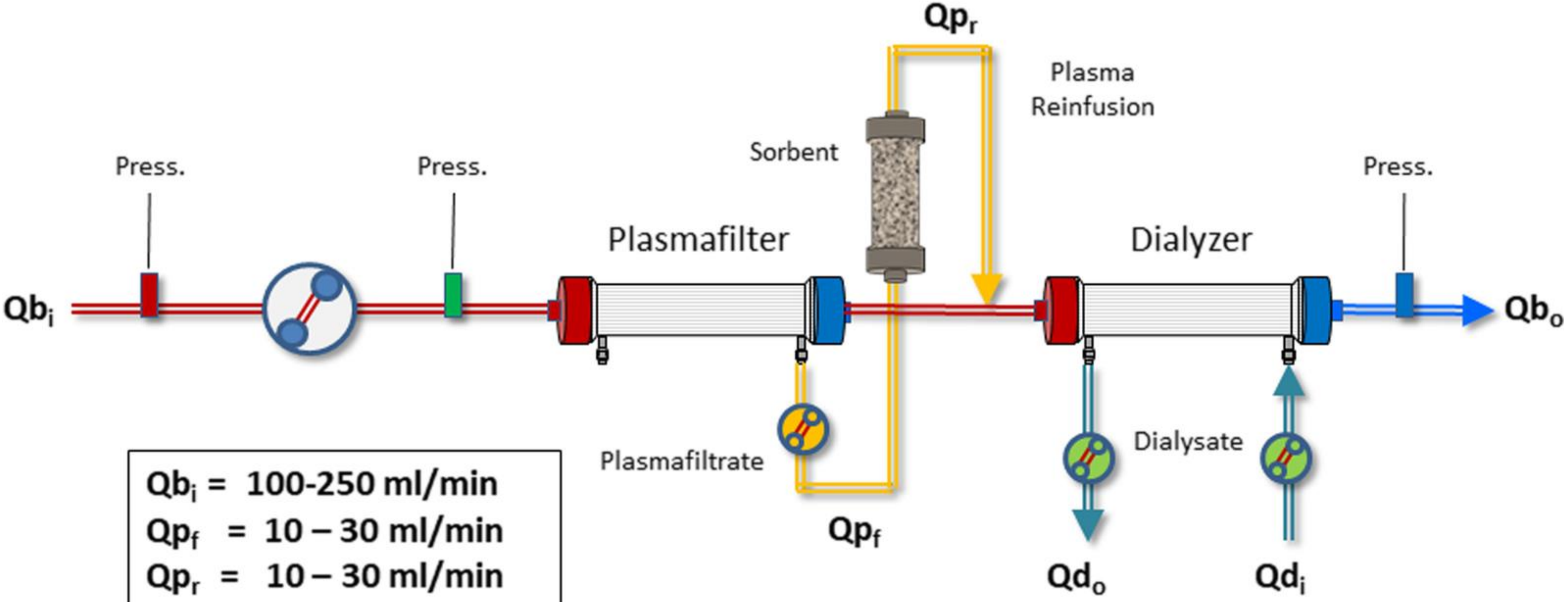


Qb_i = 150 – 250 ml/min
Qd_i = 500 ml/min (in HD); 30-50 ml/min in CRRT
Q_f^{Net} (ml/min) = $Qd_o - Qd_i$ = 0-20 ml/min

PFAD or CPFA

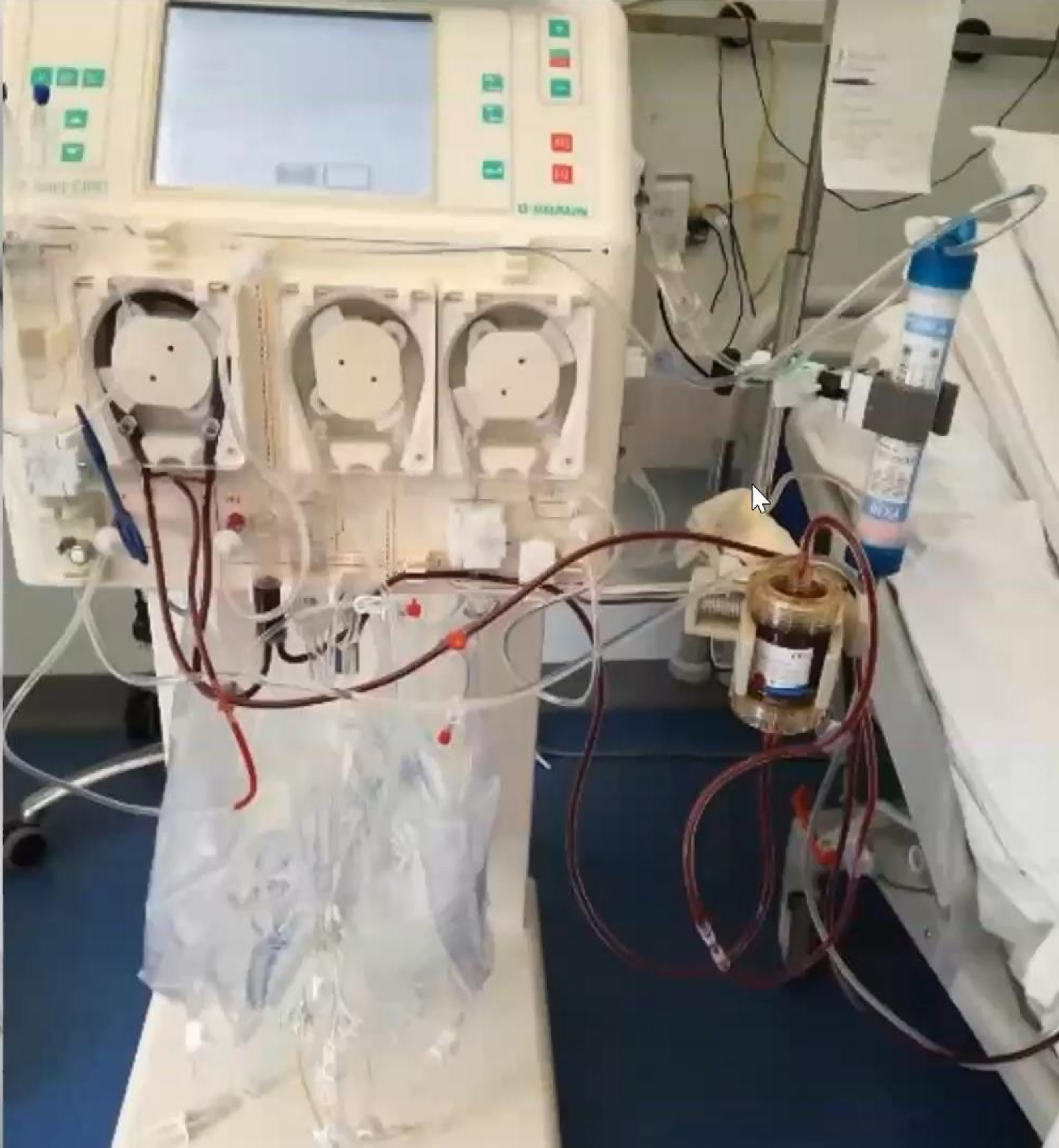

Plasma
Reinfusion
Qp_r
Press.
Press.
Press.
Plasmafilter
Qb_i
Qb_o
Sorbent
Plasmafiltrate
Qp_f
Qb_i = 100 – 150 ml/min
Qp_f = 10 – 30 ml/min
Qp_r = 10 – 30 ml/min
Q_f^{Net} (ml/min) = 0

PFAD-HD or CPFA-CRRT

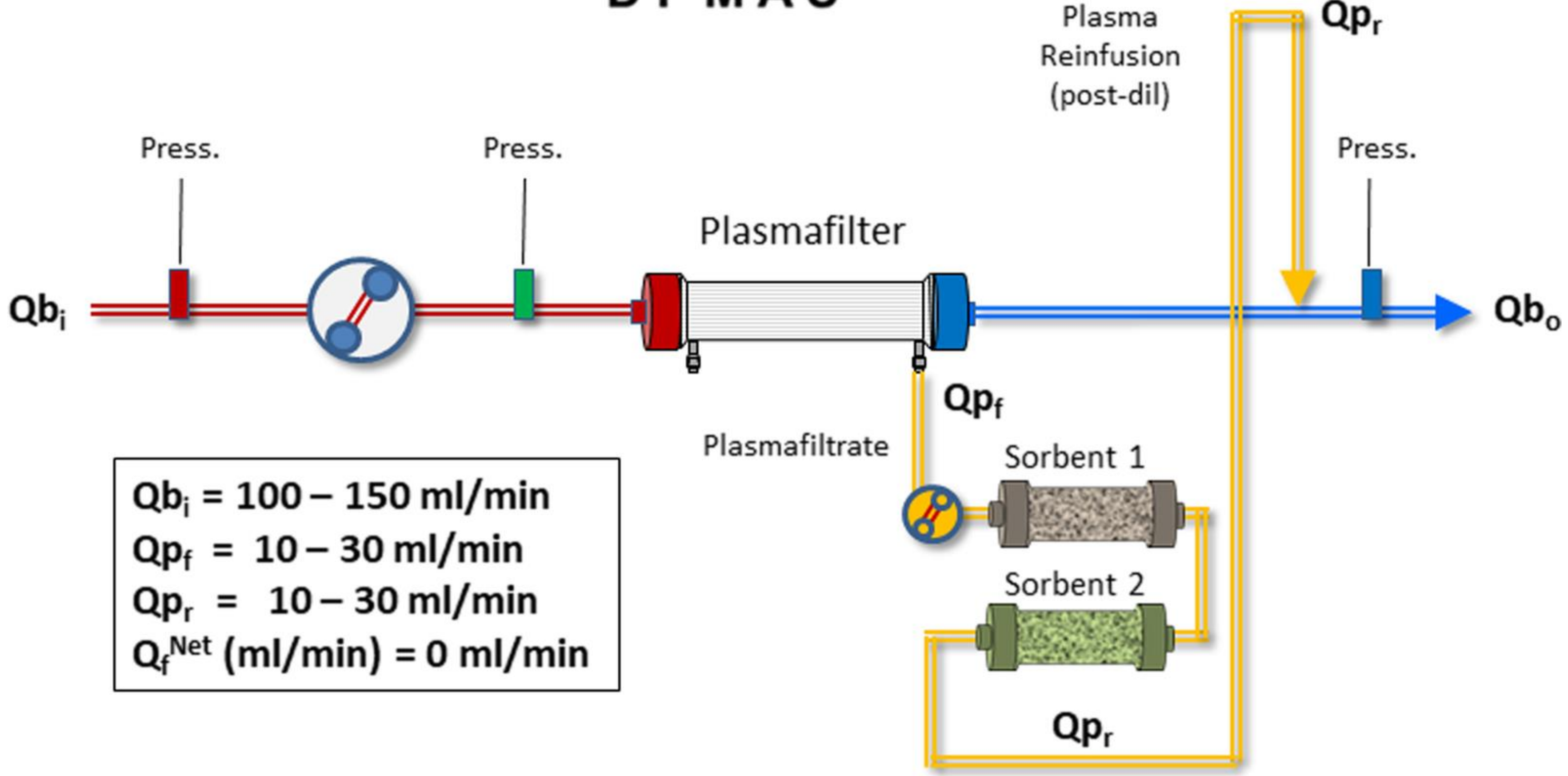


Qb_i = 100-250 ml/min
Qp_f = 10 – 30 ml/min
Qp_r = 10 – 30 ml/min
Qd_i = 500 ml/min
Q_f^{Net} (ml/min) = Qd_o -Qd_i

