Medium cut-off membranes - closer to the natural kidney removal function

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Today, most patients who require renal replacement therapy are treated using dialysis membranes. To improve the outcomes of chronic dialysis patients, unique developments have been made in the past several decades. Cellulose membranes have been mostly replaced by synthetic polymeric membranes with improved biocompatibility. The development of high-flux membranes and more efficient treatment modes, such as hemodiafiltration, have resulted in improved removal rates of uremic toxins, particularly those in the middle molecular-weight range (>500 Da). Beyond the membranes used for conventional hemodialysis, new membranes with increased pore size have been developed for specific treatments. These specialized membranes allow for the removal of higher molecular-weight molecules, such as mediators of sepsis/inflammation, or the removal of nephrotoxic light chains of immunoglobulins. However, these membranes allow the passage of plasma proteins, such as albumin (1), whose loss is undesirable. The newest generation of highly selective and permeable medium cut-off (MCO) membranes enables the removal of large molecules, as do high cut-off (HCO) membranes, while simultaneously maintaining low passage of albumin. For uremic solutes in the 15,000 to 45,000 Da- size range, the MCO membranes offer improved clearance in comparison with that of high-flux membranes used in HD mode and equivalent clearance to that of high-flux membranes used in high-volume hemodiafiltration (HDF) mode (2). Therefore, the use of MCO membranes simplifies the delivery of high-removal treatments for end-stage renal disease (ESRD) patients, with a removal spectrum that extends the current possibilities of the best available therapies. This improvement should allow clinicians to surpass the benefits of HDF while using regular HD equipment, i.e., not requiring large amounts of high-quality fluid and a more complex setup. These special MCO membranes should aid in raising the standard of treatment available for all chronic HD patients and may potentially decrease inflammation and improve general patient outcomes. Future studies are being planned to demonstrate the clinical benefits of this new membrane type.

Development of dialysis membranes with different permeabilities

Renal failure (RF) is characterized by the loss of the ability of the kidneys to excrete wastes, concentrate urine, conserve electrolytes, and maintain fluid balance. Acute kidney injury can be a life-threatening illness, with a mortality of between 50% and 80% (3). ESRD occurs in the late stages of chronic kidney disease and is associated with an irreversible loss of kidney function. Renal replacement therapy (RRT) replaces kidney function in patients with both types of renal failure. There are 2 possible alternatives to treat chronic RF: organ transplantation or, more commonly, dialysis. However, the natural secretion of kidney hormones, which influences blood pressure, cannot be achieved with dialysis treatment modalities. Over 2 million people worldwide currently receive treatment with dialysis or a kidney transplant to stay alive, yet this number may represent only 10% of people who actually need treatment to live (4). Of the 2 million people who receive treatment for kidney failure, the majority are treated in only 5 countries: the United States, Japan, Germany, Brazil, and Italy. These 5 countries represent only 12% of the world population. Only 20% are treated in approximately 100 developing countries that make up over 50% of the world population (4).

In medicine, hemodialysis (HD) is the process of removing blood from a patient, purifying the blood through an artificial kidney (dialyzer), and then returning it to the patient's bloodstream. On the basis of the developments of Willem Kolff and Nils Alwall in the 1940s, the dialyzer membrane systems have undergone multiple development cycles and are now the basis of an effective, reliable, and cost-effective treatment approach.

In the early days of dialysis, large and unwieldy plate dialyzers made of cellulose membranes were used. Until the 1970s, cellulosic membranes were used exclusively and represented the majority of membranes used in hemodialysis worldwide (5).

However, cellulosic membranes may activate the complement system (6) and induce other adverse biological reactions, e.g., leucopenia, owing to the accumulation of granulocytes in lung capillaries (7), inhibition of granulocyte metabolism, and release of enzymes from granulocytes and monocytes (8). The drawbacks associated with the decreased hemocompatibility of cellulosic membranes can be mitigated by the partial substitution of the hydroxyl groups by (i) acetylation or the (ii) introduction of diethylamino groups or (iii) benzyl groups (9). Cellulose acetate is a cellulose-derived material that has been modified by esterification. Depending on the degree of substitution, such a membrane can be categorized as cellulose acetate, cellulose diacetate, or cellulose triacetate. Another biocompatibility improvement of cellulosic membranes is surface-coating them with polyethylene glycol (PEG), polyacrylonitrile (PAN-RC®) (10), or vitamin E (Excebrane®). The use of vitamin-E-coated membranes, compared with uncoated cellulose membranes, appears to significantly decrease the activation and migration of monocytes and granulocytes (11).

