

به نام خدا





Importance of high and medium cut-off dialysis for acute kidney injury

Assistant Professor of Nephrology
Kidney Research Center
Tabriz University of Medical Sciences



Importance of high and medium cut-off dialysers for acute kidney injury

- Hemodialysis is a Life-Sustaining procedure for patients with end-stage renal disease (ESRD). But efficiency of hemodialysis is limited by the dialysis membrane **biocompatibility** and the **poor** clearance of **middle-molecule** uremic toxins.

Importance of high and medium cut-off dialysers for acute kidney injury

- During recent years, advances in dialysis membrane engineering led to the gradual design of hemodialysis membranes toward products with biological properties similar to glomerular basement membrane (GBM). Some of these advances have been motivated by the principle that **increased clearance of middle molecular weight (MW) molecules** may be associated with better clinical outcomes.

Outline

- **What is the high and medium cut-off membrane ?**
- **what is the Importance of high and medium cut-off dialysers for acute kidney injury ?**
- **what kind of acute kidney injures could be treated with medium and high cut-off dialysers?**
- **What are the results of using these new filters on prognosis of AKI ?**

Classification of Uremic Toxins

Uremic Toxin Class	Molecular Weight (kDa)	Representative Biomarkers
Small water-soluble molecules	<0.5 → LF-HD modality	Urea (60 Da), creatinine (113 Da), uric acid (168 Da)
Small-middle molecules	0.5–15 → HF-HD modality	PTH (9.5 kDa), β2-MG (11.8 kDa), cystatin C(13.3 kDa)
Medium-middle molecules	15–25 → online HF-HDF modality	Myoglobin (17 kDa), TNF-α (17 kDa), sTNFR2 (17 kDa), IL-10 (18 kDa), FGF-2 (18 kDa), prolactin (22 kDa), κ-FLC (22.5 kDa), complement factor D (23.75 kDa), IL-18 (24 kDa), IL-6 (24.5 kDa)
Large-middle molecules	25–58	sTNFR1 (27 kDa), FGF-23 (32 kDa), VEGF (34.2 kDa), YKL-40 (40 kDa), λ-FLC (45 kDa)
Large molecules	>58	AOPP (>60 kDa), modified albumin (65 kDa)
Protein-bound uremic toxins	mostly < 0.5	Homocysteine, IS, pCS

PTH, parathyroid hormone; β2-MG, β2-microglobulin; TNF, tumor necrosis factor; sTNFR, soluble tumor necrosis factor receptor; IL, interleukin; FGF, fibroblast growth factor; κ-FLC, κ free light chains; VEGF, vascular endothelial growth factor; YKL-40, chitinase-3-like protein 1; λ-FLC, λ free light chains; AOPP, advanced oxidative protein products; IS, indoxyl sulfate;

Disruptive technologies for hemodialysis

BRAZILIAN JOURNAL OF
NEPHROLOGY



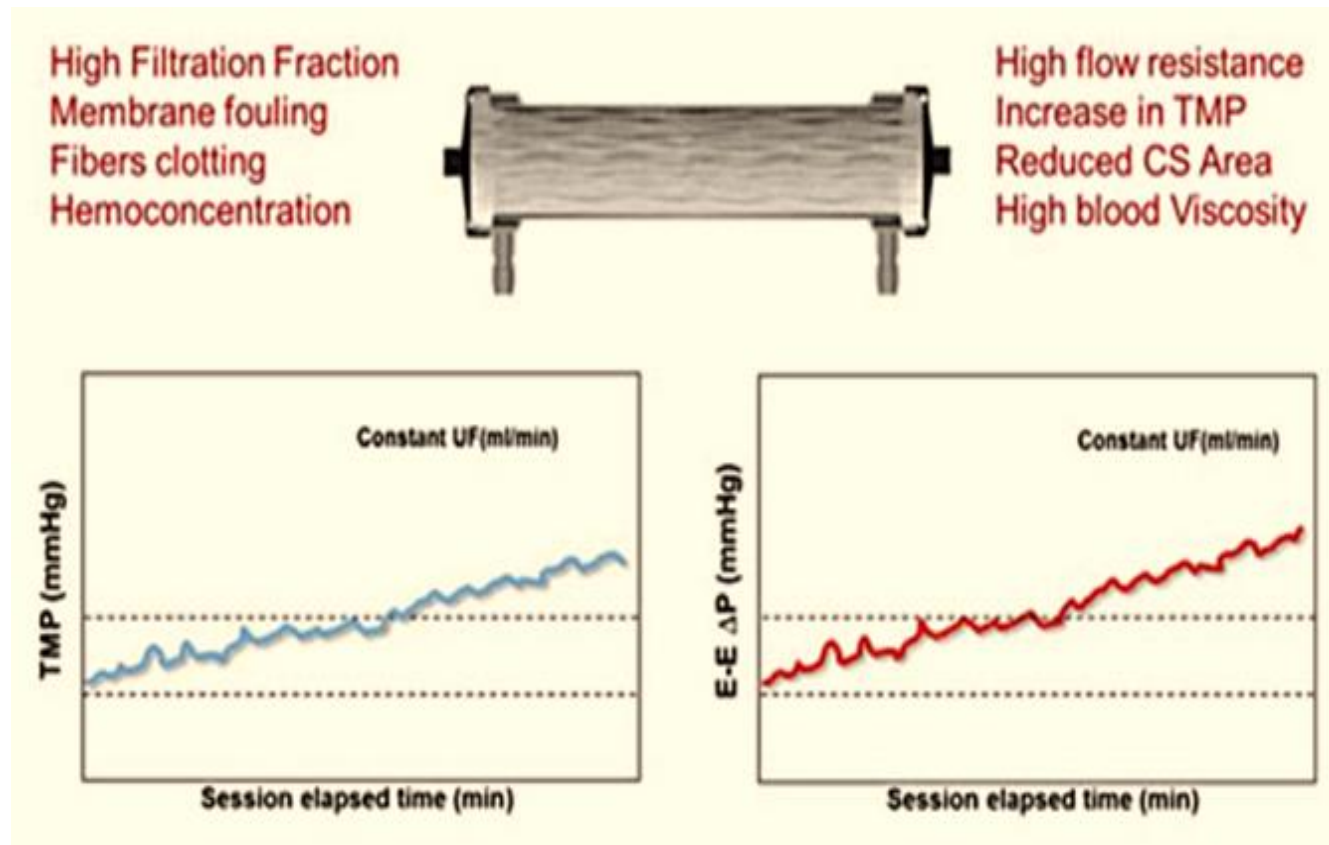
- The HF-HD modality is limited in removing solutes with molecular weight greater than **15 kDa**. In its turn, even utilizing the same membrane as in HF-HD, the online HF-HDF modality removes efficiently a broader range of molecules up to **25 kDa**, thanks to **high ultrafiltration** volumes of around 100 mL/min, which represent the convective clearance.

- Reis T, Anwar S, Neves FADR, Ronco C. Disruptive technologies for hemodialysis: medium and high cutoff membranes. Is the future now? J Bras Nefrol. 2021 Jul-Sep;43(3):410-416. doi: 10.1590/21758239-JBN-2020-0273. PMID: 33836041; PMCID: PMC8428648.

Disruptive technologies for hemodialysis

- An **inherent** consequence of high convective volumes is the **increment** in the transmembrane pressure, associated with higher deposition of proteins in the inner surface of the hollow fibers, partial obstruction of pores, and **loss** of membrane **efficiency** during the treatment, a phenomenon termed as clogging.

