Chapter 11
Innovations in Maintenance Dialysis Therapy

José A. Moura-Neto, Jyoti Baharani, Sudhir Bowry, Carsten Hornig, Christian Apel, Arduino Arduini, José Carolino Divino-Filho, and Bernard Canaud

11.1 Introduction

Innovation in dialysis aims to bring about clinical benefits and better outcomes when compared to current state-of-the-art treatment practices. In other words, innovation may be a novel idea, product, service, or care pathway that has the capacity to improve patient outcomes to facilitate care while containing costs and creating value in the provision of renal replacement therapy [1, 2]. In this perspective, innovation must primarily fulfill an unmet medical need and must be considered as an

J. A. Moura-Neto
Department of Internal Medicine, Bahiana School of Medicine and Public Health, Salvador, Bahia, Brazil

J. Baharani
Renal Unit, Birmingham Heartlands Hospital, University Hospital Birmingham, Birmingham, UK

S. Bowry
Dialysis-at-Crossroads (D@X) Advisory, Bad Nauheim, Germany

C. Hornig · C. Apel
Department of Health Economics and Market Access, Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany

A. Arduini
Department of Research and Development, CoreQuest Sagl, Lugano, Switzerland

J. C. Divino-Filho
Division of Renal Medicine, CLINTEC, Karolinska Institutet, Stockholm, Sweden

B. Canaud (✉)
School of Medicine, Montpellier University, Montpellier, France

Fresenius Medical Care Global Medical Office, Bad Homburg, Germany
e-mail: bernard.canaud@fmc-ag.com

G. Bezerra da Silva Junior, M. Nangaku (eds.), *Innovations in Nephrology*,
https://doi.org/10.1007/978-3-031-11570-7_11

effective tool and be widely applied in clinical practice to the point it induces a therapeutic paradigm shift.

11.2 Hemodialysis Innovations from a Value-Based Care Perspective

In hemodialysis (HD) therapies, innovation includes many components that involve patient experience, scientific evidence, technical advances, skills of care givers as well as care support, and delivery practices [3]. In this section, we pointedly focus on the major innovations in HD that have been shown to improve patient outcomes and to create value in renal care [2]. These innovative tools belong schematically to five main pathways that need to be considered toward the delivery of dialysis therapies.

11.2.1 Enhance Dialysis Efficacy

11.2.1.1 Convective-Based Therapies (Enhanced External and Internal Filtration)

In prescribing HD therapy, the choice is between three main treatment modalities: low-or high-flux HD and hemodiafiltration (HDF). HDF can be delivered in different configurations, high volume hemodiafiltration (HV-HDF) being currently recognized as the most efficient blood purification method per unit time [4]. The solute removal capacity of all HDF versions is higher than high-flux HD, allowing efficient removal of a broad spectrum of uremic retention solutes that are also referred to as uremic toxins. Schematically, reduction rates of hv-HDF is 10–5% higher for low molecular weight compounds (e.g., urea, creatinine), 20–30% higher with peculiar compounds (e.g., inorganic phosphate, free light-chain immunoglobulin) [5–7], and 100% higher for middle molecular weight compounds (e.g., $ß_2$M, myoglobin) [8–10]. Furthermore, solute removal capacity is positively correlated to the total ultrafiltration volume delivered, used as surrogate of dialytic convective dose [11–13]. Therefore, relying on the law of conservation of mass within the dialysis-patient system on a weekly basis by increasing solute mass removal by HDF therapy, considering a constant generation rate, and circulating concentration of solute of interest should decrease accordingly at steady state [14, 15].

In this context, circulating levels of $ß_2$M offer a highly clinically relevant uremic marker that needs to be considered as used more widely by nephrology community [16, 17]. $ß_2$M results from cell activation (expressing HLA), is triggered by inflammation, oxidative stress, and complement activation, contributes to endothelial dysfunction, and finally is cleared by kidney functions [16]. In dialysis patients, $ß_2$M circulating level has an added importance since it reflects both efficacy of renal

replacement treatment (RRT) and toxicity risk particularly for the cardiovascular system [18–20]. Clinical interest of monitoring $ß_2M$ circulating levels is highlighted by several scientific reports [17, 21]. Using $ß_2M$ as the paradigmatic marker of RRT efficacy has been emphasized in some recent reports [22] and implemented in the guidelines of the Japanese Society of Dialysis and Transplantation (JSDT) [23]. Incorporating $ß_2M$ in the panel of biomarkers required for assessing HDF dialysis dose delivery was also proposed by the EUDIAL working group [24].