Cellulosic membranes belong to the class of "low-flux" membranes, which have a low permeability: substances of up to 5,000 Da can be eliminated, whereas nearly 100% of the ß2-microglobulin is rejected. The area of synthetic polymeric membrane development began with the discovery by Geyjo in 1985 that ß2-microglobulin is the amyloidogenic precursor of AB-amyloidosis (12), together with the introduction of the hemofiltration treatment mode. Because the mass transfer of low-flux membranes is mainly diffusive and is not suitable for use in therapies that require high convective transport, such as hemofiltration (HF) and hemodiafiltration (HDF), membranes with higher permeability were required.

Synthetic polymeric membranes close this gap, showing higher permeability and better biocompatibility. The hydrophobic base material is mainly polysulfone or polyethersulfone (polyarylethersulfone). These high-flux membranes allow for the removal of so-called middle molecular-weight molecules. Membranes prepared from hydrophobic/hydrophilic polymer blends are the predominant type of synthetic polymeric membrane (9). High-flux membranes are highly permeable to β2-microglobulin. The pore structure of high-flux membranes allows for the passage of so-called middle molecules of up to 20,000 Da. In addition, significant protein loss, for example, in albumin (68,000 Da), is prevented. Beyond the immunoglobulins, albumin is the most important plasma protein that must be retained in chronic dialysis patients. High-flux membranes are suitable for hemodialysis, hemofiltration, and hemodiafiltration.

High-flux synthetic membranes show good transport properties and exhibit only slight complement activation (13), a minimal decrease in leukocytes (14), and a low release of leukocyte elastase (15). In a recent study, no significant survival benefit with either high-flux or low-flux membranes has been found in the overall population, but the use of high-flux membranes confers a significant survival benefit in patients with serum albumin ≤4 g/dL (16).

Beyond membranes used for conventional hemodialysis, high cut-off (HCO) membranes with increased pore size have been developed for specific treatments. In high cut-off membranes, the pore sizes are shifted toward a larger pore diameter than that of conventional high-flux membranes showing a higher permeability for substances above 15,000 Da (17). Examples of these substances include inflammatory cytokines, which are over-expressed in acute inflammatory diseases and contribute to the pathogenesis of septic acute kidney injury or free light-chain proteins. Monoclonal light chains of immunoglobulin are excessively produced by malignant plasma cells in patients with multiple myeloma (MM) and can cause renal lesions such as cast nephropathy. In this condition, serum concentrations may be elevated by more than 100-fold compared with normal serum concentrations.

The increase in the pore sizes of HCO membranes translates into an increase in both the convective and diffusive permeability, thus allowing for the removal of molecules, such as mediators of sepsis/inflammation (18), or the removal of nephro-toxic light chains of immunoglobulins (19). However, the albumin loss with this membrane is substantial, from approximately 9 to 23 g/treatment (20, 21), and it is not indicated for use in chronic dialysis but instead is recommended mainly for acute applications (22).

Over the past decade, various membranes, such as the cellulose triacetate-based FH 70/150 (Sureflu; Nipro (23)), the polysulfone-based APS-1050 (Asahi (24)), the PMMA-based BK-F /BG 2.1 (Toray (25)), and the Helixone polysulfone based FX-E (Fresenius Medical Care (26)), have been manufactured with the purpose of increasing membrane permeability, given the need for the increased clearance of low molecular weight proteins and protein-bound solutes.

Because the loss of albumin is associated with the removal of protein-bound uremic toxins, protein-leaking membranes have been developed for hemodialysis. Dialysis treatments with such membranes, compared with conventional high-flux dialysis membranes, provide greater clearance of those molecules, albeit at the cost of some albumin loss into the dialysate (27).

The newest generation of highly selective and permeable medium cut-off (MCO) membranes meets both requirements for high-quality and effective dialysis treatment: the removal of large middle-molecules up to a molecular weight of 45,000 Da, similar to a high cut-off membrane, and a low loss of albumin (high-flux membrane). For uremic solutes in the 15,000 to 45,000-Da size range, the MCO membranes offer improved clearance in comparison with those of high-flux membranes used in HD mode and equivalent clearance to high-flux membranes in HDF mode (2).