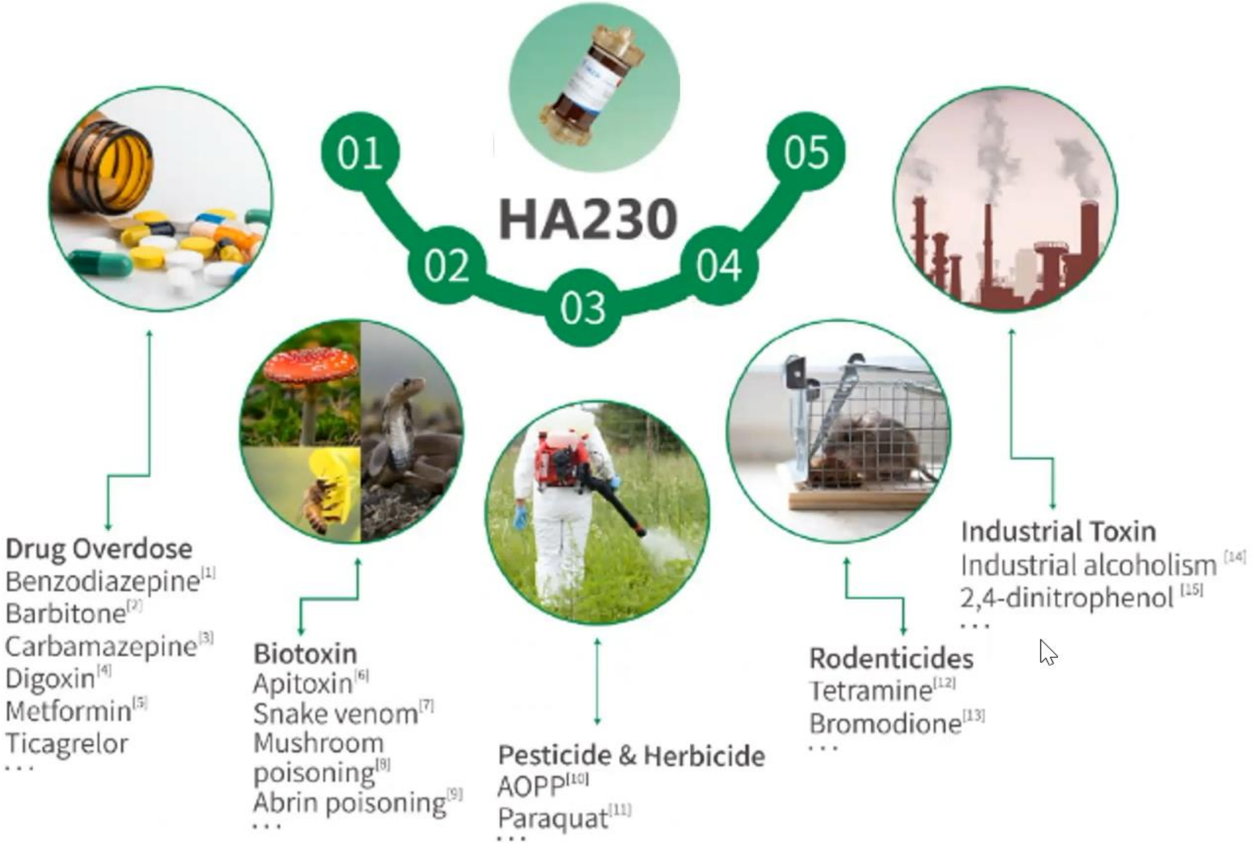

CE
rfusion Cartridge
LOT
17052730



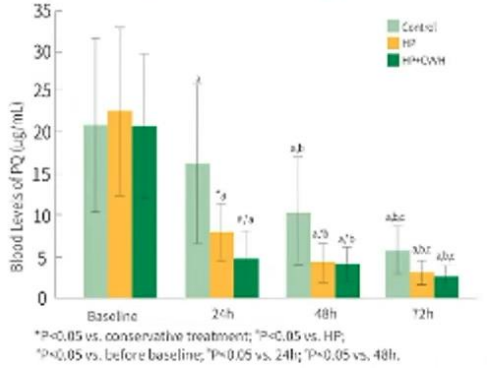
D P M A S


Plasma Reinfusion (post-dil)
Qp_r
Press.
Press.
Press.
Plasmafilter
Qb_i
Qb_o
Qp_f
Plasmafiltrate
Sorbent 1
Sorbent 2
Qp_r
Qb_i = 100 – 150 ml/min
Qp_f = 10 – 30 ml/min
Qp_r = 10 – 30 ml/min
Q_f^{Net} (ml/min) = 0 ml/min

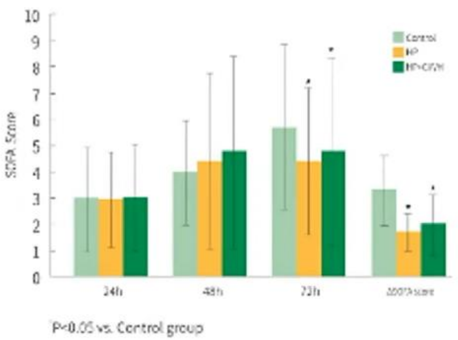
HA in Poisoning & Intoxications



Remove Overdosed Drug and Poison



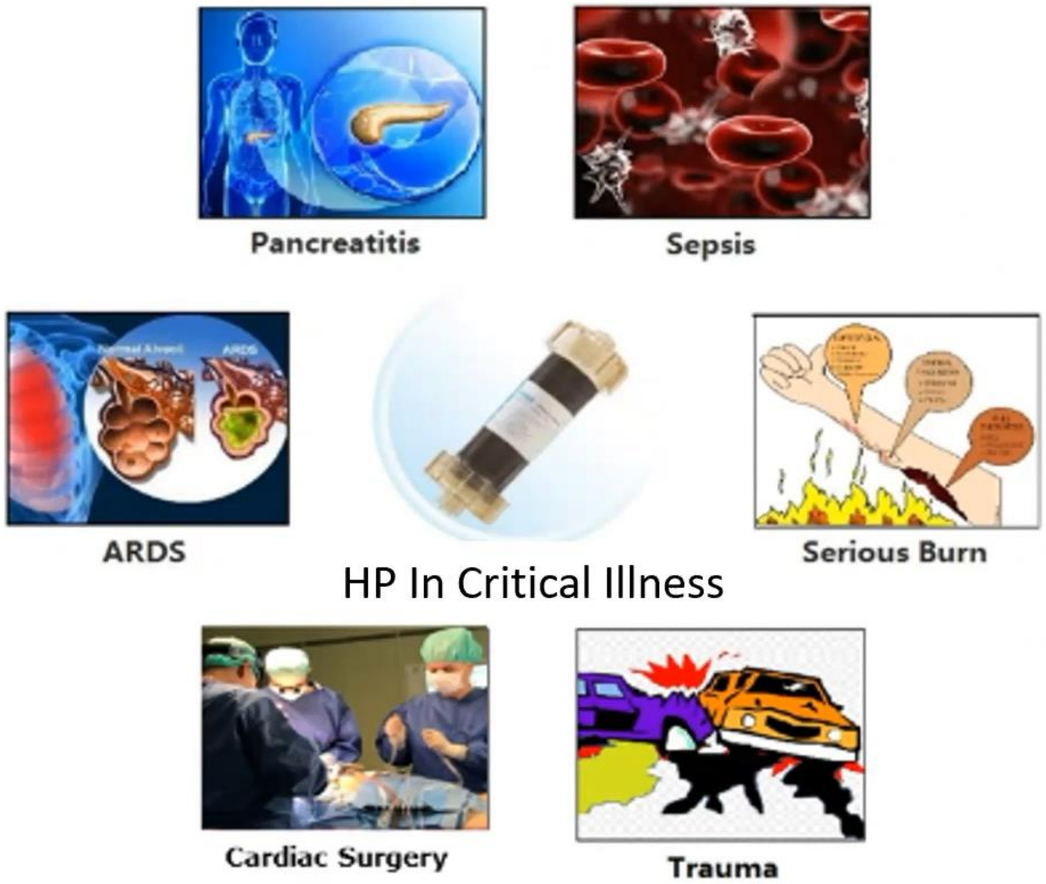
Improve Therapeutic Effect[16,17]

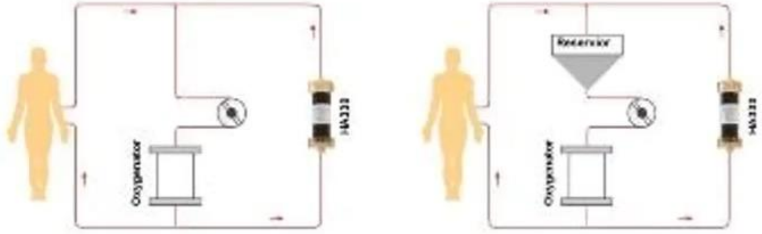


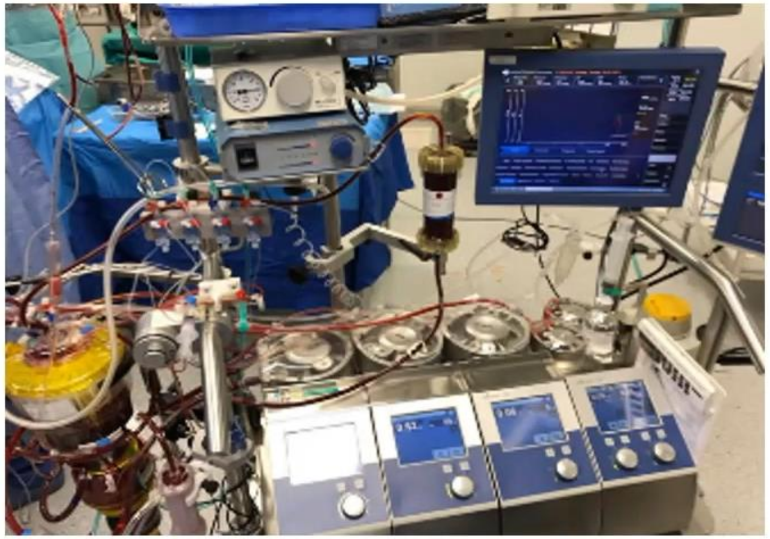
HA in Acute Nephrology

HA for Critical Disease
AKI, Sepsis, SA-AKI, ARDS, Rhabdo., Post-CABG, Pancreatitis

Target: removal of inflammatory mediators and **cytokines**







Various connection with CPB, ECMO, CVVH

Sepsis

World Journal of Critical Care Medicine

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World J Crit Care Med 2023 March 9; 12(2): 71-88

DOI: 10.5492/wjccm.v12.i2.71

ISSN 2220-3141 (online)

SYSTEMATIC REVIEWS

Extracorporeal blood purification strategies in sepsis and septic shock: An insight into recent advancements

Yatin Mehta, Rajib Paul, Abdul Samad Ansari, Tanmay Banerjee, Serdar Gunaydin, Amir Ahmad Nassiri, Federico Pappalardo, Vedran Premužić, Prachee Sathe, Vinod Singh, Emilio Rey Vela

COVID-19

Blood Purification

Research Article

Blood Purif
DOI: 10.1159/000524606

Received: November 10, 2021
Accepted: April 11, 2022
Published online: May 17, 2022

Efficacy of Hemoperfusion in Severe and Critical Cases of COVID-19

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Received: 3 March 2021 | Revised: 8 June 2021 | Accepted: 9 June 2021

DOI: 10.1111/aor.14024

MAIN TEXT

Artificial Organs WILEY

Blood purification with CytoSorb in critically ill COVID-19 patients: A case series of 26 patients

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Abstract

Severe forms of the coronavirus disease 2019 (COVID-19) can progress to sepsis-like complications accompanied by "cytokine storm" for which the most effective treatment has not yet been established. Our study describes the results of CytoSorb hemoadsorption in COVID-19 patients treated on the intensive care unit (ICU). In this retrospective study, 26 patients with COVID-19 and acute respiratory distress syndrome (ARDS) were treated with hemoadsorption therapy. Pre-, and post-treatment values (clinical and laboratory) were compared. Data are expressed as mean (confidence intervals, CI), or median [interquartile ranges, IQR], as appropriate. Patients received 2 hemoadsorption treatments. This resulted in a significant decrease in norepinephrine requirements, and inflammatory marker plasma concentrations (procalcitonin, C-reactive protein, ferritin) when comparing pre versus post treatment levels. The PaO_2/FiO_2 and overall organ function (ie, Sequential Organ Failure Assessment—SOFA score) also improved significantly. Patients stayed on the ICU for 9 days and 21 of them survived. To the best of our knowledge, this is one of the largest case series to date reporting early experiences on extracorporeal hemoadsorption therapy in SARS-CoV-2 positive patients with hyperinflammation and moderate ARDS. Treatment proved to be effective, technically feasible and well-tolerated.

KEYWORDS

COVID-19, CytoSorb, hemoadsorption, hemodynamic, hyperinflammation, lung function

ARDS

Review

IJAO The International Journal of Artificial Organs

The International Journal of Artificial Organs
2023, Vol. 46(12) 605–617

DOI: 10.1177/03913988231211740
journals.sagepub.com/home/jao
Sage

The potential role of extracorporeal cytokine removal with CytoSorb® as an adjuvant therapy in Acute Respiratory Distress Syndrome

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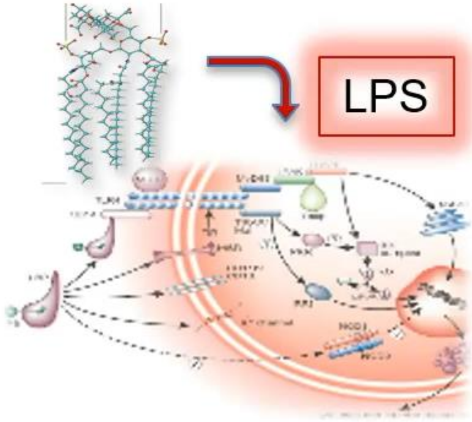
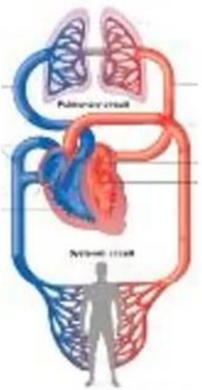
Abstract

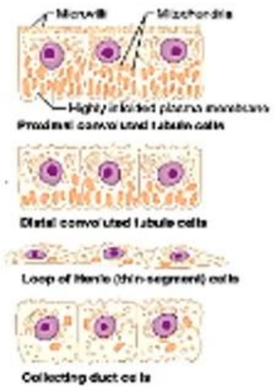
Management of acute respiratory distress syndrome (ARDS) represents one of the greatest challenges in intensive care and despite all efforts mortality remains high. One common phenotype of ARDS is that of a secondary injury to a dysregulated inflammatory host response resulting in increased capillary congestion, interstitial lung edema, atelectasis, pulmonary embolism, muscle wasting, recurring infectious episodes, and multiple organ failure. In cases of hyperinflammation, immunomodulation by extracorporeal cytokine removal such as the CytoSorb hemoadsorption cartridge could conceptually enhance lung recovery during the early course of the disease. The aim of this narrative review is to summarize the currently available data in this field and to provide an overview of pathophysiology and rationale for the use of CytoSorb hemoadsorption in patients with hyperinflammatory ARDS.