Disruptive technologies for hemodialysis



Claudio Ronco; Hemodiafiltration: Technical and Clinical Issues. Blood Purif 1 September 2015

High cut-off membranes in patients requiring renal replacement therapy:

- High Cut Off HD (HCO-HD) uses a dialysis membrane that has a cut off for protein permeability that is close to the GBM and has the highest clearance of middle MW molecules of any dialyzer. The pore size radius for the HCO 1100 membrane is **8–12 nm**; this compares to a typical dialyzer pore size radius of **2–3 nm for a LF** membrane, **3.5–5.5 nm for a HF** membrane.

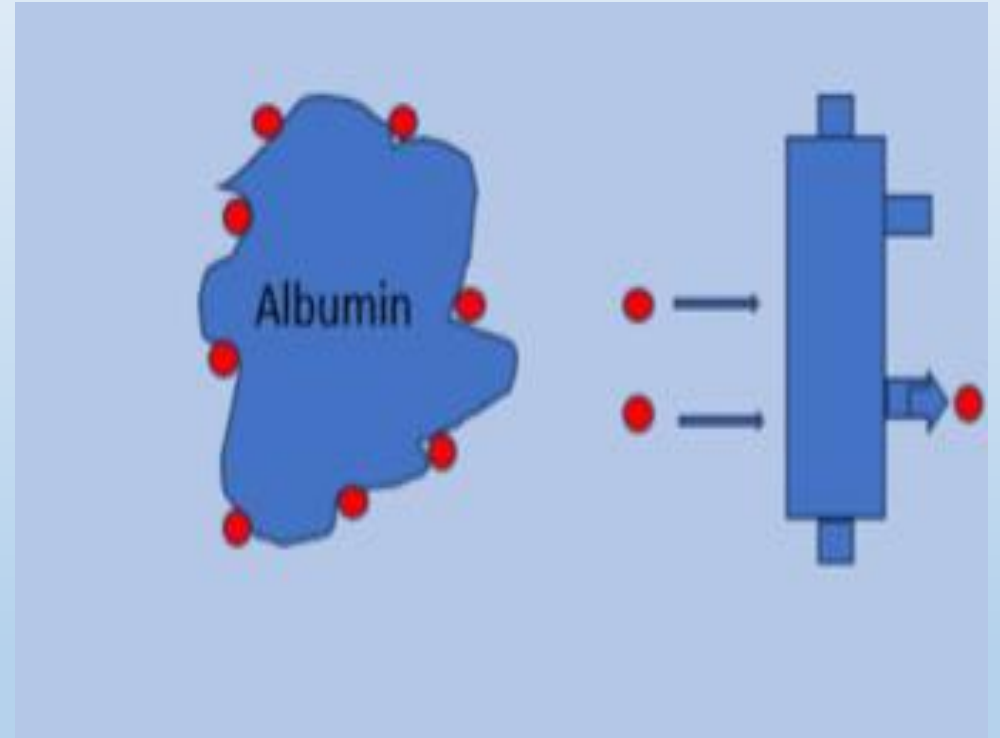
High cut-off membranes in patients requiring renal replacement therapy

- The MWCO for the HCO 1100 membrane when used in vivo is around 50 kDa; however, the distribution of pores beyond this MWCO means that there is a loss of albumin that has been quantified as up to 20 g for a single HCO 1100 dialyzer used for 4 h.

Zhou Z, Kuang H, Wang F, Liu L, Zhang L, Fu P. High cut-off membranes in patients requiring renal replacement therapy: a systematic review and meta-analysis. *Chin Med J (Engl)*. 2023 Jan 5;136(1):34-44. doi: 10.1097/CM9.0000000000002150

Protein-Bound Uremic Toxin Clearance (PBUTs)

- However, some degree of albumin leak could be theoretically accepted since this would imply concomitant removal of some PBUTs.

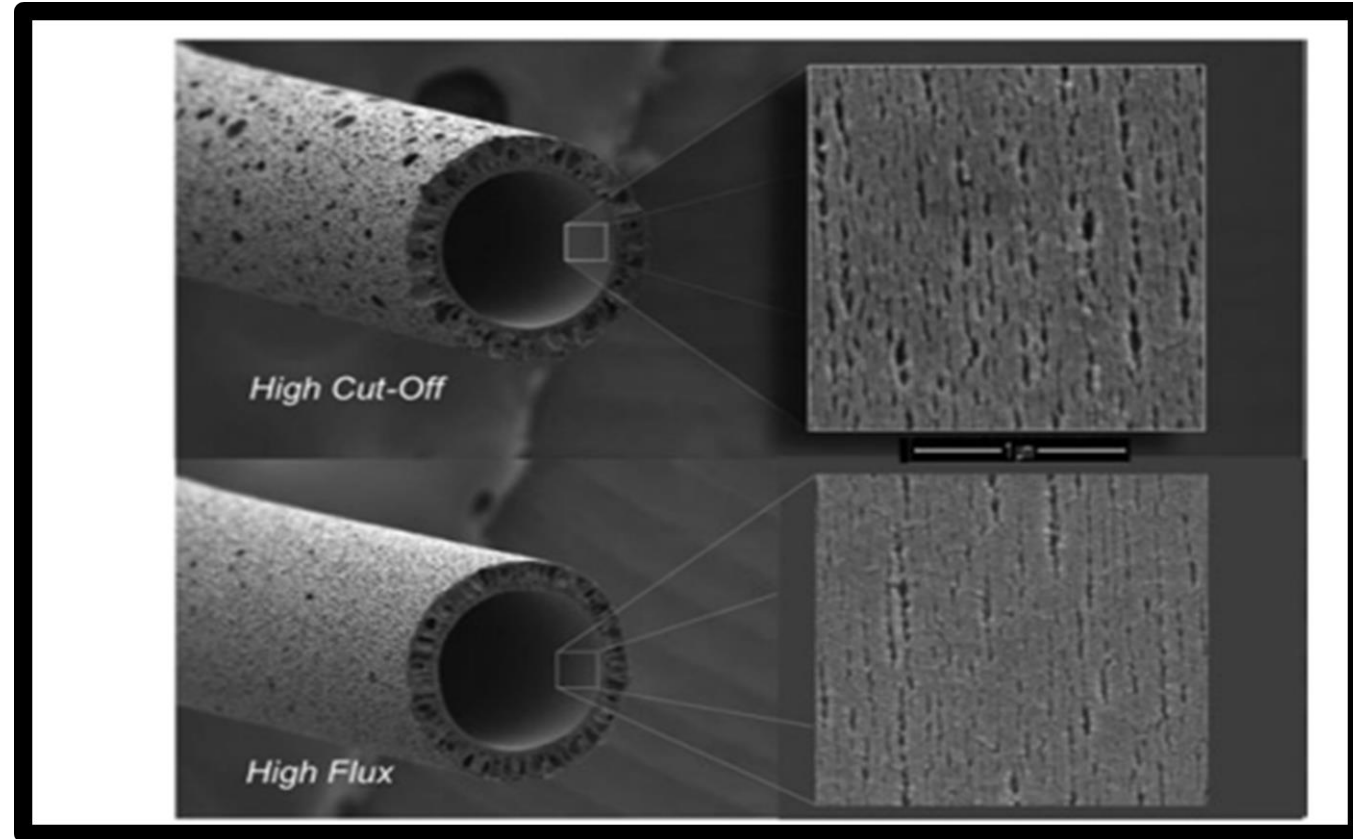


Protein-Bound Uremic Toxin Clearance (PBUTs)