Uremic toxins and removal mechanisms

Because 'artificial kidneys' remove uremic toxins primarily via size exclusion, the classification of these solutes on the basis of their molecular weight and removal behavior is key for membrane development. In maintenance hemodialysis patients, the insufficient removal of mid-sized and protein-bound uremic toxins is associated with endothelial injury and chronic inflammation, thus contributing to subsequent cardiovascular disease. Studies demonstrating the role of these uremic toxins in inducing cardiovascular effects or other negative effects, such as coordination disturbances or polyneuritis in dialysis patients, have attracted increasing attention over the past decade (28). The molecular weights of these uremic

toxins vary widely from very small compounds, such as urea (MW = 60 Da), to globulins (e.g., ß2-microglobulin MW = 11,800 Da). Generally, uremic toxins are split into 3 groups: small water-soluble compounds, middle molecules and protein-bound solutes (29). In the latest literature research performed by the European Uremic Toxin (EUTox) Work group, 56 newly reported solutes have been found (30). Examples of solutes classified into the 3 aforementioned groups are shown in Table I.

Small water-soluble compounds are also referred to as low molecular weight molecules, which have molecular weights <500 Da and are soluble in water. The second group, consisting of middle molecular weight toxins, includes compounds with molecular weights above 500 Da. Protein-bound solutes constitute the third group of uremic toxins, which have molecular weights less than 500 Da but demonstrate strong binding to albumin.

Small water-soluble compounds are easily removed, diffusively, across the semipermeable membrane, owing to the concentration gradient between the blood and dialysis fluid. Conventional hemodialysis is an effective treatment mode for the removal of those compounds, whereas it is poorly suited for middle molecules such as ß2-microglobulin, even with the use of high-flux membranes. This phenomenon is attributable to a decrease in the diffusion coefficient with increasing molecular size. Alternative therapies such as hemofiltration or hemodiafiltration include convective transport mechanisms and the improved removal of both low- and middle-molecular-weight toxins such as ß2-microglobulin (31). The driving force for convective transport is a pressure gradient across the membrane, thus leading to ultrafiltration (UF), in which the molecules are pulled from the blood into the dialysate. An increase in the ultrafiltration rate increases the solute removal of low- and middle-molecular-weight solutes. In hemodialysis, UF is limited to the removal of only excess body fluid from the blood, whereas in convective therapies UF is increased beyond the target weight loss, and fluid balance is preserved via the infusion of a physiological solution into the blood (32).

TABLE I - Examples of uremic solutes and their molecular weights, classified into 3 groups: small water-soluble compounds, middle molecules and protein-bound solutes (28, 33)

Molecule	Molecular weight	Example
Small water-soluble compounds	<500 Da	asymmetric dimethylarginine, guanidine, uric acid, oxalate, ethylamine, methylguanidine, neopterin, phenylacetic acid
Middle molecules	>500 Da	β2-microglobulin, adiponectin, α1-acid glycoprotein, cystatin C, prolactin, osteocalcin, vascular endothelial growth factor
Protein-bound solutes	Variable	p-cresylsulfate, indoxyl sulfate, phenol, indol-3-acetic acid, hippuric acid, homocysteine, carboxymethyl-lysine, acrolein

In clinical practice, the UF rate is limited by the blood flow rate because only a portion of the volume, usually 25% to 30%, is filtered before the blood cell concentration increases to a level at which cellular damage and dialyzer clotting occur (32). Given the ability to obtain ultrapure water and dialysis fluids for use in water treatment systems and online HDF machines, the use of online hemodiafiltration is increasing steadily in Europe (34). Online HDF post-dilution is considered the most effective and safest dialysis treatment, owing to its superior blood purification of all uremic toxins and its decreased association with the incidence of cardiovascular events (35). However, this therapy is more complex and requires high exchange volume rates of up to 24 L per treatment. The automated machine settings aim to optimize the filtration fraction with the lowest possible rate of machine alarms but do not regulate the 2 primary determinants of the convection volume: the treatment time and the blood flow rate (36).