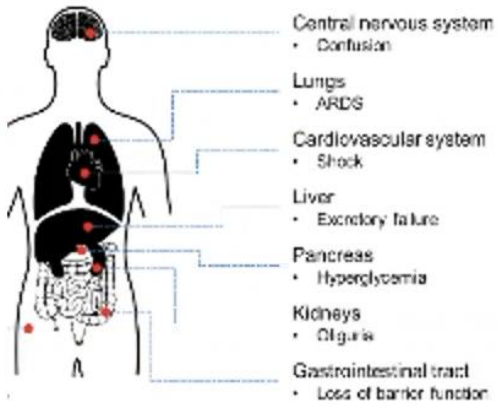
Sequential Integrated Approach to Sepsis

Infection >>> Immuno response >>> Organ Damage



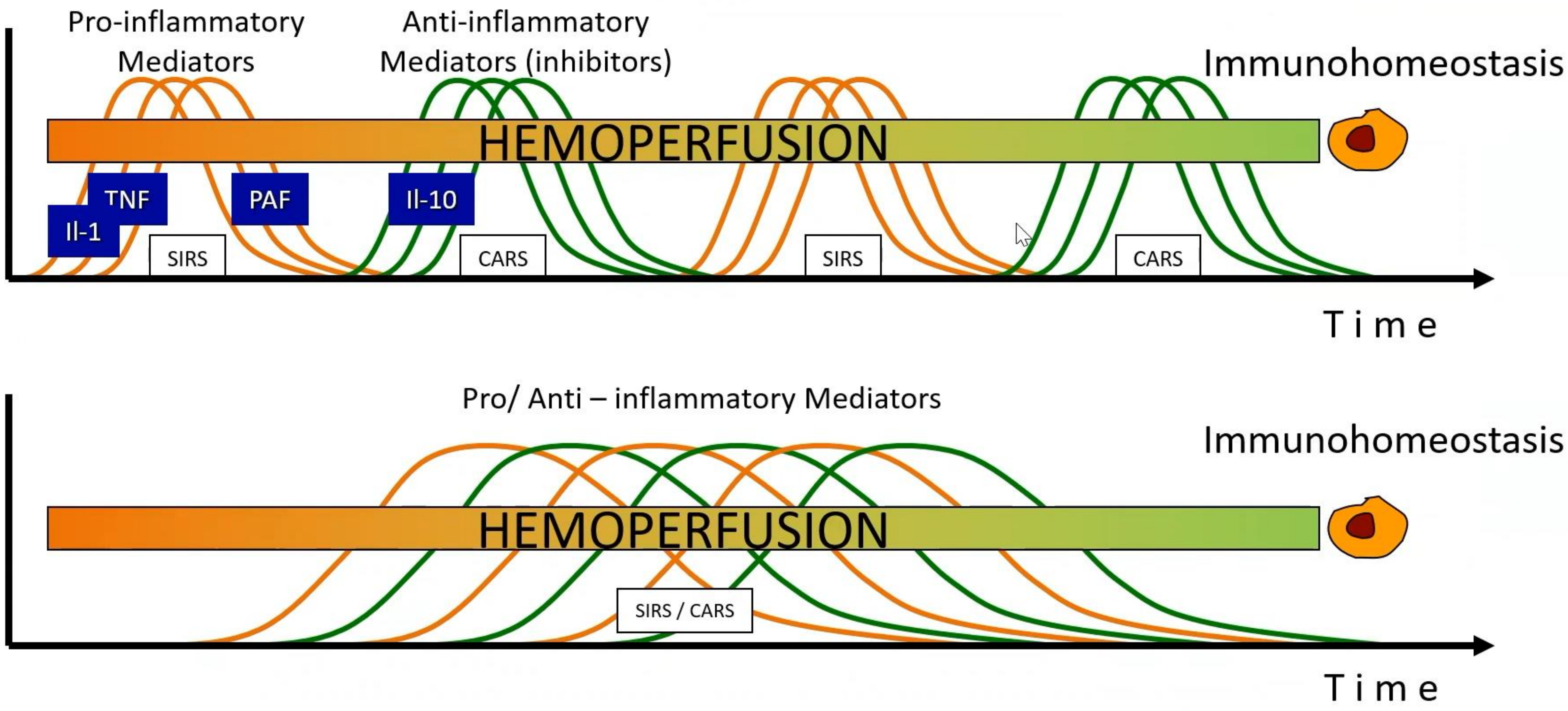


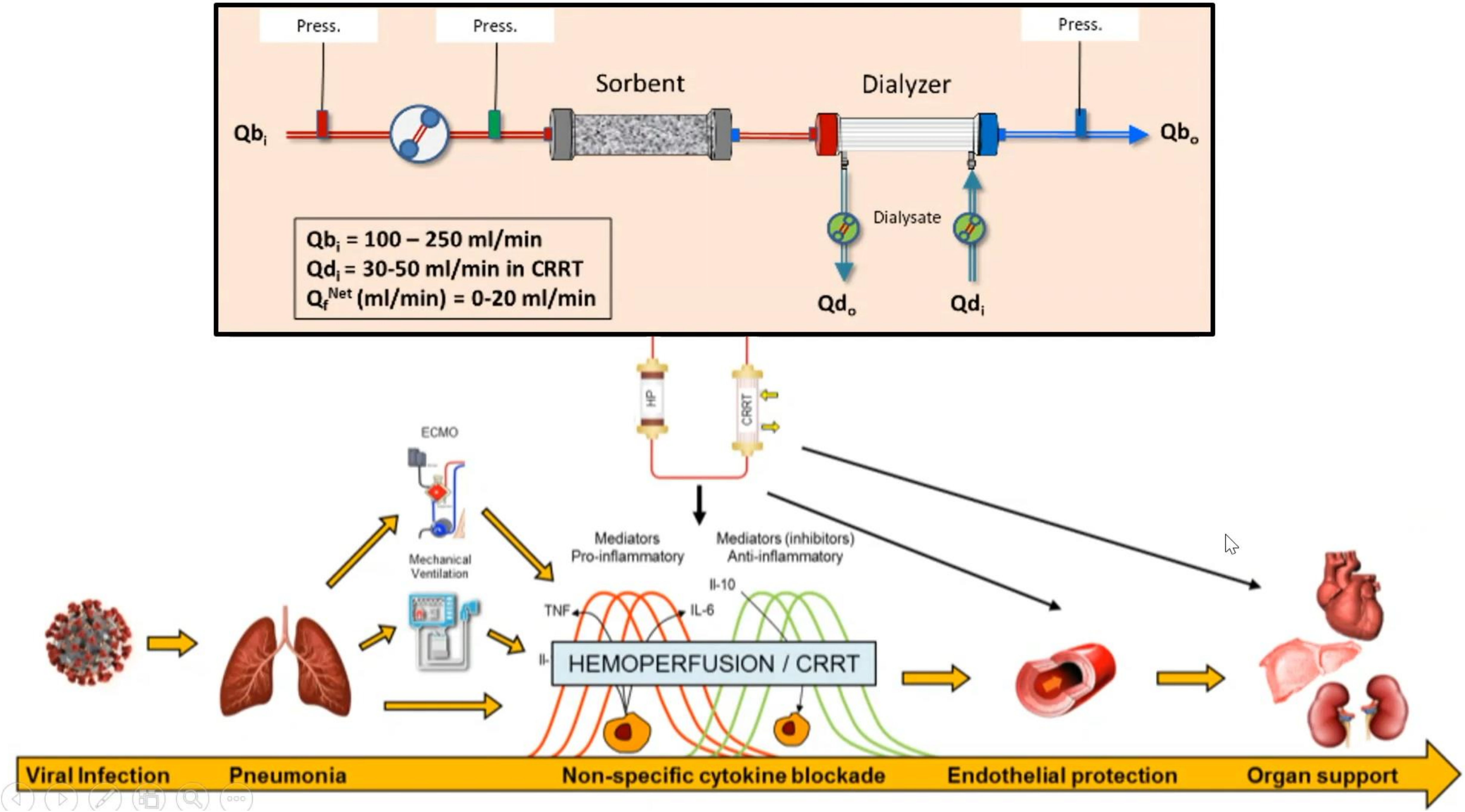




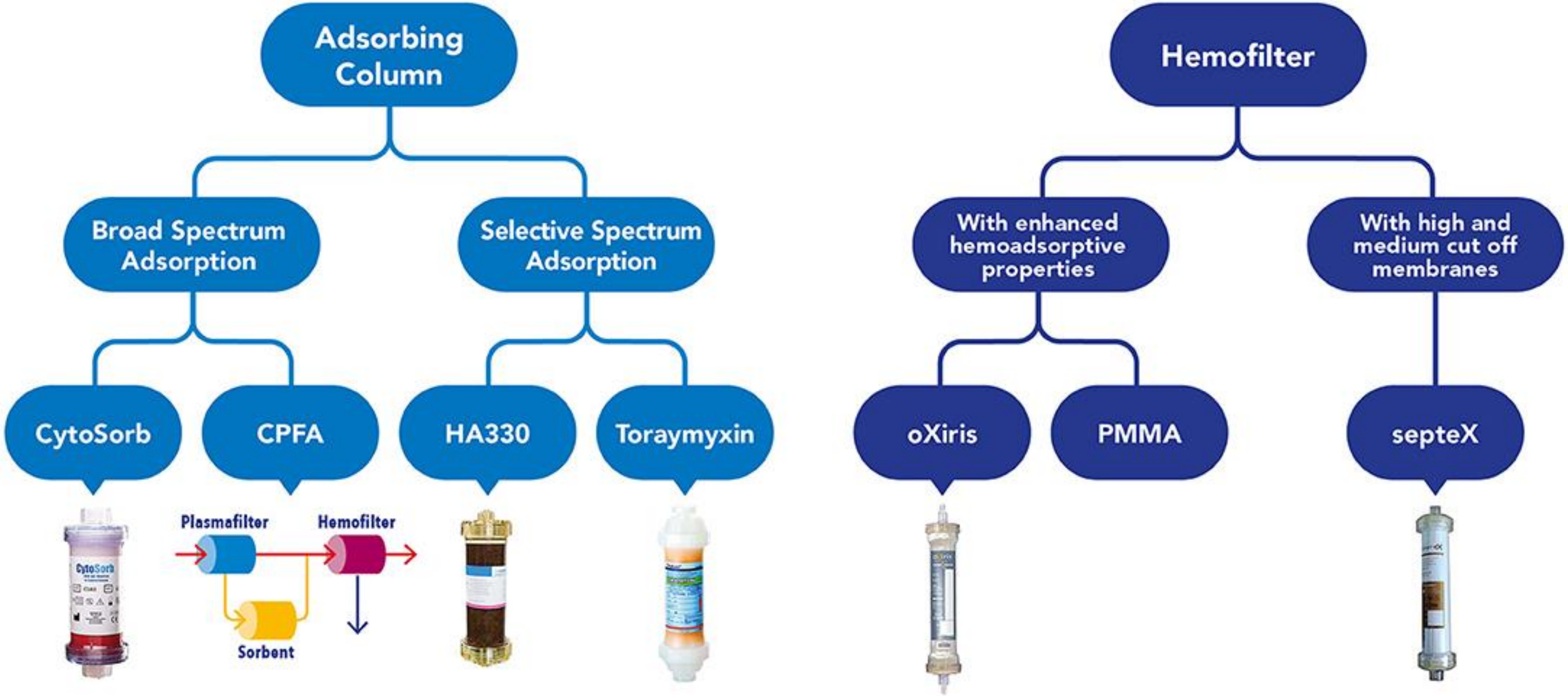
Pathogen >> Endotoxin >> Cytokines >> Organ Failure

The Peak Concentration Hypothesis





Press.
Press.
Press.
Sorbent
Dialyzer
Qb_i
Qb_o
Dialysate
Qd_o
Qd_i
Qb_i = 100 – 250 ml/min
Qd_i = 30-50 ml/min in CRRT
Q_f^{Net} (ml/min) = 0-20 ml/min
HP
CRRT
ECMO
Mechanical Ventilation
Mediators Pro-inflammatory
Mediators (inhibitors) Anti-inflammatory
Il-10
TNF
IL-6
HEMOPERFUSION / CRRT
Viral Infection
Pneumonia
Non-specific cytokine blockade
Endothelial protection
Organ support


Adsorbing Column
Broad Spectrum Adsorption
Selective Spectrum Adsorption
CytoSorb
CPFA
HA330
Toraymyxin
Plasmafilter
Hemofilter
Sorbent
Hemofilter
With enhanced hemoadsorptive properties
With high and medium cut off membranes
oXiris
PMMA
septeX

Seraph / PMX

Seraph Microbind Affinity Blood Filter

- ✓ A broad-spectrum, biomimetic hemoperfusion device.
- ✓ *Seraph 100* is a filter containing high-capacity 'adsorbent media'.
- ✓ *Seraph 200* also contains a 'supplemental adsorbent' that removes endotoxins.

Pathogens bind to heparan sulfate, a key receptor on cell surfaces. Seraph uses this affinity to bind and remove pathogens, toxins, and cytokines from flowing blood.