Recent studies have shown that by using more open membranes, and forcing internal backtransport phenomenon (internal filtration) through increasing flow resistance [25–27], comparable $ß_2M$ removal rates to HDF could be achieved [28, 29]. This is an interesting finding that confirms superiority of convective transport on $ß_2M$ clearances and other middle MW compounds, but at the expense risk of increase albumin loss due to higher and uncontrolled membrane stress [29].

Based on the most recent studies, it is suggested that maintaining a predialysis serum $ß_2M$ concentrations $\leq$25 mg/L is achievable with standard HDF and particularly hv-HDF and is an optimal target toward reducing mortality in dialysis patients [22, 23]. To comply with such key parameter indicator, dialytic convective dose needs to be probed and adjusted individually to patient $ß_2M$ kinetics [30]. As indicated by recent studies, using currently available high-flux membranes, that could be achieved in a majority of patients in postdilution HDF mode with 23–28 L per session of total convection volume [15]. In these cases, $ß_2M$ reduction rate per session is $\geq$80%, a value equivalent to a $ß_2M$ Kt/V $\geq$ 1.5 that provides a $ß_2M$ mass removal ranging between 150 and 200 mg/session for a thrice weekly 4 h treatment schedule [10, 31, 32]. Such treatment schedule is then able to remove 450–600 mg per week out of the 1000–1500 mg mass generated per week.

11.2.1.2 Intensive Dialysis

The conventional prescription of HD is three sessions/week, each of 4 h duration (12 h). Increasing weekly treatment time either through longer individual session (long or home HD, nocturnal) or through more frequent sessions (daily, alternate day), so-called intensive dialysis, has significant benefits on patient outcomes [33–35]. Intensive dialysis enhances clinical performances and treatment efficacy, reduces intradialytic morbidity and treatment burden, and improves mid-and long-term patient outcomes [32, 36, 37]. In this context, HDF has been shown to bring additional values on patient outcomes and patient perception [38–40].

Clinical benefits of intensive dialysis rely on different mechanisms. Firstly, it is associated with higher solute removal capacity and better homeostasis control of specific solutes (inorganic phosphate, $ß_2M$, indoxyl sulphate, para-cresol sulfate). Increased treatment time is currently the only way to overcome slowly moving intracorporeal compounds (low intracorporeal mass transfer coefficient or body clearance) during intermittent treatment [30, 41]. This is clearly shown in kinetic studies. Secondly, it is also coupled with a reduction of ultrafiltration rate, a condition that facilitates vascular refilling capacity, reduces hypovolemia, and then

improves hemodynamic response. In other words, slow ultrafiltration rate tends to minimize dialysis-induced systemic hemodynamic stress [42–47]. Thirdly, it restores a more physiological profile to short intermittent treatment schedule on kinetic and volume changes of solutes. This is confirmed and substantiated by reduction of time-averaged changes (solute concentration, fluid overload, pressure) as well as time-averaged deviations (up, down) [48–50]. Fourthly, it tends to reduce cardiovascular burden (left ventricular hypertrophy) as well as end organ damage (brain) and overall mortality [35, 42]. Finally, it is associated with a better patient perception, reduced impact on quality of life, and facilitated life and professional rehabilitation [34, 51, 52].