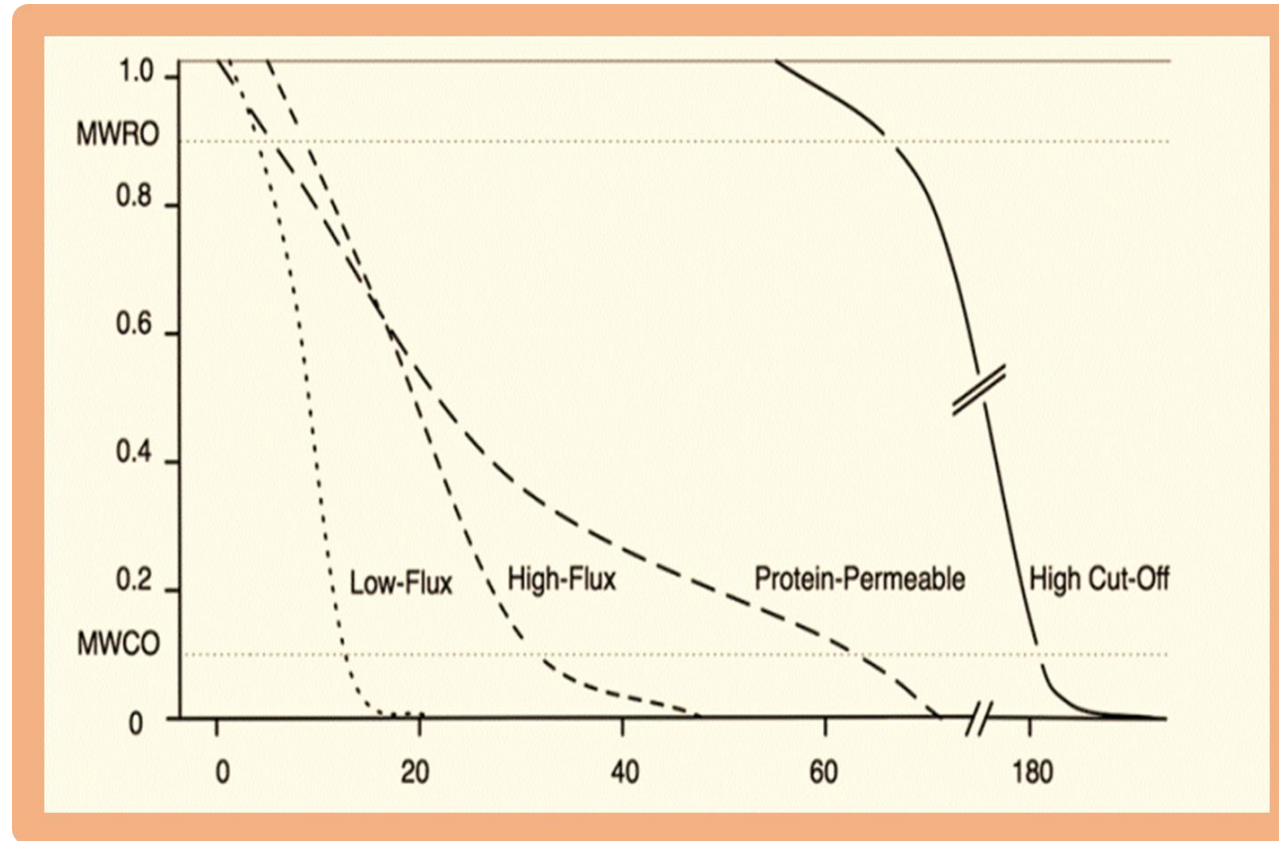
- Furthermore, the uraemic environment can alter the structure of albumin, among the other proteins, via carbamylation or oxidation, leading to malfunction and toxicity).carbamylated albumin is associated with greater mortality rates and eritropoiesis-stimulating agents resistance).

Sánchez-Ospina D, Mas-Fontao S, Gracia-Iguacel C, Avello A, González de Rivera M, Mujika-Marticorena M, Gonzalez-Parra E. Displacing the Burden: A Review of Protein-Bound Uremic Toxin Clearance Strategies in Chronic Kidney Disease. J Clin Med. 2024

High cut-off membranes in renal replacement therapy



High cut-off membranes in renal replacement therapy



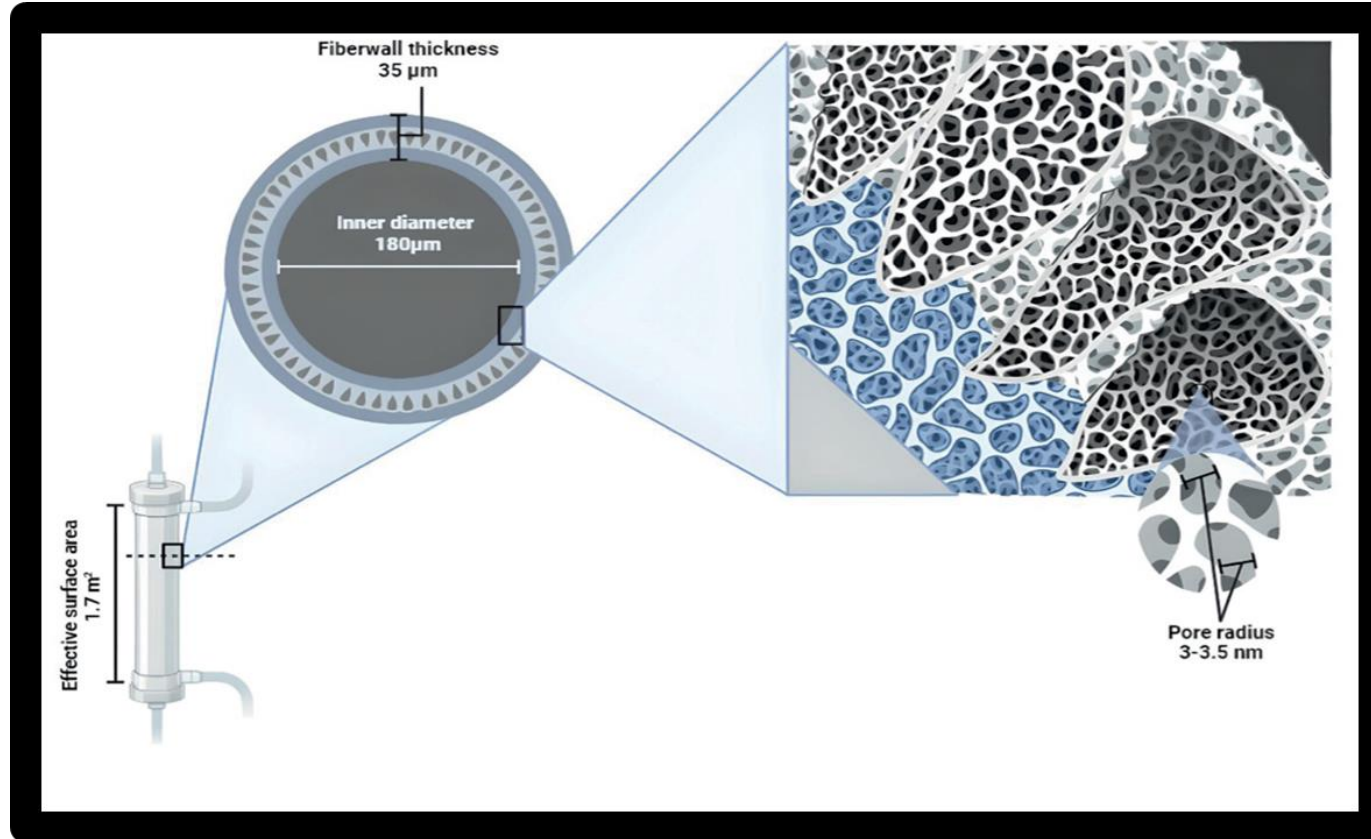
Medium Cut-off Membranes Promising Reality for Hemodialysis Patients