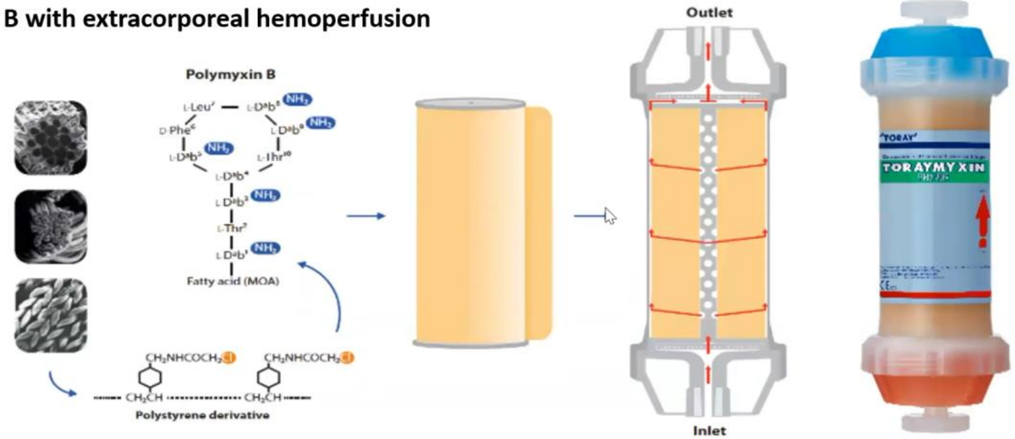
- Binding Pathogens Include:

MRSA	*E. coli*
S. aureus	*E. coli (CRE)*
K. pneumoniae	*S. pneumoniae*
K. pneumoniae (CRE)	*E. faecalis*
K. pneumoniae (MDR)	*E. faecalis (VRE)*
S. pyogenes	*E. faecium*
S. marcescens	*A. baumannii*
P. aeruginosa	*S. epidermidis*
	MRSE

ExThera Medical

Polymyxin B-based Medical Device (TORAYMYXIN - PMX-20R)

The Polymyxin B immobilized cartridge was developed to combine the potent endotoxin-neutralizing capabilities of Polymyxin B with extracorporeal hemoperfusion



PMX

In Vitro

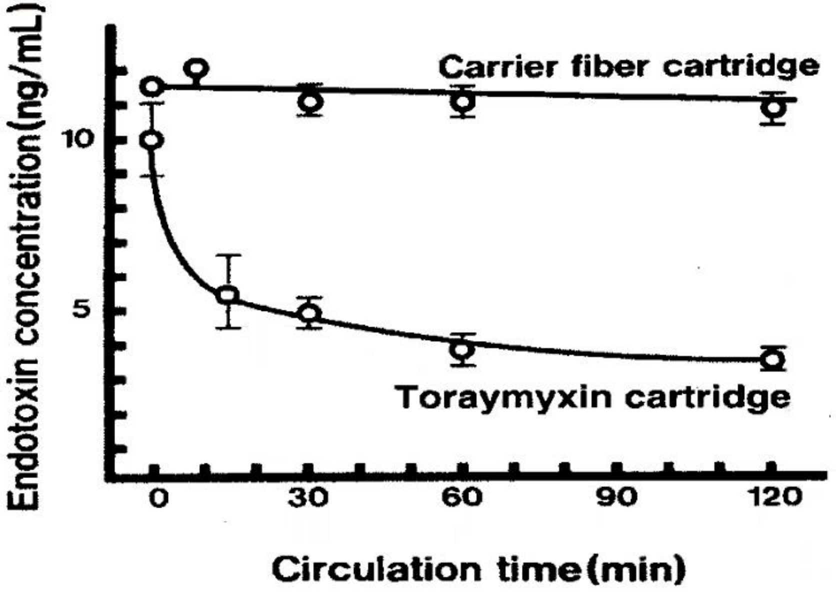
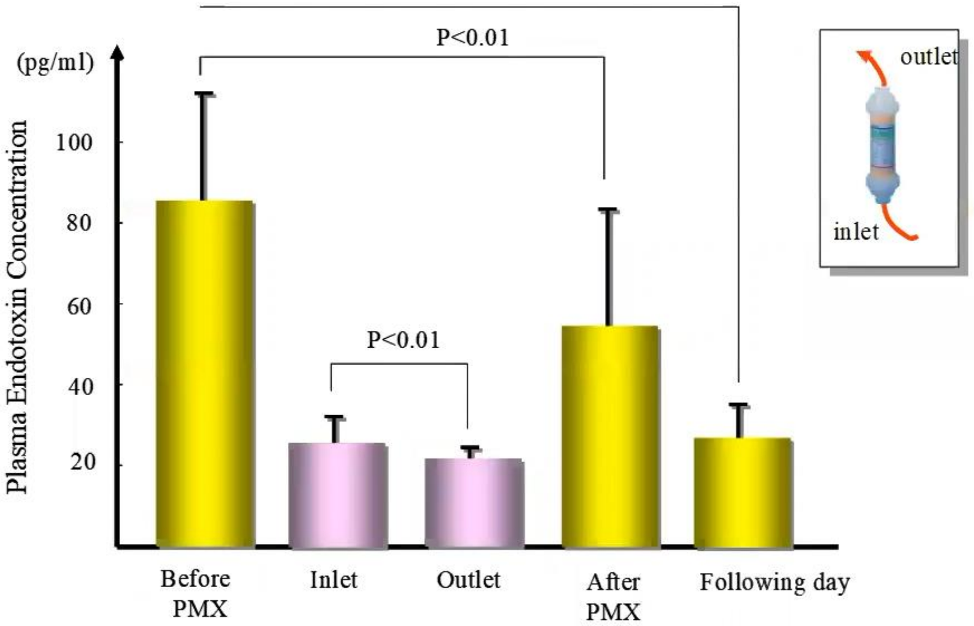


FIG. 7. Graph to show the changes in endotoxin concentration with a carrier fiber cartridge and a PMX cartridge over 2 h.

In Vivo



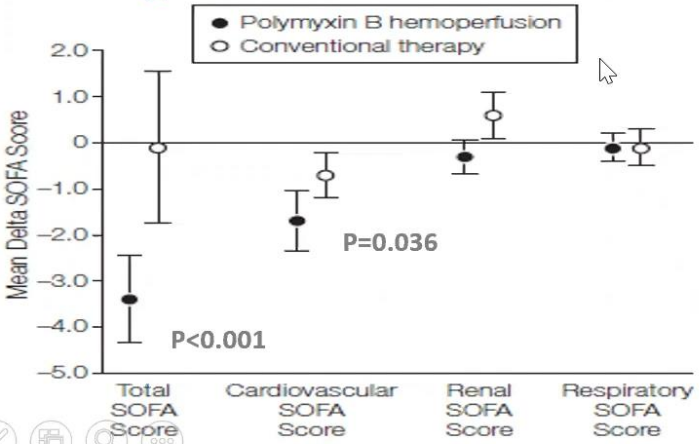
J Endotoxin Res 1997; **4**: 293-300

EUPHAS Trial

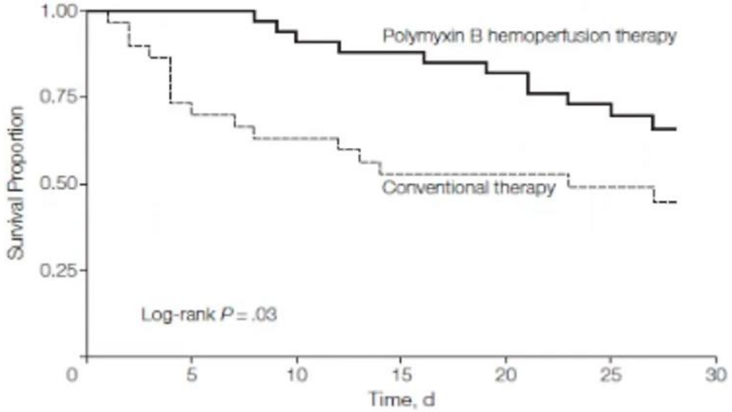
Early Use of Polymyxin B Hemoperfusion in Abdominal Septic Shock: The EUPHAS Randomized Controlled Trial

Physiological End Points	Polymyxin B Hemoperfusion, Mean (95% CI): Baseline (n = 34)	Polymyxin B Hemoperfusion, Mean (95% CI): 72 Hours (n = 34)	Polymyxin B Hemoperfusion: *P* Value	Conventional Therapy, Mean (95% CI): Baseline (n = 30)	Conventional Therapy, Mean (95% CI): 72 Hours (n = 27)	Conventional Therapy: *P* Value
Mean arterial pressure, mm Hg	76 (72-80)	84 (80-88)	.001	74 (70-78)	77 (72-82)	.37
Inotropic score	29.9 (20.4-39.4)	6.8 (2.9-10.7)	<.001	28.6 (16.6-40.7)	22.4 (9.3-35.5)	.14
Vasopressor dependency index, mm Hg^{-1}	4.3 (2.7-5.9)	0.9 (0.3-1.5)	<.001	4.1 (2.3-6.0)	3.3 (1.3-5.3)	.26
PaO_2/FIO_2	235 (206-265)	264 (236-292)	.049	217 (188-247)	228 (199-258)	.79
Renal replacement therapy, No. (%)	13 (38)	15 (44)	.50	6 (20)	8 (30)	.50