11.2.2 Improve Cardiovascular Outcomes

11.2.2.1 Fluid Management

Optimal fluid management has emerged over the last few years as a crucial component to minimize systemic hemodynamic stress and to reduce mortality in dialysis patients [53–55]. Fluid management has two pathways that need to be considered [56–58]: one, reflecting chronic fluid overload accumulated during the interdialytic period and not adequately or timely corrected by dialysis; the other one, reflecting fluid volume depletion induced during dialysis and the systemic hemodynamic response. Interestingly, both the factors have negative impact on the cardiovascular system through different pathways. Chronic fluid overload is responsible for hypervolemia, systemic and pulmonary hypertension, cardiac stretching with functional and structural remodeling, leading to left ventricular hypertrophy, cardiac dysfunction (systolic and diastolic), arrhythmia eventually associated with sudden cardiac death [47, 59]. On the other side, fluid depletion induced by ultrafiltration during the dialysis procedure exposes patient to various degrees of hypovolemia; too rapid ultrafiltration may induce critical hypovolemia and being likely responsible for relapsing intradialytic hypotension episodes causing ischemic insults and leading to repetitive end organ damages (cardiac stunning, brain injury, kidney injury) [47].

Fluid management, currently summed up by the dry weight probing approach, remains for clinicians a delicate between correcting fluid overload while preventing severe fluid depletion [58]. Several biomarkers have been proposed to ensure safer fluid management and reviewed recently. Multifrequency bioimpedance (BIA) has gained large clinical acceptance in supporting clinical dry weight probing [60, 61]. Recent large observational or controlled studies have confirmed the significant value of BIA in guiding more precisely and safely fluid management in dialysis patients to reduce mortality [61–63]. Lung ultrasound (LUS), by scoring B-lines number, used as surrogate marker of extravascular pulmonary edema (thickening of interlobular septa), has also been shown useful in guiding clinical decision [64, 65]. In recent controlled studies, LUS has proved its value in reducing dry weight and controlling hypertensive refractory patients [66, 67]. Further outcome studies are

required to confirm cardioprotective effect of these tools on a long-term basis. Cardiac biomarkers have been also used to evaluate fluid status either fluid overload (BNP, Nt pro-BNP), fluid depletion (copeptin), or cardiac damage (troponin) to guide clinical decision-making in fluid management [53, 68, 69]. In addition, these biomarkers used either alone or in combination may provide interesting predictive cardiac risk [70, 71]. Unfortunately, utilization of these biomarkers is associated with increased costs that often preclude their regular use as monitoring tool and are not part of best clinical practices.

11.2.2.2 Feedback-Controlled Tools

Feedback-controlled tools integrated in dialysis machine may provide additional options to facilitate dialytic fluid management and to improve hemodynamic stability. Among dialysis tools, two have been extensively studied: firstly, blood volume-controlled ultrafiltration; secondly, hypothermic or isothermic dialysis. Blood volume (BV)-controlled ultrafiltration is associated with improved hemodynamic stability [72, 73] as indicated by a significant reduction of incidence of hypotensive episodes and cardiac wall motion abnormalities [74]. However, this clinical benefit has not been confirmed in interventional large studies, meaning that volume control is not the only hemodynamic parameter to be considered [75]. Hypothermic or isothermic dialysis achieved either manually or automatically via blood temperature monitoring option has been shown beneficial in unfavorable patients (hypotensive-prone, cardiac, diabetic patients) and uniformly across all hemodynamic instability conditions as summarized in recent meta-analyses [76–78].

Automatic sodium management has been recently integrated in modern dialysis machines. Sodium control module loop incorporate dialysate sensors (e.g., conductivity cell) and processor unit that integrates conductivity data and dialysis fluid conductivity adjustment according to dialysate-plasma sodium prescribed [79, 80]. Validation studies have shown that zero-diffusive sodium or isonatremic condition could be achieved very reliably with less than 1.0 mmol/L plasma sodium concentration changes [81]. Furthermore, the sodium control module provides an estimate of the sodium mass balance and allows monitoring of plasma sodium concentration throughout the dialysis session. Further studies are needed to identify clinical benefits as well as long-term cardiovascular outcome improvement of this new tool [82].