- Novel generation of dialyzers
- Mean pore radius is between high-flux (HF) and high cut-off (HCO) membranes
- Pore size and distribution are similar to the glomerular basement membrane,
- **Cut-off that is close to the molecular weight of albumin .**

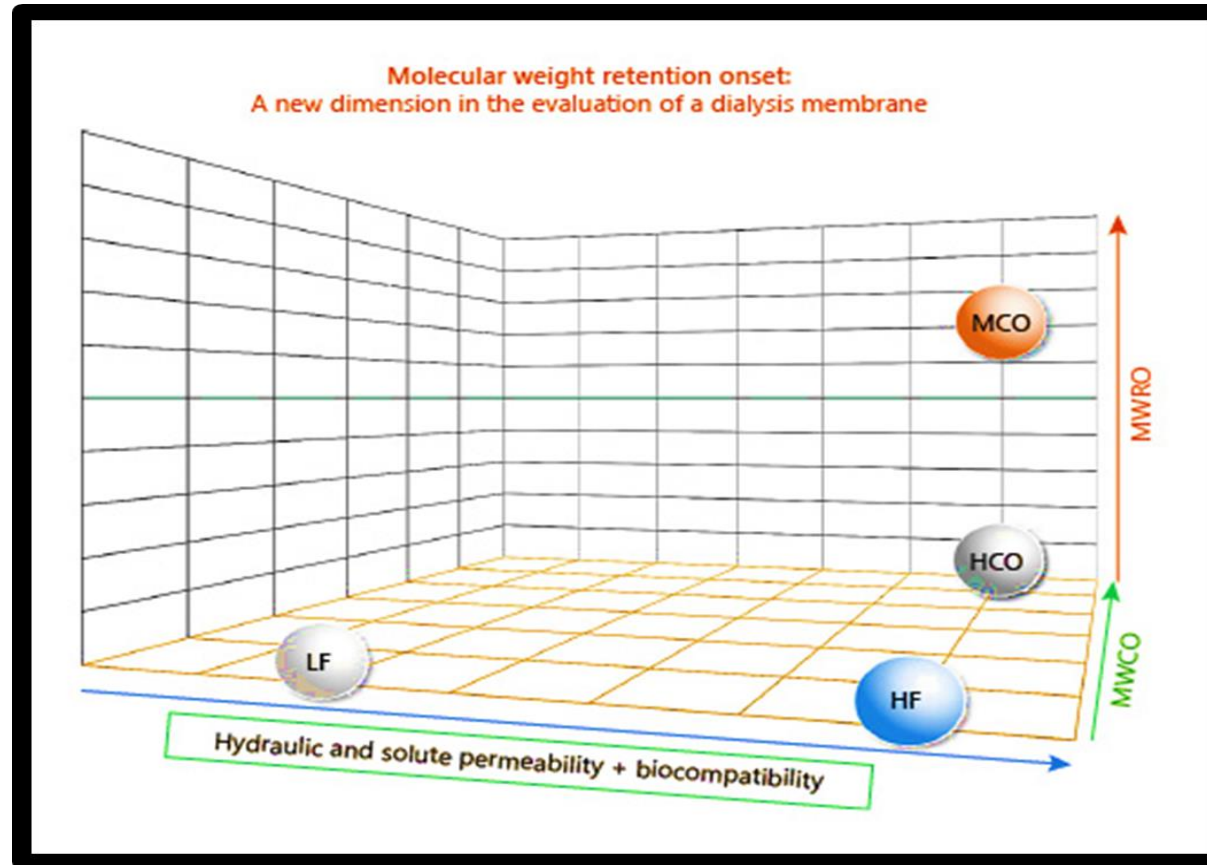
Medium Cut-off Membranes Promising Reality for Hemodialysis Patients

- In summary, they allow better removal of medium-sized molecules **without** increasing **albumin** losses.

Medium Cut-off Membranes



Medium Cut-off Membranes

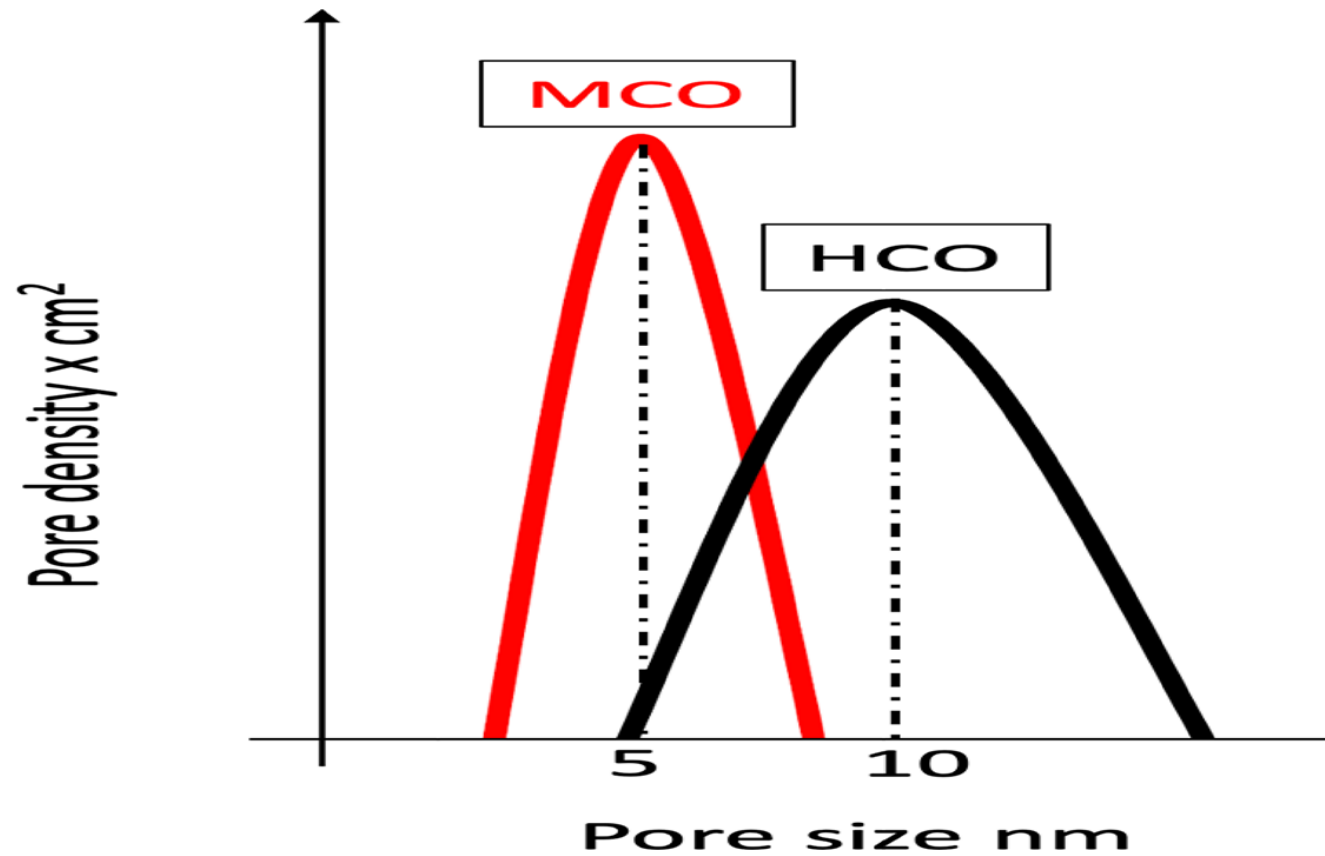


Medium Cut-off Membranes and expanded HD

- Their introduction in clinical practice has made it possible to perform a new therapy called expanded HD (HDx) with increased removal capability in a wide spectrum of MWs .