Change in SOFA scores at 72 h



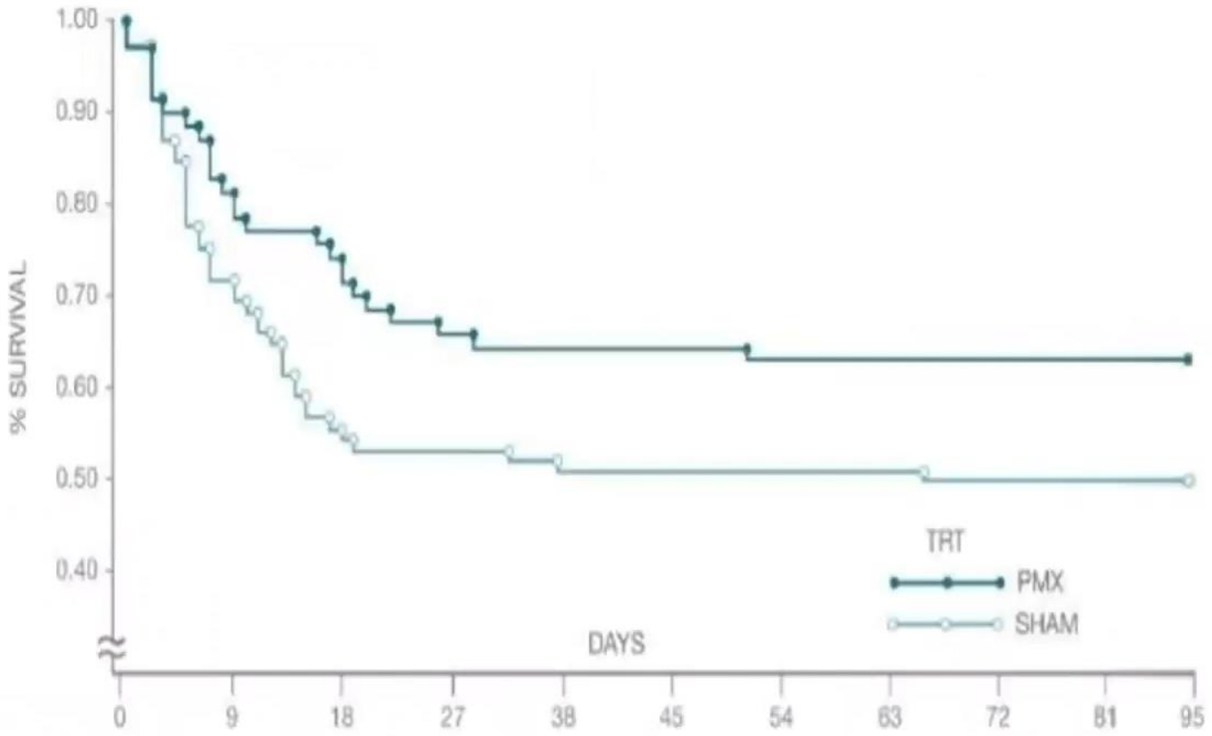
28-day Survival

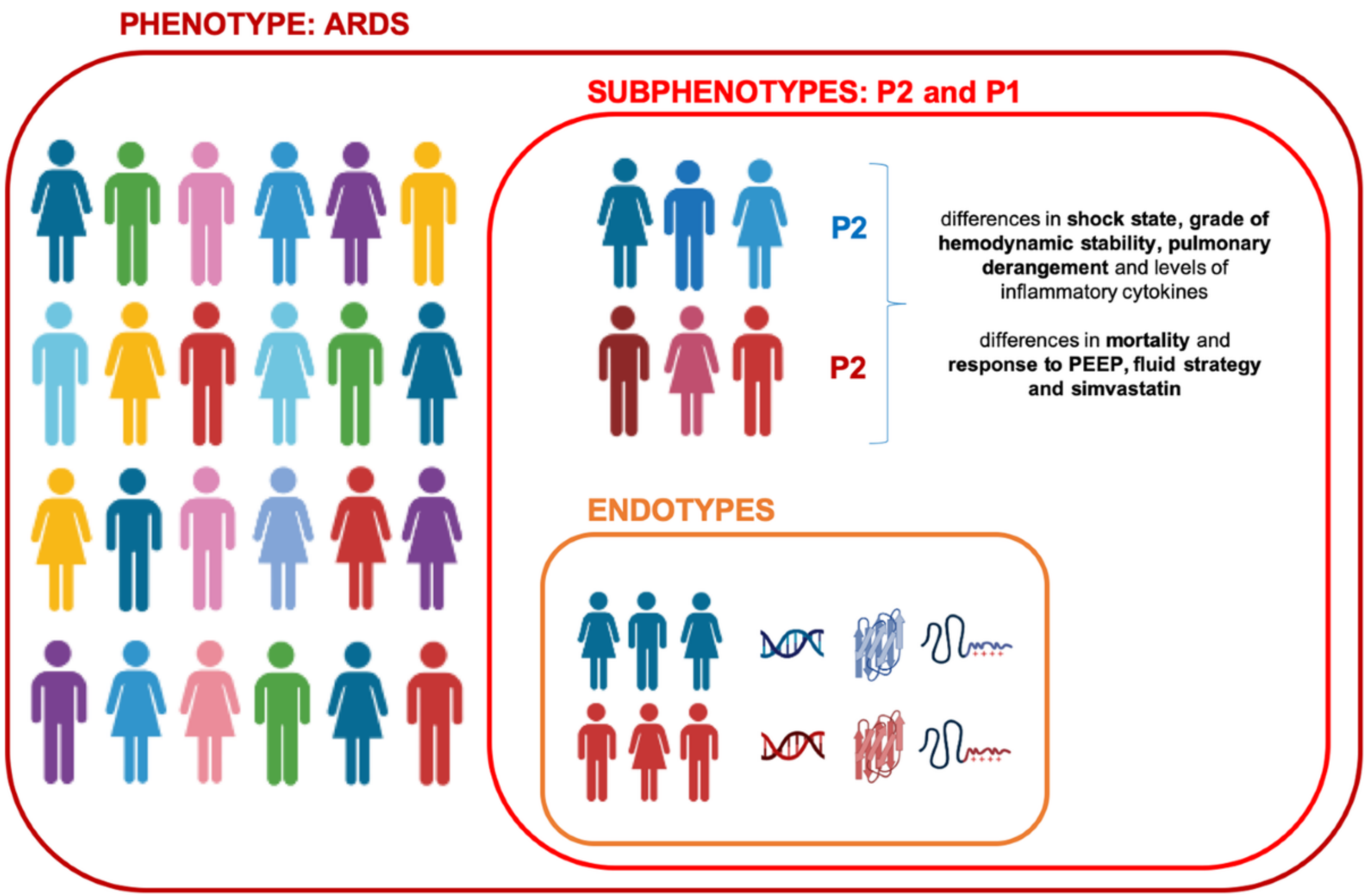


EUPHRATES trial

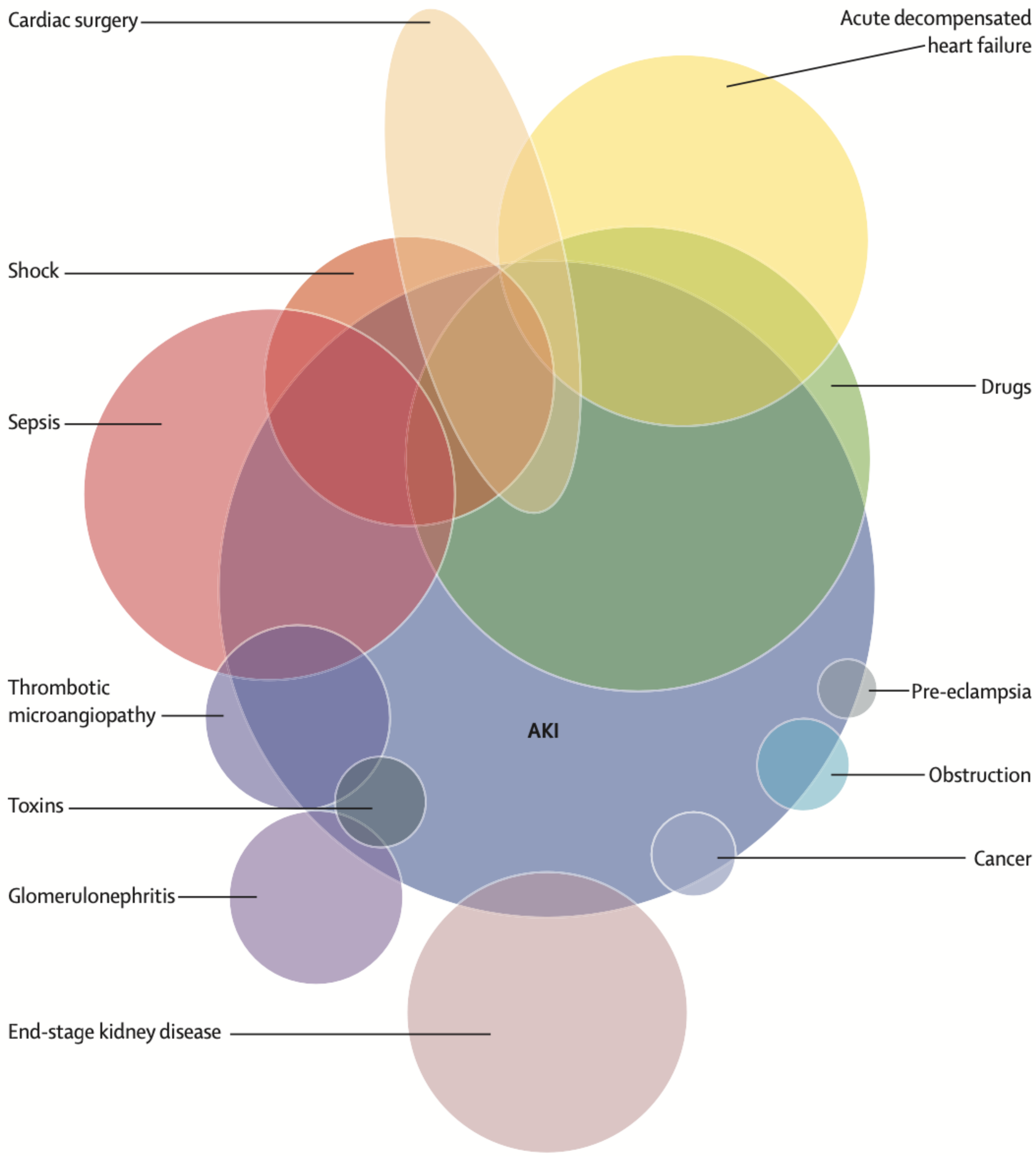
Modified per protocol population (mPP) (n=194);

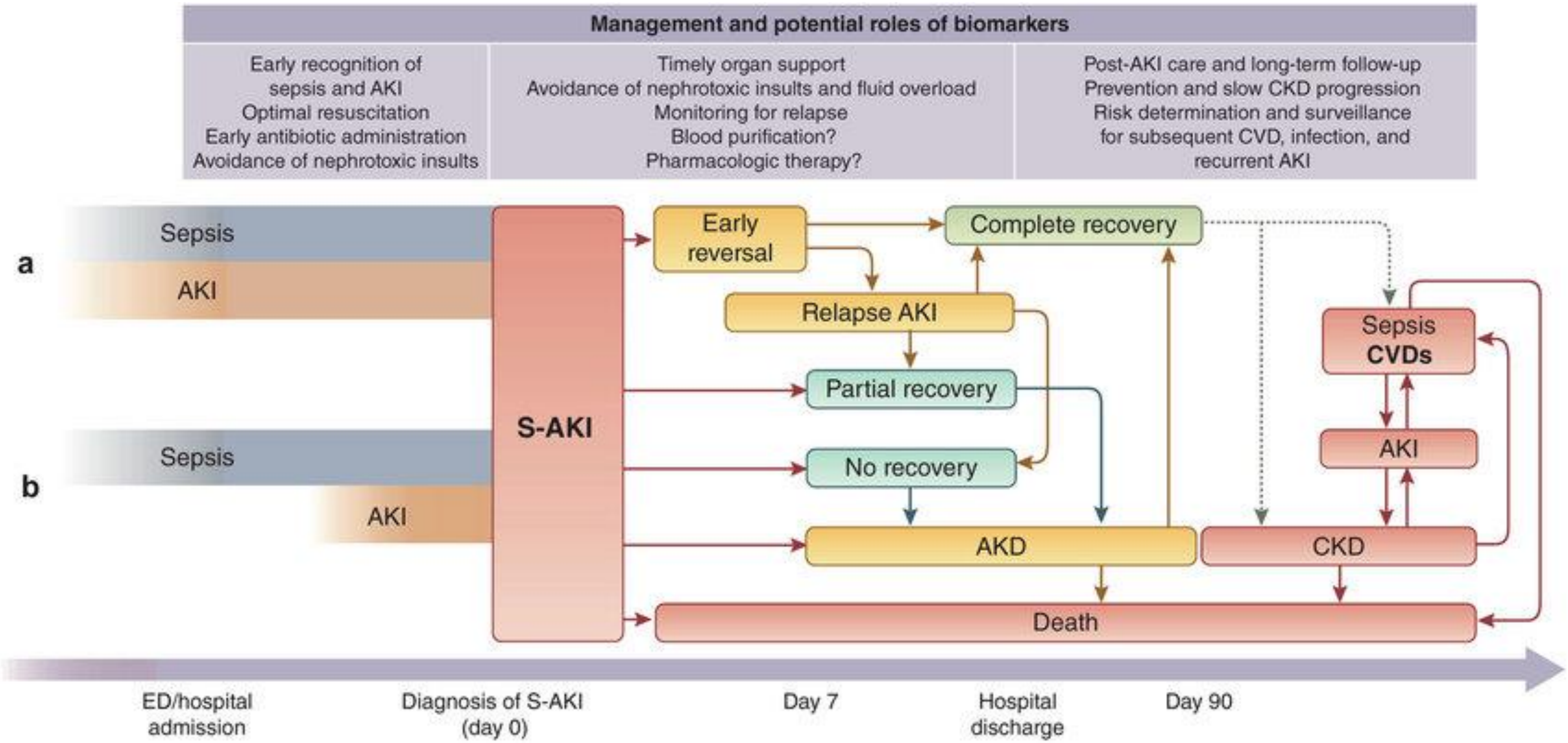
Septic Shock – 0.6 ≤ EAA < 0.9 – MODS>9

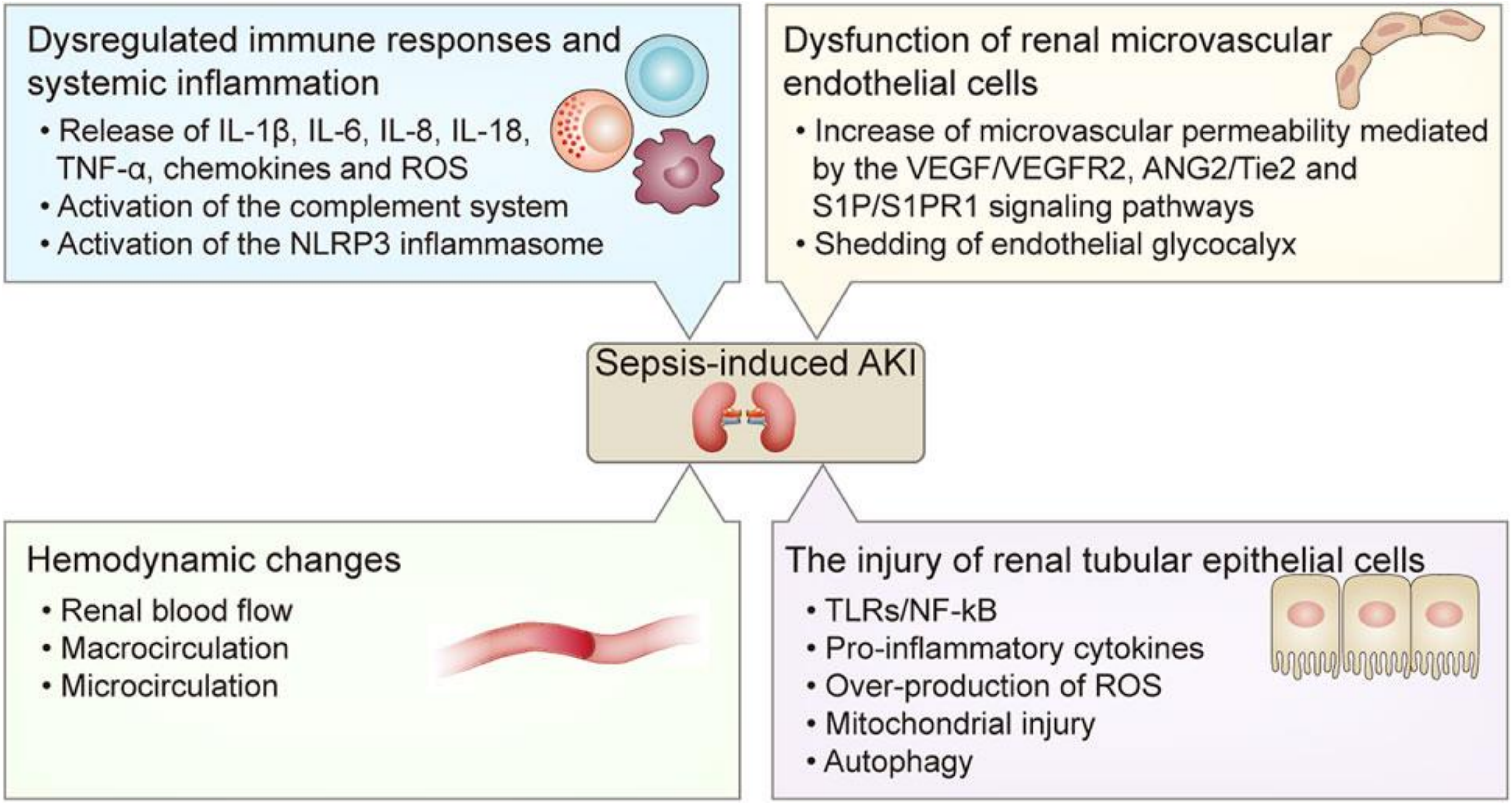




PHENOTYPE: ARDS
SUBPHENOTYPES: P2 and P1
P2
P2
differences in shock state, grade of hemodynamic stability, pulmonary derangement and levels of inflammatory cytokines
differences in mortality and response to PEEP, fluid strategy and simvastatin
ENDOTYPES


Cardiac surgery
Acute decompensated heart failure
Shock
Sepsis
Drugs
Thrombotic microangiopathy
Pre-eclampsia
AKI
Obstruction
Toxins
Cancer
Glomerulonephritis
End-stage kidney disease