Furthermore, in comparison with other dialysis modalities, HDF also provides superior removal of certain protein-bound uremic solutes (37). However, the removal of protein-bound solutes via dialysis strategies is still less efficient than the removal of non-protein-bound solutes of similar molecular weights, owing to the resistance induced by the protein binding (28). The total removal depends on how rapidly the solute unbinds from its carrier protein as the free concentration decreases (32). Investigations into protein-bound uremic toxin removal are often restricted to some representatives, such as indoxyl sulfate, conjugates of p-cresol, p-cresylsulfate, and p-cresylglucoronide, and phenylacetic acid (28, 38). With the deployment of adsorptive therapies that were first implemented for the treatment of severe liver failure, the removal of these molecules may be enhanced (38-40). Because the loss of albumin is associated with the removal of protein-bound uremic toxins, protein-leaking membranes have been developed for hemodialysis. Dialysis treatments with such membranes, compared with conventional high-flux dialysis, provide greater clearance of these molecules, but this comes at the cost of a certain degree of albumin loss into the dialysate (28).

Albumin removal in different treatment modalities

Hypoalbuminemia is associated with mortality in patients with ESRD. Albumin removal during dialysis treatment leads to a decrease in the serum albumin concentration, because it is influenced by the albumin synthesis rate, catabolism, distribution between the intra- and extravascular compartments and external loss under pathological conditions (41). The limits of albumin removal across a dialyzer in terms of patient tolerance have been addressed in 2 reviews published in 2003 and 2005, but this issue has not been resolved (27, 42). Nevertheless, albumin removal during different treatment modalities has been elucidated: a small but non-significant decrease in the serum albumin concentration has been observed over a period of 24 months in a group of 17 stable peritoneal dialysis patients, despite protein losses in the range of 5 to 7 g per day (43). The albumin removal during hemodialysis with conventional high-flux membranes is generally reported to be in the range of 0 to 2 g per 4-hour treatment, depending on the

membrane material and the surface area (27). The reported albumin removal levels in online-HDF treatments vary widely and depend on the dilution mode, degree of flux across the membrane, type of membrane, and other treatment parameters. The albumin loss per HDF treatment typically ranges from 1 to 4 g and can sometimes reach values of greater than 5 g (44).

The protein removal levels with the use of reused dialyzers after bleaching procedures are in the range of 10 to 12 g per treatment; these levels are associated with a significant decrease in the serum albumin concentration (45). However, comparable average serum albumin concentrations have been reported in another study in which bleach reprocessing was limited, equivalent to an average dialyzer albumin removal rate of 4.3 g per hemodialysis session (46).

More recent data published as an abstract at the World Congress of Nephrology 2009 have indicated dialysate albumin losses in the range of 0.48 g for Evodial, with 2.2 to 15.5 g per 4-hour session for the FDY 210 dialyzer (Nikkiso) used in hemodiafiltration mode (47). The most recent studies examining widely used membranes have reported albumin losses of 3.1 ± 2.4 g (48) and 3.0 ± 2.4 to 4.3 ± 3.5 g (49).

Currently, it is unclear how much albumin loss per treatment session is tolerated in ESRD patients. There has also been discussion on the utility of a certain degree of loss during albumin removal without triggering antioxidant effects versus facilitating the synthesis of new albumin with antioxidant effects (50).

Medium cut-off (MCO) membranes – a new generation of hemodialysis membranes

In the years since the development of hemodialysis as a treatment for ESRD, a number of improvements have been made to dialyzer membranes. Despite these advances, the overall clinical outcomes for patients still present challenges. Many observational studies have supported the hypothesis that higher-molecular-weight toxins are responsible for a number of dialysis comorbidities, such as chronic inflammation and related cardiovascular diseases (51), immune dysfunctions (52), anemia and EPO hyper responsiveness (53), thus in turn influencing the mortality risk. However, when high cut-off membranes are used to filter higher-molecular-weight toxins, the patients lose unacceptable amounts of albumin and other essential proteins. In an open, randomized, cross-over, 2-center, controlled, prospective clinical study, dialysis patients have been treated with high cut-off HCO1100 dialyzers (Baxter-Gambro, Hechingen, Germany) in series with the low-flux dialyzer PF14L (HCO/LF-HD) or the high-flux dialyzer PF210H (HF-HD) (1). The patients treated with HCO/LF-HD showed significantly greater decrease in multiple immune mediators such as sIL-2R, sTNF-R1, sTNT-R2, and FLCs but also a significant decrease in albumin from 36.2 ± 3.5 to 31.0 ± 4.7 g/L after 3 weeks. Thus, hemodialysis treatment with high cut-off membranes achieves a more effective removal of larger uremic toxins, thus decreasing inflammatory activity, at the cost of higher albumin removal.