Internal Filtration in Medium Cut-Off Membrane

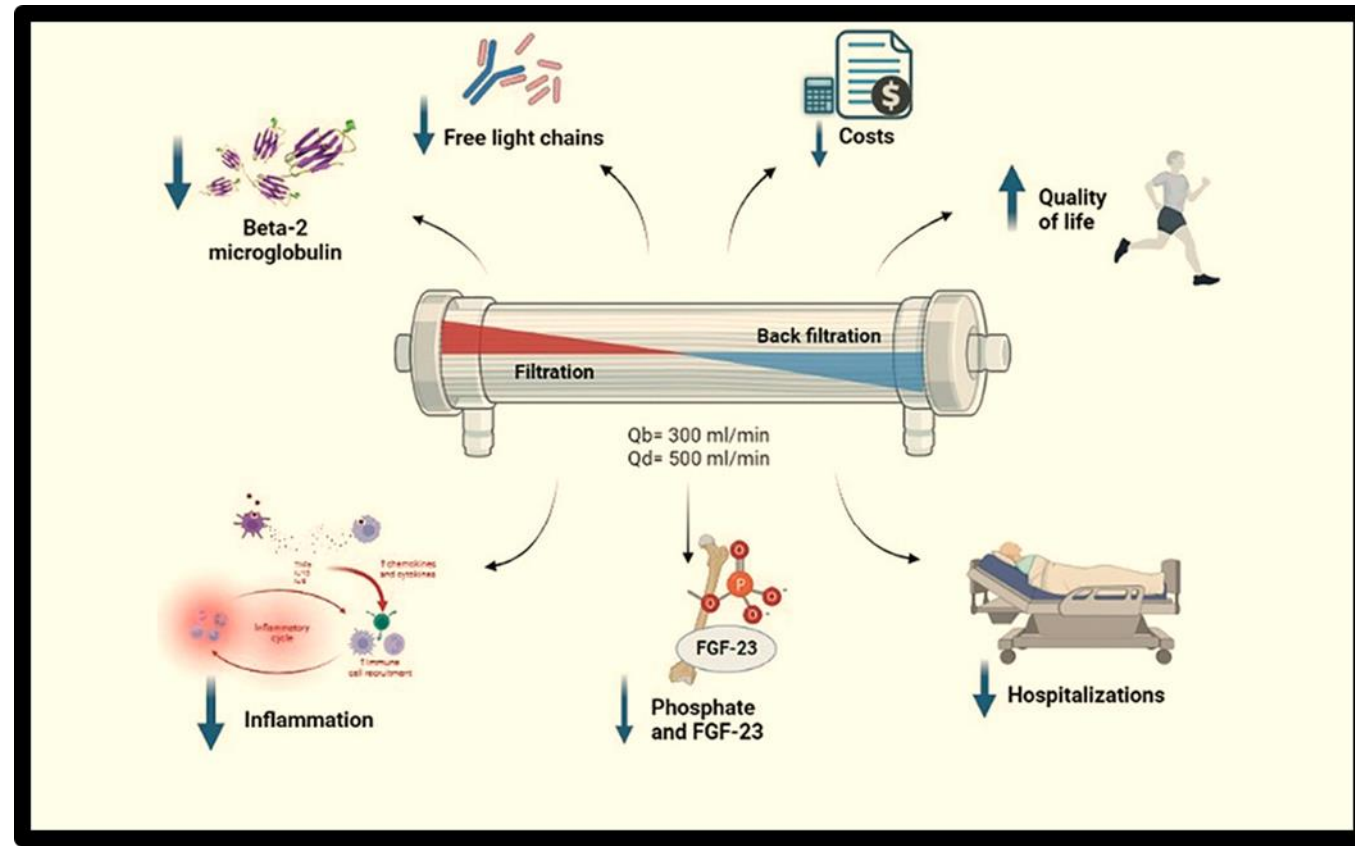
- Higher permeability of the MCO membrane observed compared to classic high-flux membranes
- Increased convective transport due to a remarkable amount of internal filtration (IF).
- IF guarantees high convective rates without requiring complex set up or fluid reinfusion (as in the case of HDF), since it is compensated by an adequate amount of backfiltration (BF) in the distal part of the hem dialyzer.



Effects of Medium Cut-Off Versus High-Flux Hemodialysis Membranes on Biomarkers: A Systematic Review and Meta-Analysis

- **MCO membranes increase middle-molecule clearance ,leading to reduced serum concentrations of β 2-microglobulin, κ -FLC, λ -FLC, and myoglobin—solutes representing the full spectrum of large middle molecular weights.**

Effects of Medium Cut-Off Versus High-Flux Hemodialysis Membranes on Biomarkers: A Systematic Review and Meta-Analysis



The Use of HCO and MCO-HD in Patients with Sepsis Syndrome

- Sepsis is a life-threatening condition in which a dysregulated release of **pro- and anti-inflammatory cytokines** can lead to multiple organ failure and increased mortality. Critically ill patients with sepsis-associated acute kidney injury (AKI) requiring kidney replacement therapy (KRT) are at particularly increased risk of death.

several hypotheses about Clearance of inflammatory cytokines

- 1-The “**peak concentration hypothesis**” proposes that during BPT excessive pro- or anti-inflammatory mediators are removed and plasma concentrations decrease to levels **below** a toxic threshold.