Management and potential roles of biomarkers
Early recognition of sepsis and AKI
Optimal resuscitation
Early antibiotic administration
Avoidance of nephrotoxic insults
Timely organ support
Avoidance of nephrotoxic insults and fluid overload
Monitoring for relapse
Blood purification?
Pharmacologic therapy?
Post-AKI care and long-term follow-up
Prevention and slow CKD progression
Risk determination and surveillance for subsequent CVD, infection, and recurrent AKI
a
Sepsis
AKI
b
Sepsis
AKI
S-AKI
Early reversal
Complete recovery
Relapse AKI
Partial recovery
No recovery
AKD
Death
Sepsis
CVDs
AKI
CKD
ED/hospital admission
Diagnosis of S-AKI (day 0)
Day 7
Hospital discharge
Day 90


Dysregulated immune responses and systemic inflammation
• Release of IL-1β, IL-6, IL-8, IL-18, TNF-α, chemokines and ROS
• Activation of the complement system
• Activation of the NLRP3 inflammasome
Dysfunction of renal microvascular endothelial cells
• Increase of microvascular permeability mediated by the VEGF/VEGFR2, ANG2/Tie2 and S1P/S1PR1 signaling pathways
• Shedding of endothelial glycocalyx
Sepsis-induced AKI
Hemodynamic changes
• Renal blood flow
• Macrocirculation
• Microcirculation
The injury of renal tubular epithelial cells
• TLRs/NF-kB
• Pro-inflammatory cytokines
• Over-production of ROS
• Mitochondrial injury
• Autophagy

nature reviews nephrology https://doi.org/10.1038/s41581-023-00683-3

Consensus statement

Check for updates

Sepsis-associated acute kidney injury: consensus report of the 28th Acute Disease Quality Initiative workgroup

A list of authors and their affiliations appears at the end of the paper

Table 3 | Characteristics of extracorporeal blood purification therapies available for sepsis and SA-AKI

Technology	Indication	Modality	Target of removal	Mass separation mechanism	Comments
PAES-PVP high-flux	KRT, hyperinflammation	HD, HFl, HDF	Fluids, electrolytes, middle molecules	Convection, diffusion	CRRT for kidney support
AN69-PEI-heparin	KRT, hyperinflammation, Gram-negative sepsis or endotoxaemia	HD, HF, HDF	Fluids, electrolytes, middle molecules, endotoxin	Adsorption, convection, diffusion	CRRT for kidney and immunomodulatory support
AN69-ST, PMMA	KRT, hyperinflammation	HD, HF, HDF	Fluids, electrolytes, middle molecules	Adsorption, convection, diffusion	CRRT for kidney and immunomodulatory support
PAES-PVP MCO and HCO	KRT, hyperinflammation	HD	Fluids, electrolytes, middle molecules	Diffusion	CRRT for kidney and immunomodulatory support
Plasmasulfone, polypropylene (for membrane plasmapheresis)	Hyperinflammation	Centrifugation or HF	Fluids, electrolytes, middle molecules, endotoxin	Convection (membrane); gravity sedimentation (centrifuge)	Immunomodulatory support
Heparin covalently bound to polyethylene	Viraemia, bacteraemia, fungaemia	Haemoadsorption	Bacteria, fungi, viruses	Adsorption	Selective immunomodulatory support
Porous polymer beads polystyrene divinylbenzene	Hyperinflammation	Haemopadsorption	Protein-bound compounds, middle molecules	Adsorption	Non-selective immunomodulatory support
PMX covalently bound to polypropylene-polystyrene fibre	Gram-negative sepsis or endotoxaemia	Haemoadsorption	Endotoxin	Adsorption	Selective immunomodulatory support

AN, acrylonitrile; CRRT, continuous renal replacement therapy; HCO, high cut-off; HD, haemodialysis; HDF, haemodiafiltration; HF, haemofiltration, HFl, high-flux; KRT, kidney replacement therapy; MCO, medium cut-off; PAES, poly(aryl ether sulfone); PEI, polyethylenimine; PMMA, poly(methyl methacrylate); PVP, polyvinylpyrrolidone.

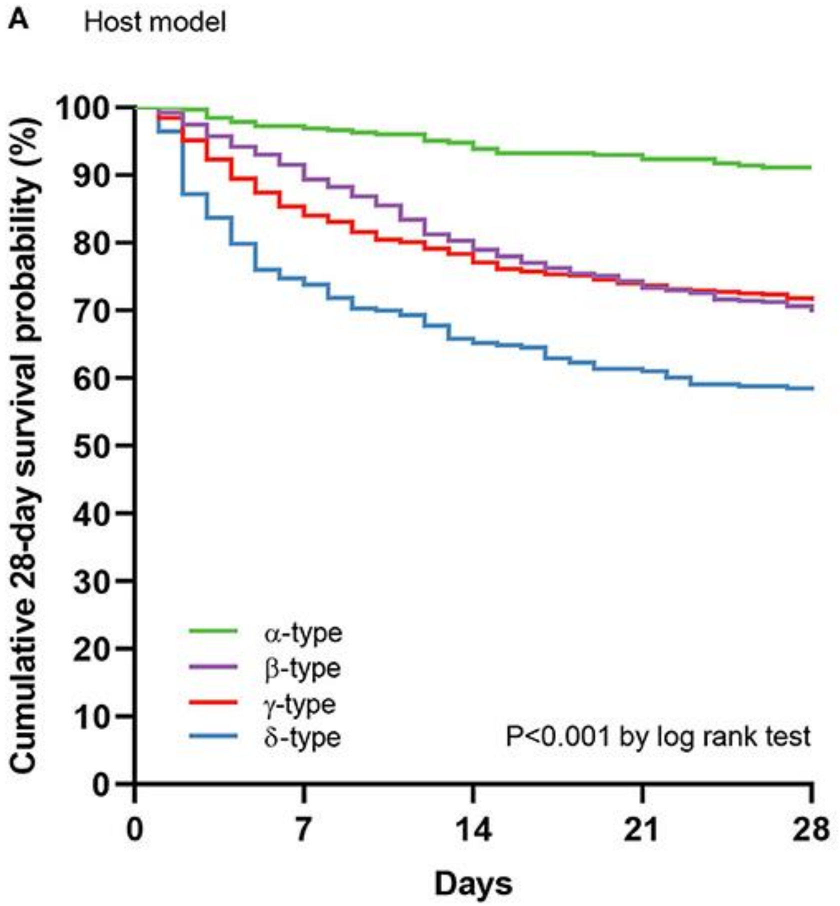
Evidence

…a good *trial* for **acute pts**…

- 1- Clarify the **phenotypes up to the endotypes** of the pts that we want to treat in order to achieve:
- clear indication criteria
- Good selection of pts
- Identification of sub-phenotypes
- Definition of target effect

- 2- **Endpoints** in HA trials :
- **Biochemical** (different molecular targets)
- **Biological** (cellular & tissue effects)
- **Physiological** (vital parameters)
- **Clinical** (organ function/severity score)
- **Ultimate outcomes** (recovery/survival)

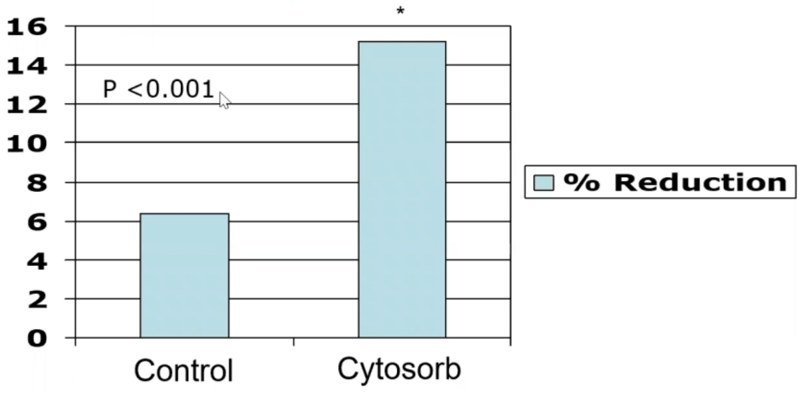
Define Sub-types & Endo-types


A
Host model
B
Host-pathogen model
Cumulative 28-day survival probability (%)
Days
α-type
β-type
γ-type
δ-type
P<0.001 by log rank test

Biochemical Effects (IL-18)

IL-18 Changes with Dialysis Alone and Combined with CytoSorb™ in ESRD

n=12



Winchester JF et al. Blood Purif 2004; 22:73-77

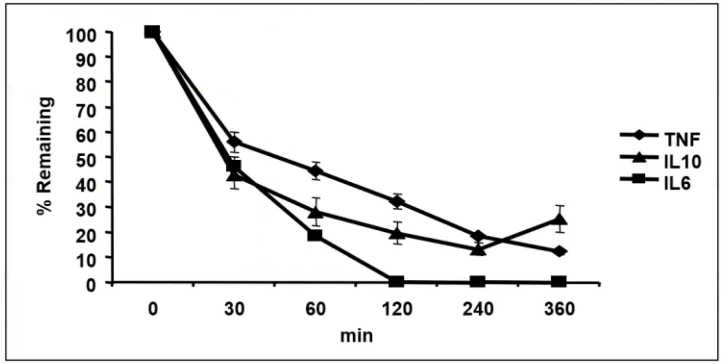
In Vitro Reduction of Cytokines with CytoSorb™ Resin

LPS injection – animals sacrificed 4 hours late

CytoSorb™ resin 10g

Blood reservoir 24 ml

BFR 0.8 ml/min



Time 0 Conc. (pg/ml)

TNF 5,984

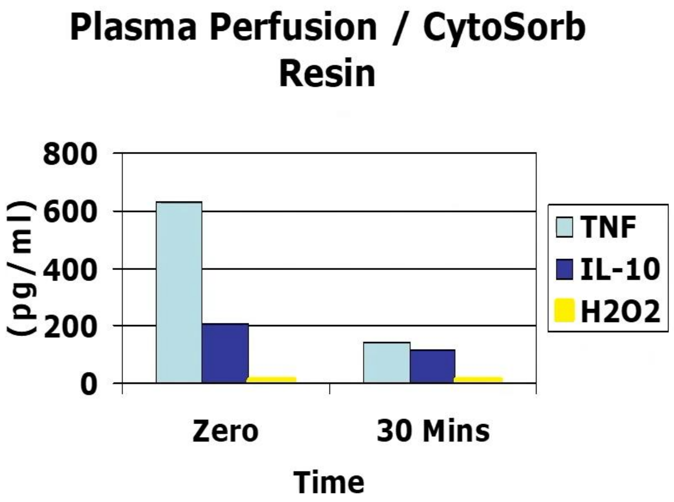
IL-10 9,584

IL-6 118,284

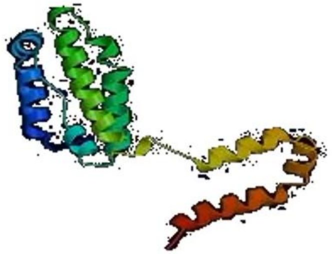
Kellum JA et al Crit Care Med 2004;32:801-805

Biochemical Effects (toxins removal)