The existing gap in the high selective membrane permeability has now been closed with the development of

medium cut-off membranes (MCO). Today, advances in polymer recipes, spinning technologies, and the whole dialyzer-manufacturing concept, including the increased use of high-tech equipment, have resulted in the production of improved, safer and higher-quality dialyzer products. Different approaches in terms of the membrane and dialyzer design, such as fiber undulation, high package density, and improved flow distribution of dialysate fluid as well as decreased fiber diameter to increase internal filtration, have led to improved dialyzer performance but remain insufficient with regard to the removal of middle-molecular-weight products and simultaneous retention of proteins such as albumin. These goals require an extremely narrow pore-size distribution of the dialysis membrane, which has not previously been obtained through the phase inversion method but has recently been achieved through a tailored and well-controlled spinning technology that creates larger, uniformly sized, and densely distributed pores. The newly developed medium cut-off membrane exhibits high selective membrane permeability. After the in vitro characterization of the membrane properties in the context of dextran filtration, Boschetti-de-Fierro et al (54) have classified MCO membranes as having permeabilities closest to that of the natural kidney, as compared with other conventional dialysis membranes, including all permeability classes (low- and high-flux membranes, high cut-off, and protein-leaking membranes). This classification has introduced a new term, the molecular weight retention onset (MWRO). According to the authors' definition, the MWRO is the molecular weight at which the sieving coefficient is 0.9. Together with the general known molecular weight cut-off (MWCO), at which the sieving coefficient is 0.1, it is possible to map different types of blood purification membranes. Different dialyzer families can be distinguished on the basis of their membranes, such as low-flux, high-flux, protein-leaking, high cut-off and medium cut-off membranes. Medium cut-off membranes expand the known limits of high-flux membranes. This expansion in membrane permeability and selectivity represents a large step toward the realization of ideal dialysis membrane separation properties. Boschetti-de-Fierro et al have described 4 dialysis membrane groups in their general classification and their typical performances (17). The data, including the water permeabilities and sieving coefficients of ß2-microglobulin and albumin, of these dialysis membrane groups, extended to include the class of MCO membranes, are given in Table II.

In vitro data suggest expanded toxin removal similar to that observed with high cut-off membranes, with simultaneous retention of albumin, such that medium cut-off membranes are appropriate for regular use in conventional treatment schedules and treatment modes, e.g., 4-hour treatments, 3 times weekly, in Europe. The first 2 studies, which were designed to compare MCO dialyzers with the last generation of high-flux dialyzers, have confirmed this assumption (2). In the first randomized hemodialysis study, 3 different MCO prototype versions MCO AA, BB, and CC (Gambro Dialysatoreny, a subsidiary of Baxter International) with different membrane pore sizes/permeabilities AA <BB <CC54 were compared with a high-flux FX CorDiax 80 dialyzer (Fresenius Medical Care) (55). The study was conducted in the LKH University hospital in Graz and at the

TABLE II - General classifications and typical performance of membranes used in dialysis

Dialyzer type	Water permeability[a] (mL/ (m²*h*mmHg))	Sieving coefficient[b]	
		ß2-Microglobulin	Albumin
Low-flux	10-20	-	<0.01
High-flux	200-400	0.7-0.8	<0.01
Protein-leaking	50-500	0.9-1.0	0.02-0.03
High cut-off	1100	1.0	0.2
Medium cut-off	600-850	1.0	0.008

[a] with 0.9% wt.-% sodium chloride at 37°C ± 1°C and QB 100-500 mL/min.
[b] according to EN1283.