several hypotheses about Clearance of inflammatory cytokines

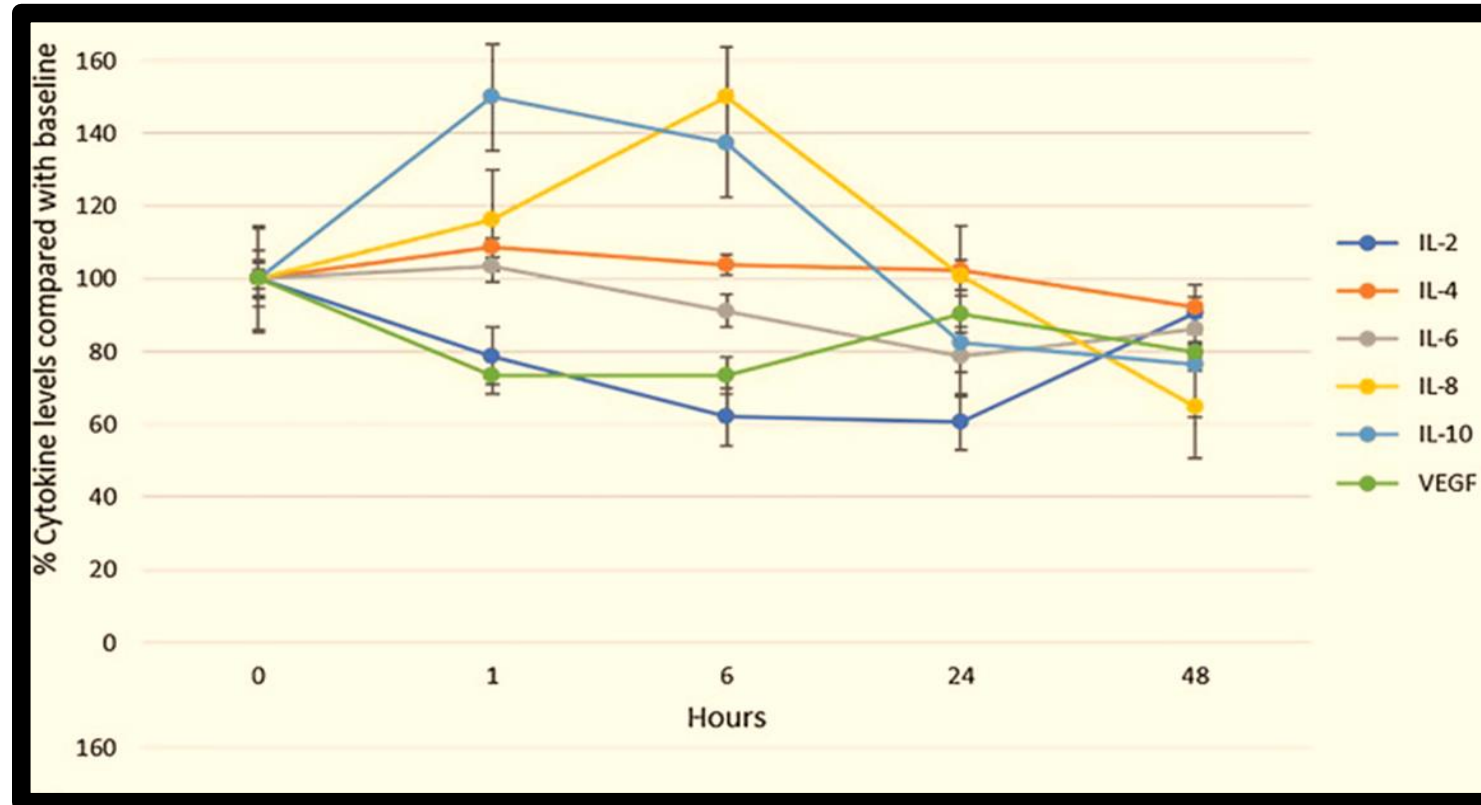
- 2-The “cytokinetic theory” proposes that cytokine removal creates a **decreased cytokine gradient** between tissues and the bloodstream and promotes leukocyte chemotaxis towards the infected tissues.

-

The Use of HCO and MCO-HD in Patients with Sepsis Syndrome

- For this reason, critically ill patients with sepsis-associated AKI may benefit from extracorporeal blood purification therapies in an effort to remove inflammatory mediators and decrease cytokine gradient between blood and tissues, leading to restoration of immune balance and **reducing** the risk of **organ failure**.

Clearance of inflammatory cytokines in patients with septic acute kidney injury during renal replacement therapy using the EMiC2 filter (is a medium cut-off)



Lumlertgul N, Hall ACamporota L, Crichton S, Ostermann M. Clearance of inflammatory cytokines in patients with septic acute kidney injury during renal replacement therapy using the EMiC2 filter (Clic-AKI study). Critical care (London, England). 2021;25(1):39.

Clearance of inflammatory cytokines in patients with septic acute kidney injury during renal replacement therapy using the EMiC2 filter

Additional file 4 Spearman's correlation between serum levels and clearances by adsorption and effluent

Cytokines	Adsorption	P value	Effluent	P value
IL-2	-0.52	0.03	0.35	0.17
IL-4	0.52	0.0008	-0.71	<0.001
IL-6	-0.53	0.0005	0.54	0.0004
IL-8	0.18	0.28	-0.09	0.57
IL-10	0.29	0.01	-0.15	0.37
VEGF	0.08	0.65	0.22	0.20
IFN- γ	0.12	0.60	0.22	0.35
TNF- α	0.12	0.45	0.23	0.16
IL-1 α	-0.56	0.02	0.28	0.26
IL-1 β	-0.10	0.67	0.50	0.03
MCP-1	-0.24	0.14	0.008	0.96
EGF	0.06	0.77	-0.32	0.13

$$Cl_{\text{eff}} \left(\frac{\text{ml}}{\text{min}} \right) = \frac{Q_{\text{df}}}{60} \times \frac{C_{\text{effluent}}}{(C_{\text{predialyzer}} + C_{\text{postdialyzer}})/2}$$

Clearance of inflammatory cytokines in patients with septic acute kidney injury during renal replacement therapy

- **Although the decline** in serum concentrations of most cytokines during the study period but were **unable to detect** an obvious correlation between serum concentration and cytokine clearance. The results suggest that mechanisms other than (**dynamic nature of sepsis**) extracorporeal removal involved.

JOURNAL ARTICLE

High permeability haemofiltration improves peripheral blood mononuclear cell proliferation in septic patients with acute renal failure

Stanislao Morgera ✉, Michael Haase, Jens Rocktäschel, Torsten Böhler, Christian von Heymann, Ortrud Vargas-Hein, Dietmar Krausch, Heidrun Zuckermann-Becker, Joachim M. Müller, Wolfgang J. Kox ... Show more

Nephrology Dialysis Transplantation, Volume 18, Issue 12, December 2003, Pages 2570–