In Vitro Removal of Toxins from Uremic Plasma



TNF, 21.5-28 kDa

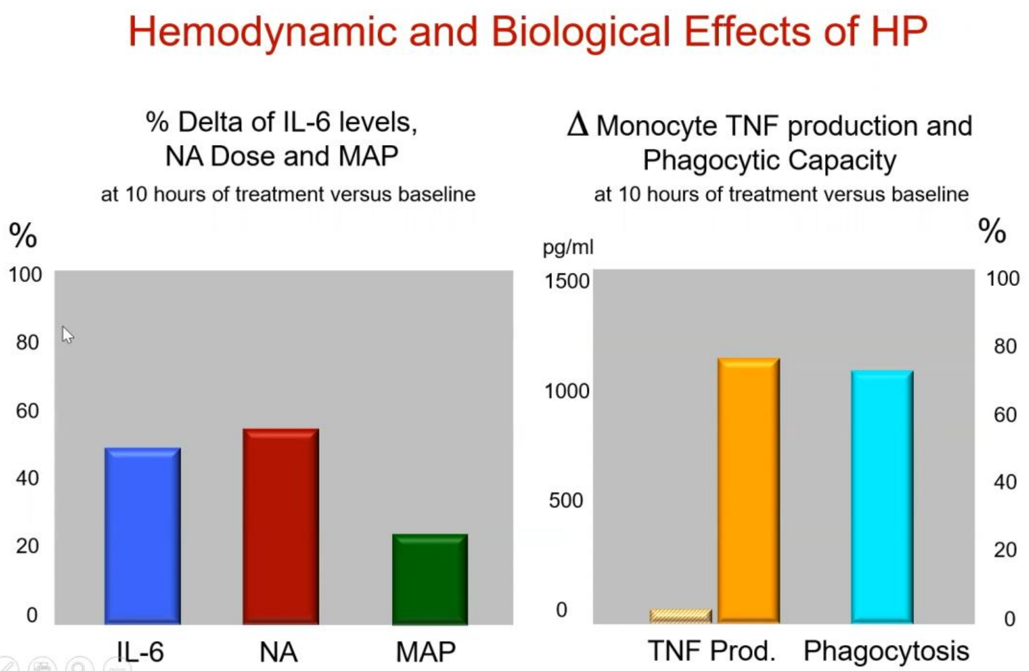


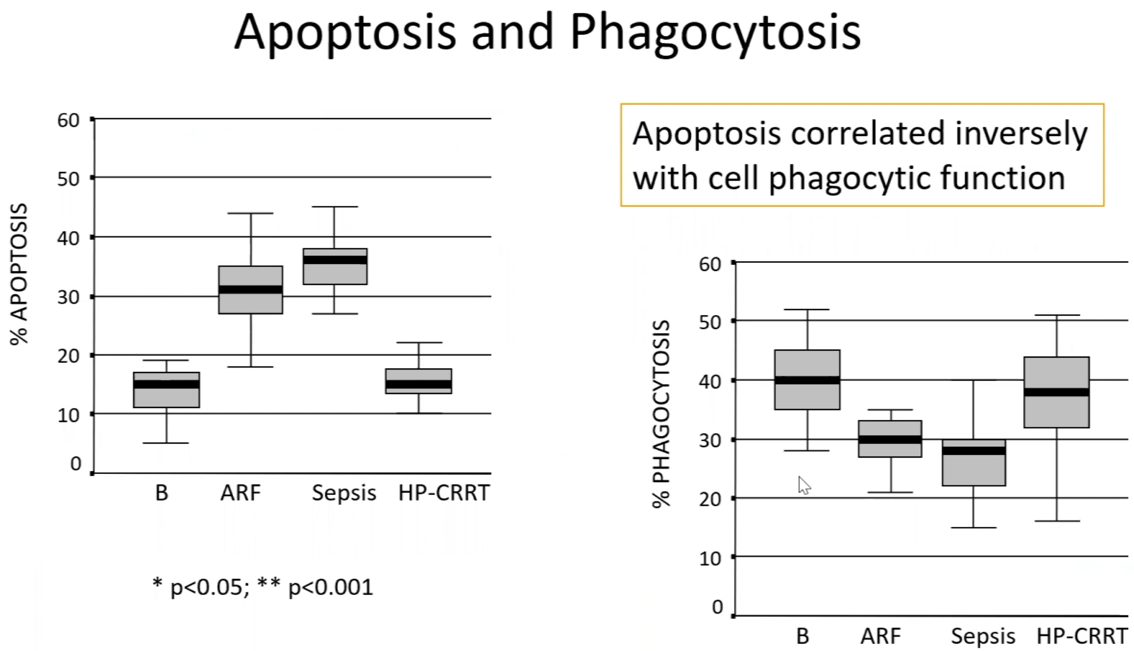
IL-10, 18 kDa

LPS stimulated THP-1 monocytes in uremic plasma (n=5)

Morena MD et al. Kidney Int 2003;63:1150

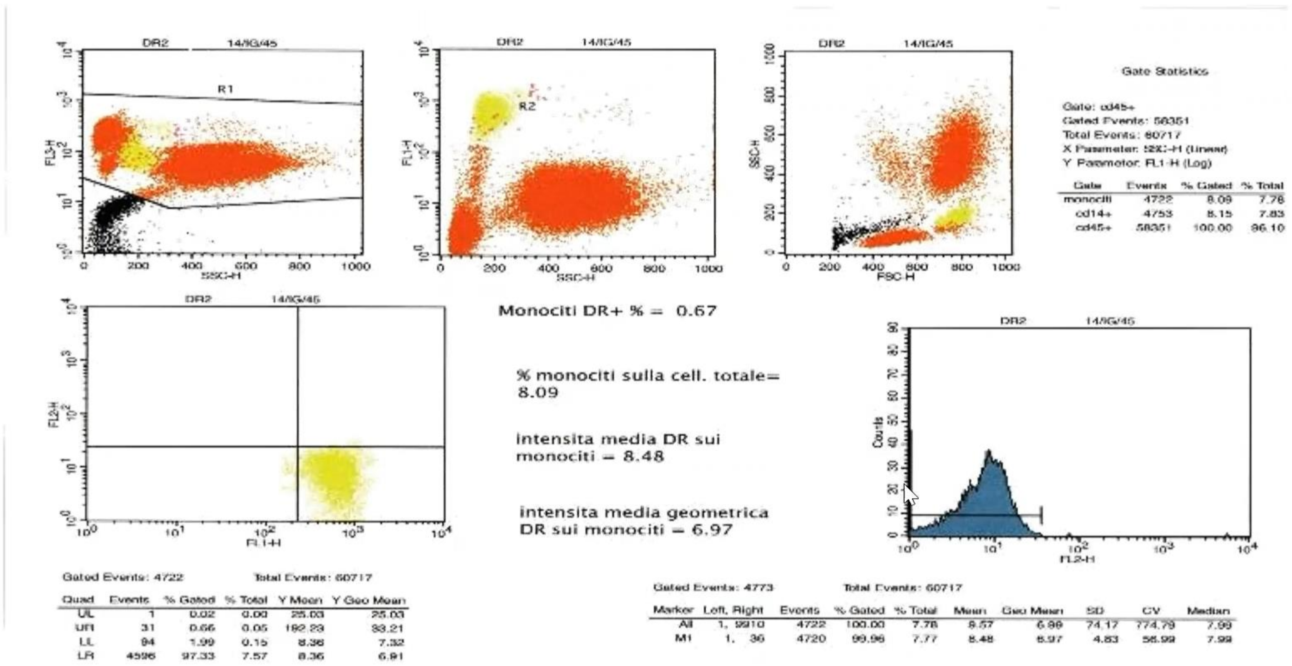
Hemodynamic & Biological Effects

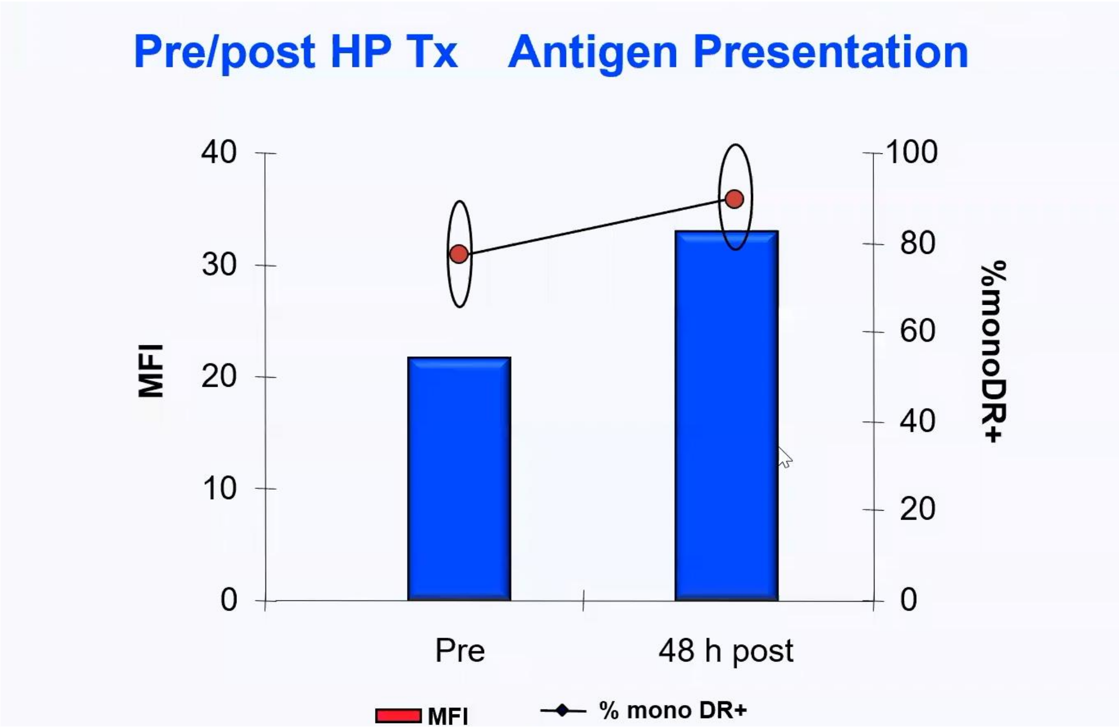




Increased HLA-DR expression by monocytes = return of the capacity of Ag presentation

Example of cytoflow analysis for HLA-DR





Physiological/Clinical Effects (SOFA score)

Removal of Humoral Mediators and the Effect on the Survival of Septic Patients by Hemoperfusion With Neutral Microporous Resin Column

Zhao Huang, Si-Rong Wang, Wei Su, and Ji-Yun Liu

Intensive Care Unit, First Municipal People's Hospital Affiliated to Guangzhou Medical College, Guangzhou, China

HA 380

- N=44. Severe sepsis or septic shock patients.
- Standard therapy vs standard therapy plus HP (2hr session daily X3days).
- Change in IL-6 and IL-8 and SOFA score (p<0.05)

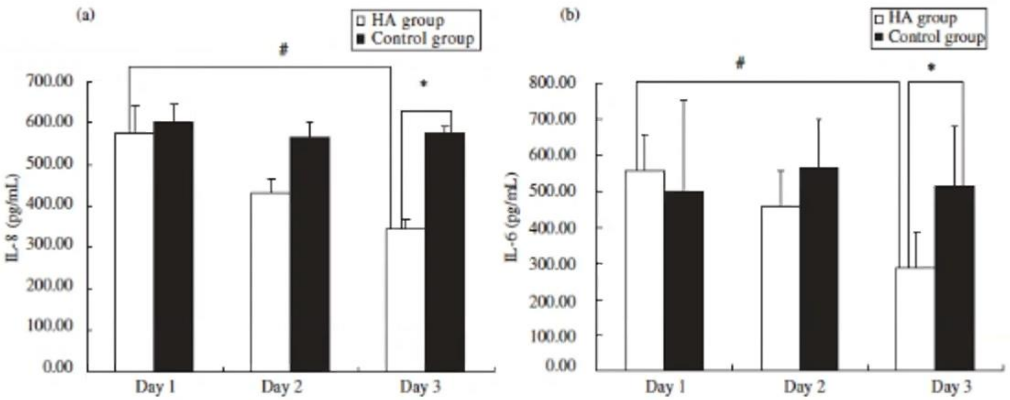


FIG. 1. Changes of circulating (a) interleukin (IL)-8, and (b) IL-6 between the HA group and the control group. The level of circulating IL-6 and IL-8 decreased post hemoperfusion compared with the baseline. In the control group the levels showed a tendency to increase during the study between the values at baseline and on day 2; however, this was not statistically significant ($P = 0.32, 0.67$). *There were statistically significant differences in the IL-6 and IL-8 levels between the two groups at day 3 ((a) $P = 0.03$; (b) $P = 0.01$). #Compared to the first day, the concentration of IL-6 and IL-8 reduced significantly at day 3 ((a) $P = 0.04$; (b) $P = 0.03$).

COVID-19

Admission:
Fever
Hypotension
Respiratory failure
> Mech. Ventilation

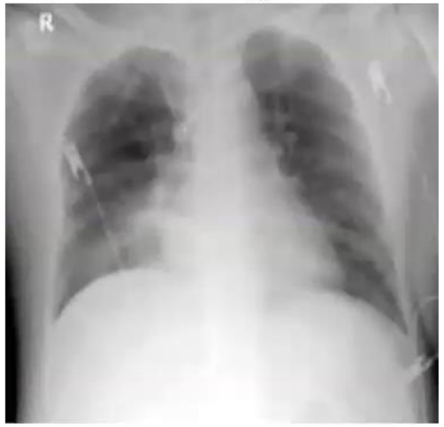
Hemodynamic instability
High Cytokine Levels
High Ferritin
High CRP
Hypercoagulability

Hemodynamic stabilization
Normalization of Cytokine Levels
Decrease in inflammatory parameters
Improved pulmonary exchanges
Extubation

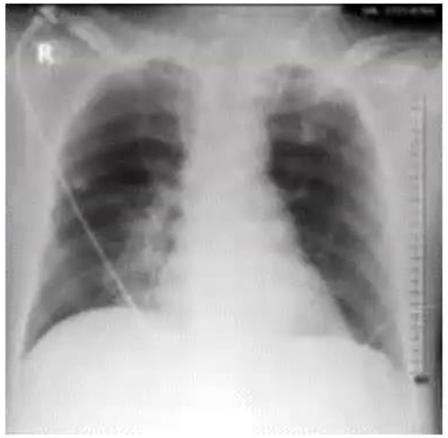
Day 1

Day 3

Days 4-5-6



Day 8



Day 12

Clinical Effects

CASE REPORT

WILEY

Recovery of Symmetrical Peripheral Gangrene of Limbs in a Patient After Performing Hemoadsorption in Septic Shock

Received: 29 August 2020 | Revised: 6 March 2021 | Accepted: 9 March 2021

DOI: 10.1002/jca.21893

Background

- The mortality risk of Symmetrical peripheral gangrene (SPG) is high (up to 40%) and almost half of the survivors need amputation.
- Currently, there is no specific treatment for SPG, as sepsis is one of the leading causes of DIC and SPG, there has been increasing interest in the use of extracorporeal devices for the removal of pathogenic components observed during sepsis.

Methods

- A 42-year-old male patient who had Hodgkin lymphoma and developed bilateral SPG in the feet and hands, which occurred during septic shock after autologous hematopoietic stem-cell transplantation (ASCT).
- Three HA330 absorbers were used over 3 days (2.5h each).

Results

- By the third day of HA, the vasopressors were discontinued.
- SPG in both feet and hands started to recover, and the patient was discharged from the hospital 38 days after ASCT.
- Three months after autologous transplantation, the patient was in complete remission, and his bilateral distal extremities fully recovered.

Ischemic changes observed in both feet and hand after septic shock. (B) Patient's extremities 15 months after autologous hematopoietic stem cell transplantation.

Conclusion

Early management of septic shock with massive fluid replacement, antibiotics, and especially the administration of HA within <24 hours in sepsis contributed to prevent need for amputation.