11.2.3 Facilitate Acceptance of Alternative HD Delivery Modes

11.2.3.1 Home Therapy

Despite proven clinical and economic benefits, home hemodialysis (HHD) remains still marginal (<3% of share) as compared to in-center HD, except in few countries (e.g., New Zealand, Australia, Canada, Denmark, Finland, Sweden, UK) that have

initiated programmes to promote this therapeutic option [83]. A renewed interest for HHD is emerging due to the availability of new specifically designed, more friendly and connected dialysis machines target to meet the needs of patient autonomy and mobility, and attractivity of daily treatment and healthcare regulatory policies [84, 85]. Several manufacturers have developed new, innovative, and well featured HHD machines that includes NxStage System One, Quanta SelfCare+, Physidia S3, and Tablo Outset Medical [86]. These HHD machines have been approved by appropriate notified bodies and are being currently implemented and assessed worldwide for home dialysis treatment. Presently, it is too early to draw any conclusions on the prevalent acceptance and use of HHD, but it seems that this new technology has already triggered an upswing for home dialysis therapy.

11.2.3.2 Personalized Therapy

Incremental dialysis and more flexible dialysis treatment schedules are currently being developed not only to facilitate transitioning from end stage kidney disease to dialysis and improve patient's treatment acceptance [87–89], but also to solve renal care issues in fast-developing countries (e.g., China, India) [90–92]. Incremental or flexible dialysis relies mainly on the preservation and support of residual kidney function [93–95], or by adding an additional oral component acting on the gut and reducing uremic toxins generated [96, 97] by means of adsorber (ST120) or pro-or antibiotics mixtures [98]. In this context, several recent reports have shown potential clinical benefits, cost-effectiveness, and usefulness of such individualized approaches. However, it remains to be proved by controlled studies that such incremental or flexible dialysis schedules are applicable and generalizable to unselected populations.

11.2.4 Ensure Vascular Access Sustainability

Vascular access sustainability remains source of concern in most dialysis patients. Failure or dysfunction of arteriovenous fistula or graft is one of the first causes of hospitalization and morbidity in HD patients. In this context, tunneled central venous catheters represent an easy and comfortable alternative, although unfortunately associated with additional risks (inadequate dialysis, infection, vein stenosis) [99, 100]. Vascular access management represents a highly ranked priority in most best practice clinical guidelines [101]. Over the last few years, various new options have emerged to improve vascular access outcomes [102]: firstly, increased success of native arteriovenous fistula creation by pre-or intra-operative vasculature assessment [103–107]; secondly, percutaneous creation of proximal arteriovenous fistula [108–111]; thirdly, the use of bioengineered blood vessel in patients with exhausted vasculature [112–115]; fourthly, better handling of tunneled central venous catheter or implanted port devices and use of locking solutions [116–119].

11.2.4.1 Implement Continuous Quality Improvement Programs with Support of Digital, Advanced Analytics, and Artificial Intelligence

Outcomes of dialysis patients result from a complex equation involving individual patient profiles, renal replacement modality, multiple dimensional measures [120], skills of care givers, and therapy delivery practices. In this complex therapeutic chain involving several stakeholders with multiple sources of data, implementation of a continuous quality improvement process supported by digital and advanced analytic tools providing balanced scorecard is an attractive way to achieve targets and to improve patient outcomes in a more structured and comprehensive manner [121, 122]. The benefits of such a strategic approach has been reported in a recent study developed in a large dialysis chain provider [123]. In this study involving a cohort of 4270 incident dialysis patients, 2-year mortality was analyzed according to achievement of key performance indicators (KPI) prior (group A, 2397 patients) to and after (group B, 1873 patients) medical peer review involving continuous quality improvement (MPR CQI) onset. After MPR-CQI implementation, a significant improvement in KPI targets was achieved associated with a 30% risk reduction of mortality [123].