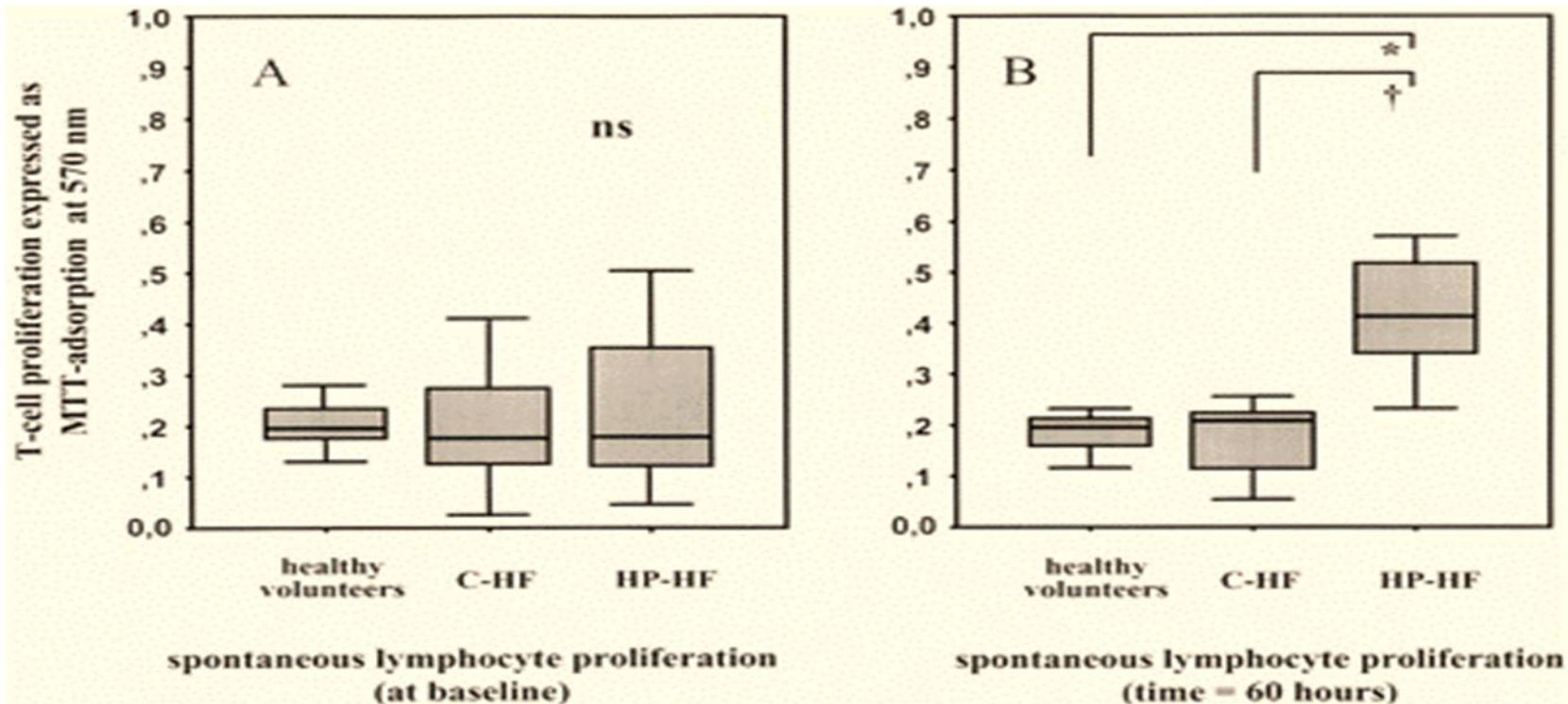
Explore articles on
**cardio-kidney
research**



High permeability haemofiltration improves peripheral blood mononuclear cell proliferation in septic patients

- **The proliferative capacity of lymphocytes has proven to be reduced during sepsis that leads to a significant depression in T-lymphocyte-mediated immunity.**
- **Twenty-eight patients with sepsis syndrome and AKI were randomized to receive 12-h cycles of hemofiltration using HCO membrane or a conventional HF dialyzer.**

High permeability haemofiltration improves peripheral blood mononuclear cell proliferation in septic patients with acute renal failure



The Use of HCO and MCO-HD in Patients with Sepsis Syndrome

- key finding of this study was that initiating HP-HF led to a **restoration** of the PBMC **proliferation capacity** by eliminating immunomodulatory mediator in the HP-HF but not in the C-HF group.

Morgera S, Haase M, Rocktäschel J, Böhler T, Heymann Cv, Vargas-Hein O, et al. High permeability haemofiltration improves peripheral blood mononuclear cell proliferation in septic patients with acute renal failure. *Nephrology Dialysis Transplantation*.

Effects of Medium Cutoff Membranes on Pro-Inflammatory Cytokine and Oxidative Marker

- in a cohort of 38 patients with sepsis-associated AKI, who received (19 patients started treatment with a high flux membrane and then switched to a medium cut-off membrane, the remaining 19 patients were first treated with a medium cut-off membrane, and then switched to a high flux membrane) .The reduction of **TNF- α , IL-6 and IL-1 β** was **significantly higher** during HD treatment with medium cut-off membranes than with high flux, while no differences were reported among markers of **oxidative stress**.

Effects of Medium Cutoff Membranes on Pro-Inflammatory Cytokine and Oxidative Marker

Table 5. Total comparison of MCO and HF membranes overall dialysis sessions

Variable	MCO-HD	HF-HD	<i>p</i> value
TNF- α , ng/L			
RR, %	18.9 (0.5–68.1)	6.3 (–19.3–60.1)	0.001
IL-1 β , pg/L			
RR, %	10.4 (1.3–74.3)	4.5 (–10.5–31.1)	<0.001
IL-6, ng/L			
RR, %	18.0 (0.0–78.5)	4.9 (–12.6–77.7)	0.006
TAS, U/mL			
RR, %	0.0 (–52.7–63.7)	0.0 (–185.1–68.9)	0.893
TOS, U/mL			
RR, %	2.1 (–281.9–69.1)	–0.5 (–173.3–71.2)	0.304
MPO, ng/mL			
RR, %	0.0 (–51.1–67.0)	3.5 (–9.1–77.5)	0.136

Importance of high and medium cut-off dialysis for acute kidney injury

- Multiple myeloma (MM) constitutes the second most common hematological malignancy and is associated with significant mortality and morbidity .Its incidence has been increasing worldwide and renal impairment occurs in up to 50% of patients, with 10% of patients developing severe renal failure requiring dialysis