Ultimate Effects (survival)

Blood hemoperfusion with resin adsorption combined continuous veno-venous hemofiltration for patients with multiple organ dysfunction syndrome

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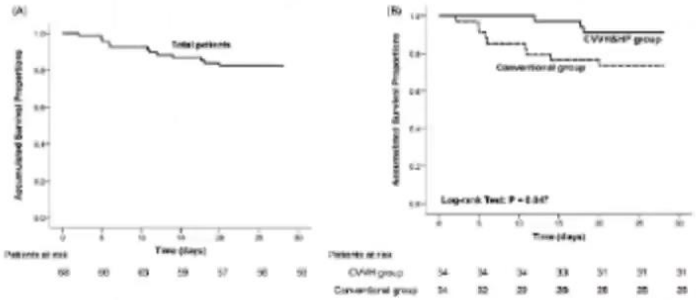
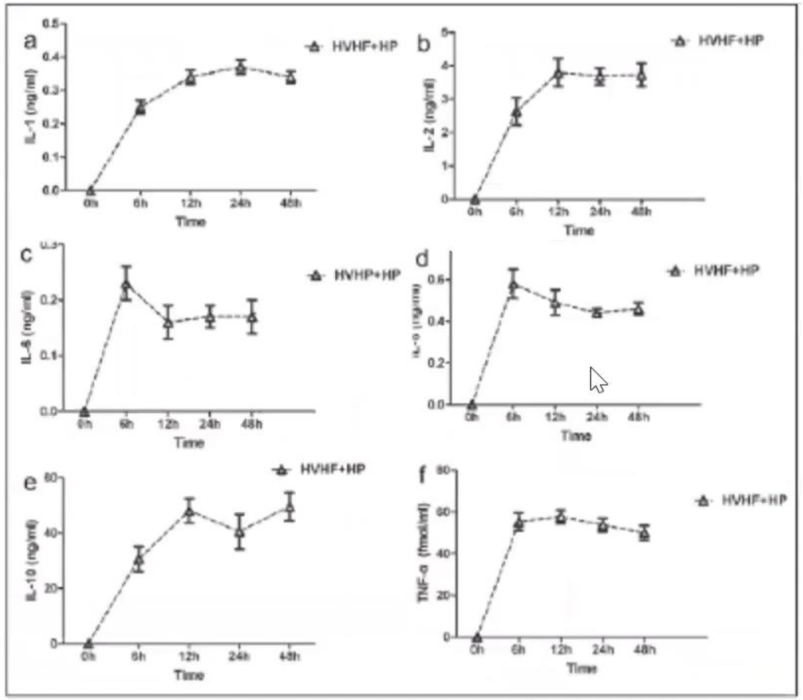
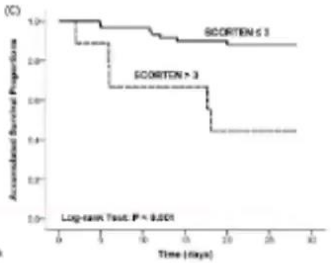
HA 380

Patients in the CVVH&HP group had a significantly improved 28-day survival compared with the conventional group (91.2%, versus 73.5 p=0.047).

n.30

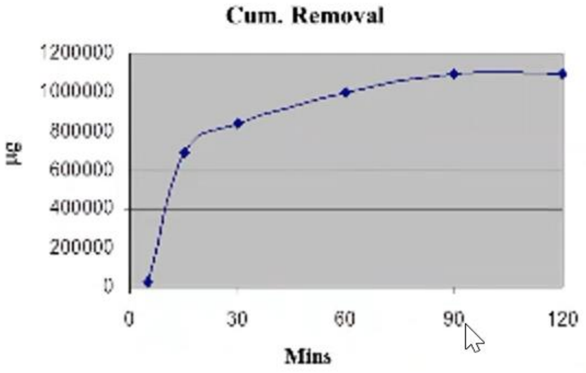




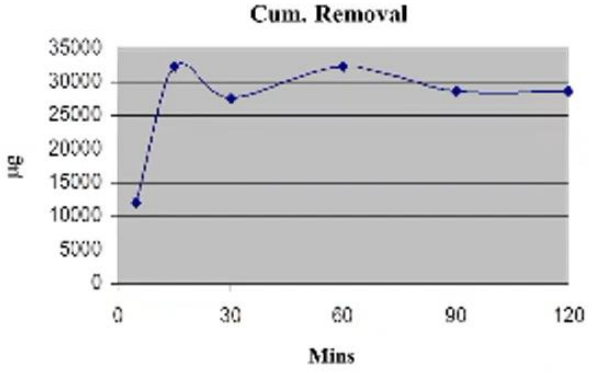


We remove beneficial drugs !

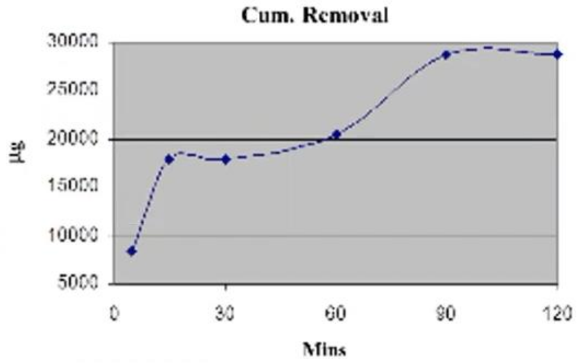
Vancomycin



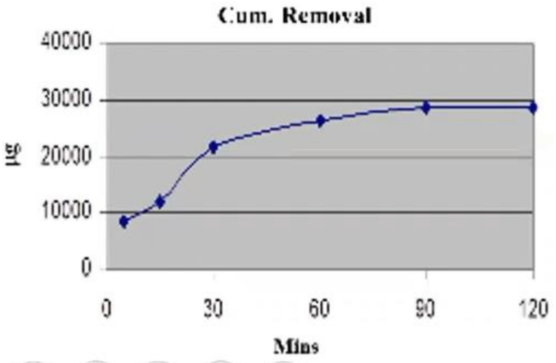
Amikacin



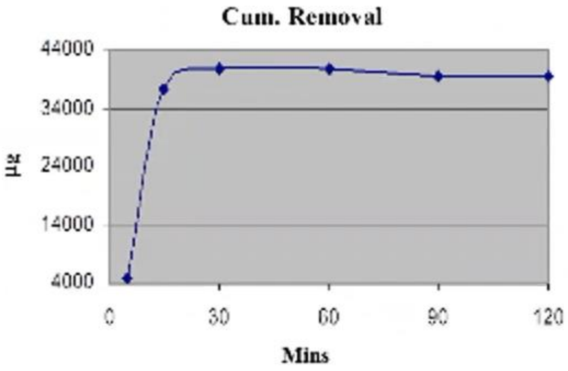
Gentamycin



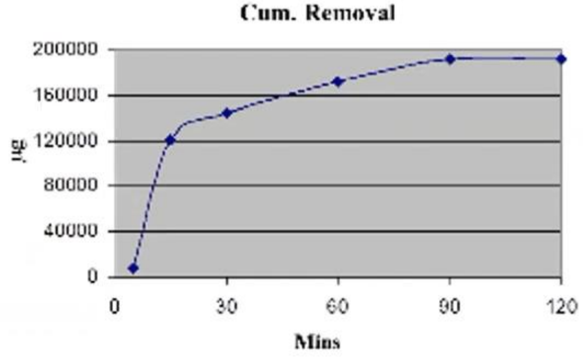
Tombramycin



Netilmycin



Teicoplanin



Where we are ?

Ronco and Bellomo Critical Care (2022) 26:135
https://doi.org/10.1186/s13054-022-04009-w

CRITICAL CARE

REVIEW — Open Access

Hemoperfusion: technical aspects and state of the art

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Abstract

Background: Blood purification through the removal of plasma solutes by adsorption to beads of charcoal or resins contained in a cartridge (hemoperfusion) has a long and imperfect history. Developments in production and coating technology, however, have recently increased the biocompatibility of sorbents and have spurred renewed interest in hemoperfusion.

Methods: We performed a narrative assessment of the literature with focus on the technology, characteristics, and principles of hemoperfusion. We assessed publications in ex vivo, animal, and human studies. We synthesized such literature in a technical and state of the art summary.

Results: Early hemoperfusion studies were hampered by bioincompatibility. Recent technology, however, has improved its safety. Hemoperfusion has been used with positive effects in chronic dialysis and chronic liver disease. It has also demonstrated extraction of a variety of toxins and drugs during episodes of overdose. Trials with endotoxin binding polymyxin B have shown mixed results in septic shock and are under active investigation. The role of non selective hemoperfusion in sepsis or inflammation remains. Although new technologies have made sorbents more biocompatible, the research agenda in the field remains vast.

Conclusion: New sorbents markedly differ from those used in the past because of greater biocompatibility and safety. Initial studies of novel sorbent based hemoperfusion show some promise in specific chronic conditions and some acute states. Systematic studies of novel sorbent based hemoperfusion are now both necessary and justified.

Introduction

The removal on unwanted plasma solutes by direct adsorption has an established long history. However, early sorbent technology had major bioincompatibility problems (e.g., thrombocytopenia, leukopenia, hypoglycemia, hypocalcemia). This held back the development and clinical application of hemoperfusion. Sorbent biocompatibility, however, has improved triggering renewed interest, investigations, and application of hemoperfusion in clinical practice.

Hemoperfusion: characteristics and principles

Extracorporeal blood purification can be achieved by different mass separation processes [1]. Diffusion, as in standard hemodialysis (HD), convection as in hemofiltration or their combination as in hemodiafiltration (HDF) [2]. While these techniques are based on membrane separation, a third mechanism, solute adsorption, is based on mass separation by a solid agent (sorbent) [3]. As current dialysis techniques present limitations due to membrane permeability characteristic, extracorporeal hemoperfusion represents an additional option for blood purification.

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Intensive Care Med
https://doi.org/10.1007/s00134-022-06810-1

INTENSIVE CARE MEDICINE

NARRATIVE REVIEW

Hemoperfusion in the intensive care unit

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Abstract

Multiple organ failure following a septic event derives from immune dysregulation. Many of the mediators of this process are humoral factors (cytokines), which could theoretically be cleared by direct adsorption through a process called hemoperfusion. Hemoperfusion through devices, which bind specific molecules like endotoxin or theoretically provide non-specific adsorption of pro-inflammatory mediators has been attempted and studied for several decades with variable results. More recently, technological evolution has led to the increasing application of adsorption due to more biocompatible and possibly more efficient biomaterials. As a result, new indications are developing in this field, and novel tools are available for clinical use. This narrative review will describe current knowledge regarding technical concepts, safety, and clinical results of hemoperfusion. Finally, it will focus on the most recent literature regarding adsorption applied in critically ill patients and their indications, including recent randomized controlled trials and future areas of investigation.

Keywords: Sepsis, Cytokine, Blood purification, Adsorption, Hemoperfusion, COVID-19, Lipopolysaccharide

Pathophysiology of sepsis

Sepsis is a complex clinical and biological syndrome defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. It begins as an infection that produces an inflammatory response in the host, triggered by the interaction between multiple soluble mediators [2]. The inflammatory response to infection by innate immunity is usually controlled, localized, and protective [3]. The interaction between resistance (inflammatory response) and resilience (limiting inflammation by the adaptive immunity) is the key to survival, but in some circumstances not completely understood, this complex and delicate balance is lost, and sepsis syndrome may develop. In this process of dysregulated response, both the infected and distal organs may be injured, leading to a life-threatening clinical condition [1]. Such a process tends to cause excessive production or suppression of cytokines and other mediators that affect vital organ function and triggers further inflammatory and counter-inflammatory pathways [4, 5]. The dominant clinical phenotypes of these biological events are sepsis and septic shock where patients may die due to intractable inflammation or persistent immunoparalysis.

The blood purification hypothesis

Blocking or attenuating the impact of soluble mediators offers protection in acute animal models of fulminant infections [6]. Thus, manipulating the soluble components of the host response is theoretically attractive. This approach represents the target of several studies although remaining controversial [3]. Previous attempts to modulate the immune response by targeting single cytokines have failed [7]. Thus, the blood purification concept based on the non-specific manipulation of several mediators' plasma levels has been proposed [8, 9]. Hemoperfusion can theoretically deliver non-specific treatment, as discussed below.

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HA in Critical Medicine

- We are today where CRRT was 30 years ago, and we need structured research
- We need to identify patient’s endophenotypes that are likely to benefit from HP
- We need to establish adequate dose, frequency, and criteria for HP application
- We need to identify target molecules and biomarkers and do biomonitoring
- We need to identify adequate end points for clinical trials to establish evidence
- We need to consider potential side effects and contraindications for this therapy
- We need to promote a medical academic alliance with industry for progress
- We need homogeneous terminology and standardized nomenclature in the field

Conclusions

1) Adsorption represents an interesting option for blood purification;
2) Different sorbent materials are available and modern chemistry can help to achieve specific and aspecific solute removal;
3) Optimal biocompatibility, mechanical strength and low toxicity are characteristics of modern sorbents;
4) Adsorption capacity can be tested with specific isotherms;
5) Different options are available for utilization of sorbents in practice
6) Sorbents may be the dorway to wearable and waterless dialysis
7) Adsorption represents the new frontier in extr. blood purification, but more research is required to achieve adequate levels of evidence

Concluding Thoughts

- HA is an **important therapeutic technique** in the management of patients with **acute kidney injury (AKI)** and other **acute nephrology conditions**, especially in critically ill patients.
- HA can help to **reduce inflammation, remove toxins, prevents further kidney damage, and improve patient outcomes**.
- Its ability to be **combined with CRRT** makes it particularly versatile in managing complex cases, such as septic shock or toxin-mediated kidney injury.
- HA is generally **well-tolerated**. However, there can be risks such as **coagulation disturbances** or **hypotension,** (especially + CRRT).

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