Reimagining Dialysis: Innovations/Challenges in Reducing Uremic Toxins and Advancing Personalized Kidney Replacement Therapies

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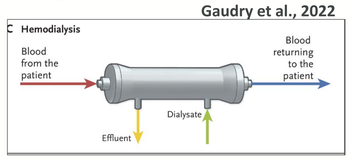
Background:

Hemodialysis-
most common method of uremic toxin removal in patients with kidney failure

Gaudry et al., 2022



➢ Blood Flow
- Blood flows into the dialyser (artificial kidney)
- typically filtered 200-400 ml of blood per minute in a typical dialysis session.

➢ Dialyser
- The dialyser contains a semipermeable membrane.
- Blood flows on one side
- Small waste molecules, ex: urea, creatinine, excess electrolytes and fluid pass into the dialysate flowing on the other side
- Larger components ex: red blood cells, proteins, are retained in the blood

➢ Waste Removal
- Waste products and excess fluid move by diffusion (molecules moving from an area of high concentration to an area of low concentration) and ultrafiltration (fluid removal under pressure)
- Clean blood is returned to the vascular point

➔ 3-5 hour long session about 3x weekly

Introduction:

➢ 550,000 Americans rely on dialysis to manage kidney failure annually[2]

➢ Median survival rates as low as 50% in 5 years[1]

➢ Standard dialysis approach- filtration through a semipermeable membrane- remains insufficient for removing larger uremic toxins and restoring optimal health[3] and has remained largely unchanged

Large push for patient-centered care and improved outcomes has lead to the creation of novel therapies & the innovation of existing ones.

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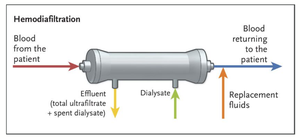
Innovations in Dialysis:

➢ **Hemodiafiltration:**

Hybrid dialysis method combining convection and diffusion to remove both small and large toxins

Gaudry et al., 2022



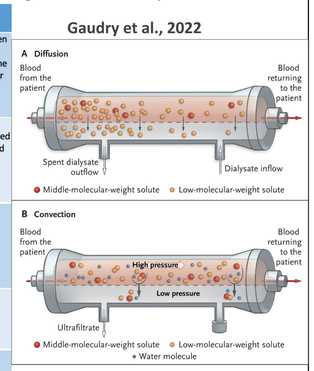
- Blood is pumped into dialyser containing a semipermeable membrane
- Diffusion: small molecules (ex: urea, creatinine) move into the dialysate
- Convection: larger molecule are removed along with plasma water (ultrafiltration)
- Replacement fluid is added (pre or post-dilution) to maintain blood volume
- Clean blood returned to the body
- Dialysate+ filtered plasma water discarded

CONVINCE Trial: 17.3% mortality rate in hemodiafiltration-treated patients vs. a 21.9% in high-flux hemodialysis

Evan Zeitler et al., 2025

Trial	No. of patients	Mean HDF volume	Interventions	Main findings	Limitations	Post-hoc analysis
CONTRAST	714	20.7L/session	OL-HDF vs Low flux HD	mean follow up of 3 years did not show survival benefit of online HDF compared to low flux HD and no difference in all cause-mortality	Failure to deliver target convection volume	Positive association between all-cause mortality and a delivered convection volume >21.95 L/ session even after adjusting for potential confounders and dialysis facility
THFDS	782	19.6LL/session	OL-HDF vs High flux HD	no survival advantage of online HDF compared to high flux HD.	Low event rate, high drop-out rate. 10% of patients from the HDF arm were excluded after randomization because their blood flow rates speeds were not adequate.	substitution volume above 17.4 L/session was associated with improved all-cause and CV mortality compared to high flux HD
ESHOL	906	22.9-23.9L/session	OL-HDF vs High flux HD	1. 30% lower risk of all-cause mortality 2. 33% lower risk of CV mortality 3. statistically significant reduction in stroke 4. 55% lower risk of infection-related mortality 5. lower rates of intradialytic hypotension 6. lower rates of all-cause hospitalizations compared to HD group.	10% of patients from the HDF arm were excluded after randomization because their blood flow rates were not adequate.	
FRENCHIE	381 (> age 65 years)	21L/session	OL-HDF vs High flux HD	1. Treatment related adverse events did not differ between 2 groups. 2. Lower occurrence of IDH 3.No difference between health related QoL, mortality or morbidity.	Underpowered, recruitment target not met	
CONVINCE	1360	25.3L/session	OL-HDF vs High Flux HD	1. lower risk of all-cause mortality in HDF group 2. lower risk of infection related mortality in HDF group 3.No difference with CV events or CV mortality	Mostly recruited European white population, so not generalizable to non-whites.	