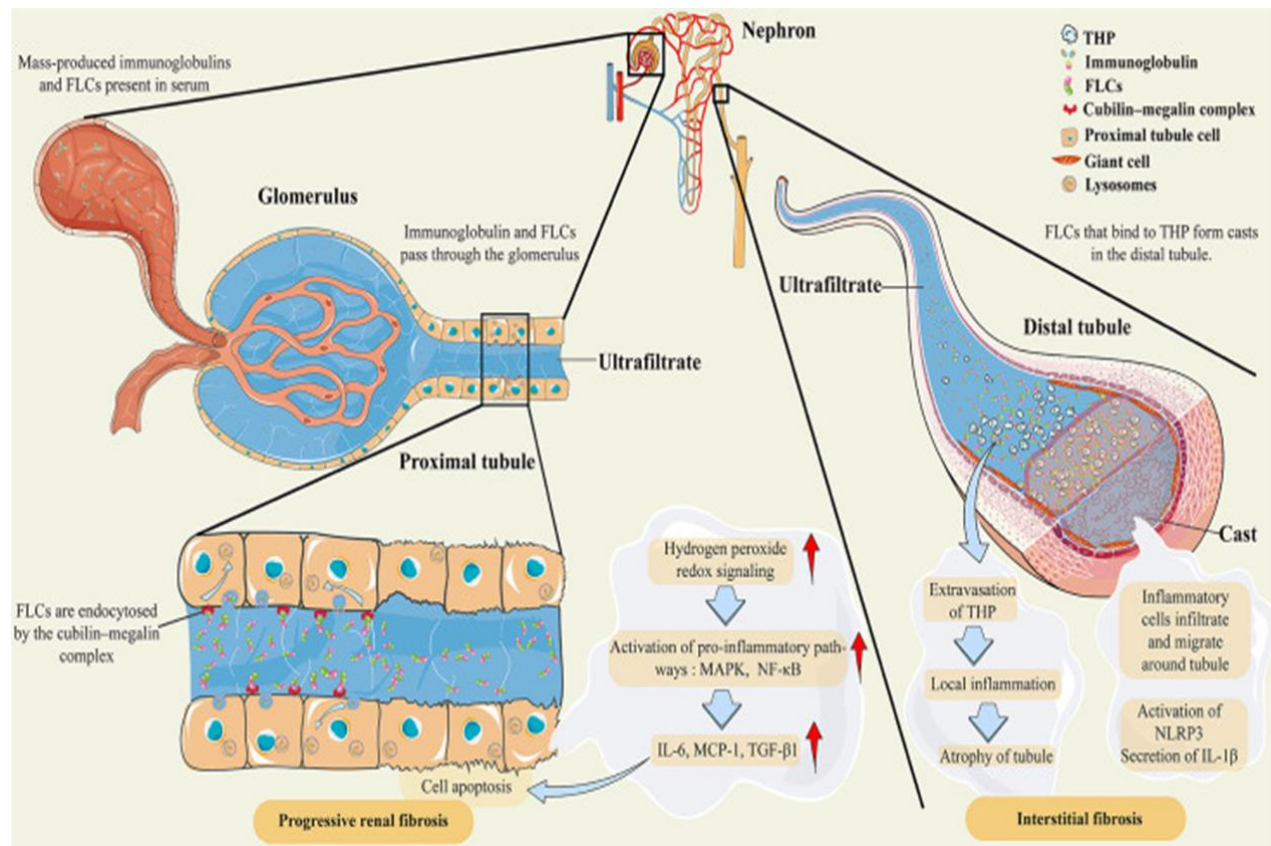
Cast nephropathy

- Treatment of cast nephropathy is directed at reducing sFLC levels, using treatments such as bortezomib (BTZ). In addition, mechanical removal of sFLC via haemodialysis (HD) or plasmapheresis has been considered as another biologically plausible therapeutic path for management of patients with cast nephropathy.

Cast nephropathy

- However, due to the size of the membrane pores, HF-HD can only remove molecules of approximately 10–20 kDa, while the molecular weights for the κ and λ chains of FLCs are 22.5 and 45 kDa, respectively.

acute kidney injury secondary to cast nephropathy in patients with multiple myeloma



Effect of high cut-off dialysis for acute kidney injury secondary to cast nephropathy in patients with multiple myeloma:

- This systematic review, including 276 patients with a mean follow-up of 18.7 months. Although Patients receiving HCO dialysis had a **greater reduction** in serum kappa and light chain levels, HCO-HD was not associated with a survival benefit at 12 months or at the end of the studies at an average of 34 months .There was no **difference in HD independence at 90 days or 12 months.**

European trial of free light chain removal by extended haemodialysis in cast nephropathy (EuLITE)

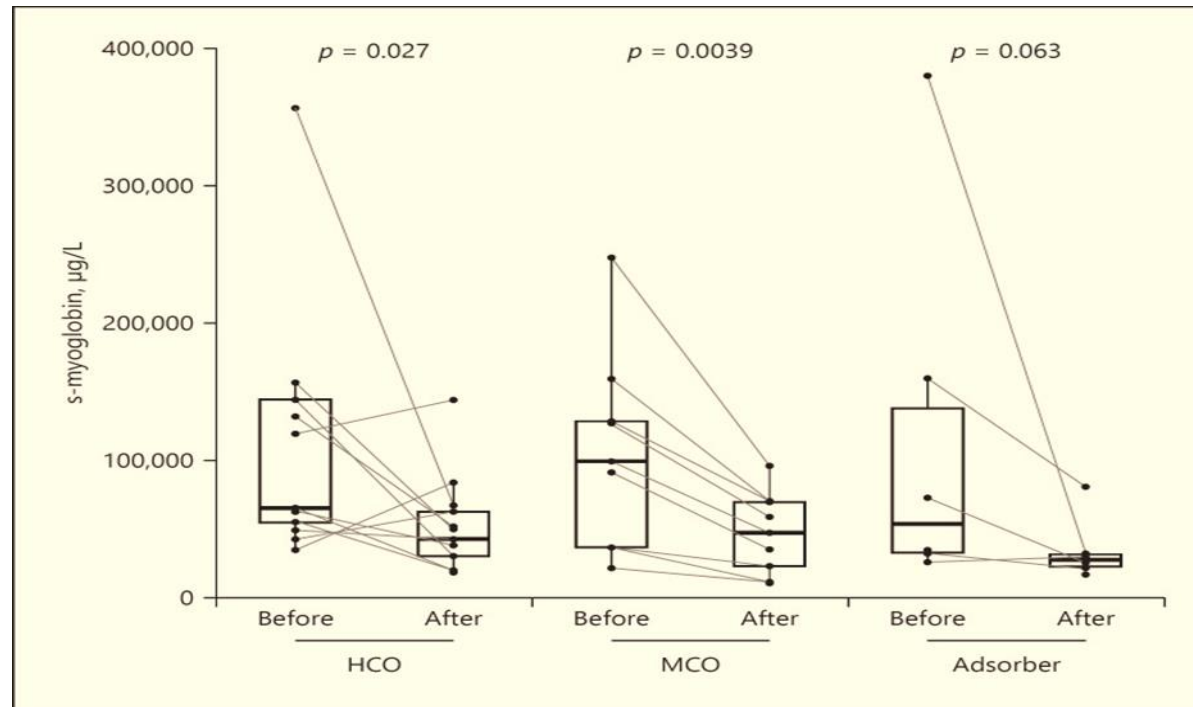
- The EuLITE trial randomized 90 patients. **no difference** in dialysis independence **at 3 months** was found. The authors hypothesized that bortezomib-based chemotherapy **alone** is highly effective for early reductions in FLC, potentially blunting beneficial effects of the mechanical removal of FLC by the HCO dialyzer.

Importance of high and medium cut-off dialysis for acute kidney injury

- **Acute kidney injury (AKI) is the most common complication of rhabdomyolysis, occurring in more than half of patients with severe rhabdomyolysis and requiring hemodialysis in about 10–20%.**

Myoglobin half-life is greatly dependent on renal excretion and metabolism and is therefore significantly prolonged in patients with significant AKI, which further aggravates its toxicity. Given its molecular size (18 kDa), extracorporeal removal of myoglobin is achievable with newer hemodialysis membranes and adsorption techniques.

Extracorporeal Removal of Myoglobin in Patients with Rhabdomyolysis and Acute Kidney Injury:



Extracorporeal Removal of Myoglobin in Patients with Rhabdomyolysis and Acute Kidney Injury: Blood purification.

2022



دوازدهمین سمینار سراسری انجمن علمی نفرولوژی ایران کلیه در شرایط کریتیکال

The 12th National Congress of the Iranian Society of Nephrology (NirSN)



Importance of high and medium cut-off dialysis for acute kidney injury

- MCO membranes represent an **interesting innovation** in the field of hemodialysis. Given the correlation between large (PM >25 kDa) middle molecules (LMM) and clinical outcomes, the possibility of solutes removed in hemodialysis with MCO membranes introduces a new perspective for ESRD patients.

Summary:

- This **innovative** profile guarantees an enhanced clearance of middle molecular weight solutes compared to standard high-flux dialyzers and negligible losses of albumin compared to the high cutoff membrane.

Summary

- **Despite the proven effects of this type of membranes on the prognosis of chronic hemodialysis patients, their beneficial effects on acute kidney failure are not known and more studies are needed in this field.**



دوازدهمین سمینار سراسری انجمن علمی نفرولوژی ایران کلیه در شرایط کریتیکال

The 12th National Congress of the Iranian Society of Nephrology (NirSN)





دوازدهمین سمینار سراسری انجمن علمی نفرولوژی ایران کلیه در شرایط کریتیکال

The 12th National Congress of the Iranian Society of Nephrology (NirSN)





دوازدهمین سمینار سراسری انجمن علمی نفرولوژی ایران کلیه در شرایط کریتیکال

The 12th National Congress of the Iranian Society of Nephrology (NirSN)