LKH in Bruck, both in Austria, and 19 ESRD patients were included. The primary endpoint was the overall clearance of λ–free light chains (λ-FLCs) with a molecular weight of ~45,000 Da. The secondary outcomes were the removal of medium-sized solutes such as κ–Ig (MW ~22,500 Da) free light chains, α1-microglobulin, complement factor D, myoglobin, ß2-microglobulin and small solutes, as well as the safety of these prototypes. The studied MCO dialyzer prototypes achieved significantly higher overall clearances of κ-FLC and λ-FLC (MCO AA, BB and CC vs. FX CorDiax 80: 8.5 ± 0.54, 11.3 ± 0.51, 15.0 ± 0.53 vs. 3.6 ± 0.51 mL/min), and the removal of other medium-sized solutes was significantly greater, whereas the total mass of the albumin removal was moderate (medians [range] of MCO AA, BB and CC vs. FX Cor-Diax 80: 2.9 g [1.5 – 3.9], 4.8 g [2.2 – 6.7] and 7.3 g [1.9 – 9.7] vs. <0.3 g [<0.3-<0.3]).

In the second study, the performance of 2 MCO prototype dialyzers (MCO AA and MCO BB) in hemodialysis mode was compared with the performance of 2 high-flux dialyzers, FX CorDiax 80 and FX CorDiax 800 (Fresenius Medical Care) in hemodialysis and high-volume hemodiafiltration modes (post-dilution volume-controlled mode with a target total convective ultrafiltration volume of ≥23 L). The study was conducted at the dialysis center in Elsenfeld am Main, Germany. The primary outcome of this study was the λ-FLC overall clearance of MCO prototypes in hemodialysis mode in comparison to the high-flux dialyzers used in hemodialysis and hemodiafiltration mode. The results of this study indicated greater overall λ-FLC clearance by the MCO dialyzers in hemodialysis mode compared with both the HD and HDF treatments with the last-generation high-flux dialyzers ([least squares mean (standard error)]): MCO AA 10.0 (0.57), MCO BB 12.5 (0.57) vs. high-flux HD 4.4 (0.57) and HDF 6.2 (0.58) mL/min. The clearances of α1-microglobulin, complement factor D, κ-FLC, and myoglobin were generally greater for MCO than for high-flux HD and similar or greater than in HDF treatments, whereas the albumin removal was moderate with MCO but greater than that of high-flux HD and HDF (medians [range] of MCO AA and BB vs. FX CorDiax 80 and FX CorDiax 800; 3.2 g [1.9 – 3.9] and 4.9 g [1.1 – 7.2] vs. 0.2 g [0.2 – 0.9] and 0.4 g [0.3-0.8]).

On the basis of both studies, the MCO membranes in hemodialysis mode demonstrate the effective removal of a wide range of middle molecules and exhibit substantially better performance than that of standard high-flux hemodialysis treatment, even exceeding the performance of high-volume postdilution HDF for large solutes, particularly λ-FLC. Because MCO membranes are associated with albumin removal in the range reported in the literature for HDF, the effects of albumin removal with MCO dialyzers on serum albumin levels would be expected to be similarly low, thus providing safe treatment in routine hemodialysis mode.

Conclusions

The newest generation of highly selective and permeable MCO membranes meets both requirements for high quality and good performance for dialysis treatment, featuring the removal of large middle-molecules up to a molecular weight of 45,000 Da typical of a high cut-off membrane, and the low removal of albumin as in state-of-the-art high-flux membranes.

For uremic solutes in the 15,000- to 45,000-Da size range, MCO membranes offer improved clearance compared with that of high-flux membranes used in HD mode and equivalent clearance to that of high-flux membranes in high-volume HDF mode. The benefit is performance equivalent to that of high-volume HDF without a need for the online production of substitution fluid or for vascular access required for high blood flow rates. Therefore, the use of MCO membranes simplifies the delivery of high-removal treatment for ESRD patients, providing a removal spectrum that extends the current capabilities of the best therapy available. This improvement should allow clinicians to surpass the benefits provided by hemodiafiltration, which requires large amounts of high-quality fluid and a more complex setup, while utilizing regular HD equipment. These special MCO membranes should raise the standard of treatment available for all chronic HD patients, potentially decrease inflammatory responses, and generally improve patient outcomes. Future studies are planned to demonstrate the clinical benefits of this innovative product.

Disclosures

Conflict of interest: All authors are employees of the Gambro Dialysatoren GmbH, Hechingen (Germany) or Gambro Lundia AB. Gambro AB (including all direct and indirect subsidiaries) is now part of Baxter International Inc. Baxter is a manufacturer of dialysis devices. None of the authors has proprietary interest. All experimental information is given in great detail to exclude any bias on the results.

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