11.2.5 Final Considerations for HD Innovations

In the last decade, industry has developed a number of innovative technologies that support the nephrological community in monitoring and individualizing therapies toward the overall target of improving outcomes and well-being. For example, estimation of sodium levels is crucial toward maintaining fluid status and hypertension–both of which impact cardiovascular outcomes in HD patients; the automated sodium management tool of the 6008-dialysis machine (FMC, Bad Homburg, Germany) helps achieve an individualized and precise sodium prescription without adding any workload to the dialysis care staff. Such strategies that enable clinical decision-making to improve patient well-being without additional organizational effort are examples of the new trend toward value-based healthcare. This concept is graphically summarized in Fig. 11.1. In this section, we have attempted to delineate various "innovations"—grouped in five pathways—that have the potential to fulfill the aim of improving the hitherto poor outcomes associated with the dialysis patient populations (Fig. 11.1). Collectively, each of the five pathways (enhanced dialysis efficacy through convective-based therapies and intensive dialysis; improved cardiovascular outcomes through active fluid management, feedback-controlled loops and automated sodium management; facilitated patient acceptance of treatment through home-based and personalized therapies; ensured vascular access sustainability through non-invasive pre-implantation vasculature assessment, availability of bioengineered blood vessels, and better handling of tunneled central venous catheters or port devices; implementation of continuous quality

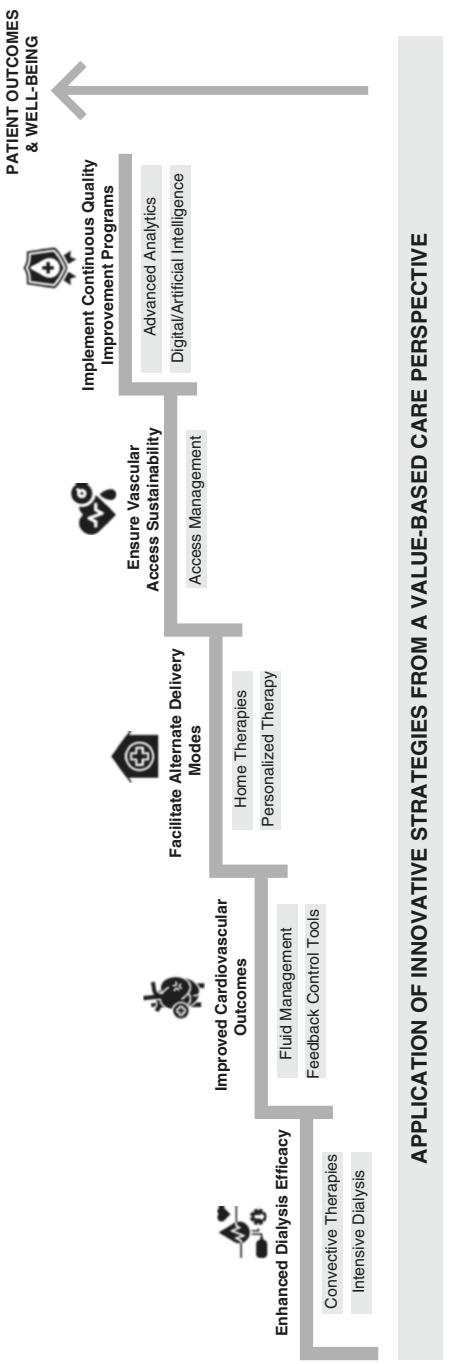

Fig. 11.1 Incremental and collective application of different strategies to target improvement of patient outcomes in terms of reducing morbidity and mortality that is still high for the dialysis population. Until now, the emphasis has mainly been on addressing issues related directly to the treatment procedure itself; today, there is evidence to suggest that a number of pathways related to the overall care of the individual dialysis patient may help achieve better outcomes

improvement program with support of digital, advanced analytics, and artificial intelligence) has a higher probability of achieving better therapy outcomes and increased patient well-being, rather than addressing each pathway separately and fragmented manner.

11.3 Peritoneal Dialysis Innovations

The advent of Continuous Ambulatory Peritoneal Dialysis (CAPD) in 1976 can be considered as a simple and fabulous innovation in the home dialysis therapy scenario [124–126], leading to a significant increase in peritoneal and home dialysis utilization. Since those days, innovations mainly in the area of peritoneal dialysis (PD) bag designs, connectivity and monitoring have kept a steady pace of development, opposite to what happens in the area of the base PD solutions and its mostly used osmotic agent, glucose.

11.3.1 Innovations in PD Access, Catheter Design, and Insertion Techniques

It is correct to say that functional peritoneal dialysis access remains the cornerstone and Achilles' heel for successful initiation and time on therapy. If catheter insertion is free of complications, then it goes to follow that patients will most likely have a successful time on peritoneal dialysis.