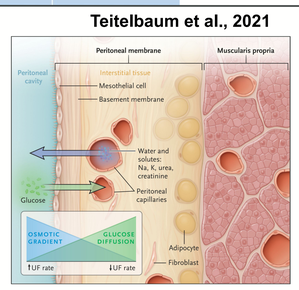
Gaudry et al., 2022

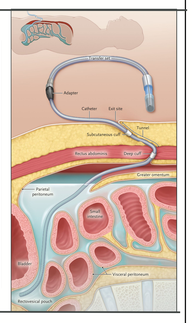


➢ **Peritoneal Dialysis**

Home-based method that uses the peritoneal membrane (abdomen lining) as natural filter:

Teitelbaum et al., 2021

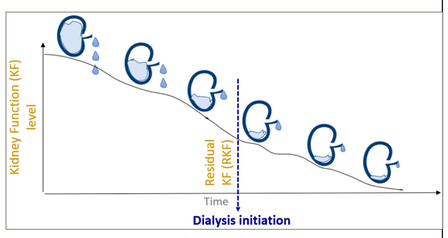




- Dialysate placed into abdomen through catheter
- The peritoneal membrane acts as a filter:
- ➔ wastes and excess fluid move from the blood vessels in abdominal lining
- ➔ Move into the dialysate via osmosis and diffusion
- Dwell time of a few hours, the used fluid is drained and replaced
- 3-4x daily

➢ **Incremental Hemodialysis**

Adjustment of HD frequency based on residual kidney function (RKF):



Evan Zeitler et al., 2025

- start with less frequent dialysis (ex: 2x weekly instead of 3x)
- Increase as RKF declines
- ➔ Observational studies: comparable outcomes in selected patients, preserved RKF, reduced treatment burden
- ➔ Theory: Gradual initiation may preserve "super nephrons"- intact nephrons adapt and sustain function. This remains unproven in large RCTs but is a promising area of research.

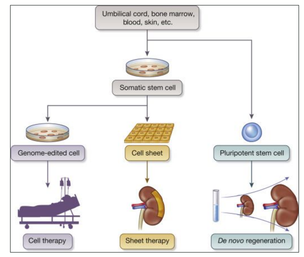
➢ **Timing/Intensity**
- Early vs. delayed therapy- large RCTs show no mortality difference
- Delayed therapy is safe without urgent indications (critical hyperkalemia, fluid overload, acidosis, etc.)
- higher doses/frequencies do not improve survival and may worsen kidney recovery
- may delay kidney recovery and increase hypotension, hypophosphatemia,

Dialysis Alternatives:

➢ **Regenerative Medicine**

Stem-cell based approaches for kidney creation and repair:

Yokoo, 2021

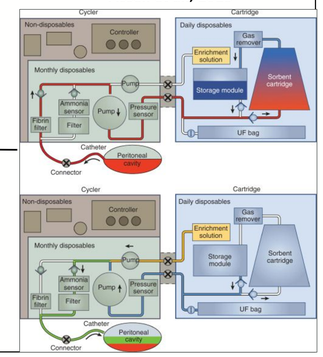


- Bioengineered kidneys structural kidney-like features
- ➔ Sub-optimal filtration capabilities
- ➔ Applications limited to small animals
- Stem cells for damaged kidney repair
- ➔ Mesenchymal stem cells (MSCs) - multipotent cells from various tissues
- ➔ Promote repair of damaged kidneys
- ➔ Improved renal function in animals
- ➔ improved quality of life in humans vs dialysis
- ➔ lower organ rejection risk

➢ **Green Dialysis**

Sustainable approaches to reduce water and waste:
- Recycling of water
- ➔ Reverse osmosis reject (used to purify dialysis water) for water reused for non-clinical purposes
- ➔ Dialysate Regeneration- removal of toxins so water can be reused
- Emerging technologies
- ➔ Sorbent-based systems (chemical cartridges to remove toxins)-
- ➔ Portable dialysis machines to recycle dialysate continually
- ➔ Projects around the world reusing RO rejection water & minimizing wasted water

Fissell et al., 2013



➢ **Portable & wearable artificial kidneys**

Next generation compact dialysis systems
- Wearable Artificial Kidney- sorbent-based dialysate regeneration
- (reuses cleaning fluid) and aims to deliver slow, continuous dialysis, mimicking natural kidney function.
- Still in early development and clinical trials

Conclusion: The Future of Nephrology

➢ Moving beyond one-size-fits-all to tailored dialysis care
➢ Treatment should consider lab values, residual kidney function (RKF), comorbidities, and quality of life
➢ Innovations include:
➔ Hemodiafiltration
➔ Peritoneal dialysis
➔ Incremental hemodialysis
➔ Timing/intensity of therapy
➔ Regenerative medicine
➔ Green dialysis
➔ Portable & wearable artificial kidney
➢ Key challenges:
➔ Infrastructure limitations
➔ Limited clinical evidence
➔ Strict safety requirements
➢ Future research should prioritize:
➔ Clinical effectiveness
➔ Patient-reported outcomes
➔ Healthcare equity
➔ match or improve upon current dialysis standards