Catheter type and the tendency of catheter migration therefore influence failure potential. Many innovative PD catheter designs have been produced along the years. Here, we highlight two of them:

(a) The weighted catheter designed by Di Paolo [127, 128] to overcome the problem of catheter dislocation. It is a straight catheter, weighted at the end with 12 g of silastic coated tungsten, an inert biocompatible element which is denser than dialysate and gravitates into the pre-rectal peritoneal pouch (Fig. 11.2). The weighted catheter's first reported use was in 1996 with further publications in 2004 of a series of 746 patients with fewer complications and dislocations when compared with Tenckhoff catheters. In 2019, Stonelake et al. presented results that the weighted catheter was associated with lowest failure rates when compared with surgically inserted non-weighted catheters in a group of patients with increased risk factors for adverse catheter outcome [129].

(b) A new catheter design by Al-Hwiesh [130], the new triple-cuff PD catheter has demonstrated a zero rate of catheter migration, improved catheter survival, and lower peritonitis rates (Fig. 11.3)

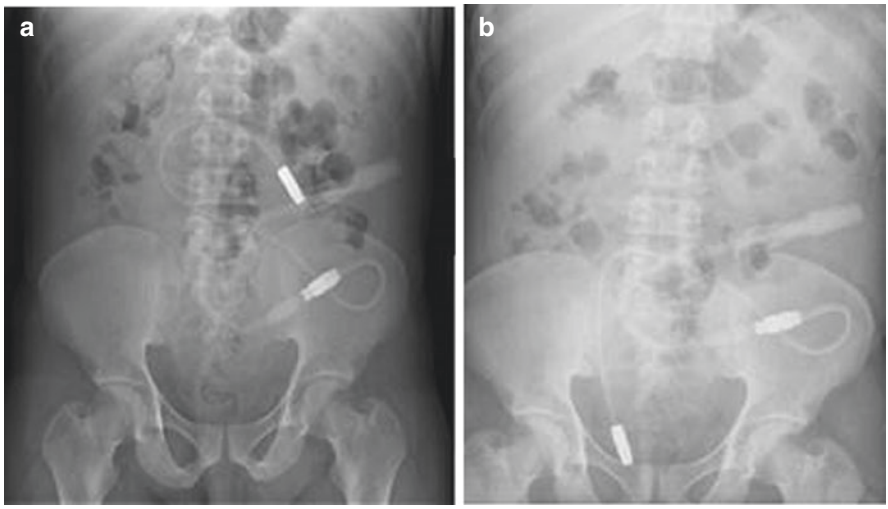

Fig. 11.2 The weighted PD catheter designed by Di Paolo. (**a**) PD catheter with weighted tip "flipped" secondary to constipation; (**b**) Same PD catheter 2 days after constipation treatment–weighted element back in satisfactory position. (Courtesy of Dr. Jyoti Baharani, Birmingham Heartlands Hospital, Birmingham, United Kingdom)

Fig. 11.3 The triple-cuff PD catheter designed by Al-Hwiesh. (Courtesy of Dr. Abdulla Al-Hwiesh, Al-Khobar, Saudi Arabia)

11.3.2 Connectology Assistance

Although assisted PD has increased the repertoire and numbers being enabled to have therapy, there are practical measures that need to be taken into consideration before an assisted service can be offered. Efforts to create devices that further

facilitate the management of the PD exchanges by patients and/or by healthcare professionals assisting the therapy are needed, for example, new connectors for PD exchanges as well as devices to manage patient training, prescriptions, therapy outcomes, and even bi-directional communication.

PeriSafe, a new connectology device, connects the transfer set and the PD bag system inside of a protected area. Manual contact of the patient with the open transfer set is prevented, and breaking the frangible or clamping the tubes can be performed by pushing a button. The PeriSafe system removes the old protective cap, and the pull-ring connects the transfer set and PD bag system, guiding the patient through the therapy with buttons. After dialysis, the transfer set is disconnected from the PD bag system and protected with a new protective cap. All the steps are performed inside of the protected device [131].

11.3.3 Peritonitis Diagnosis

Point of care (POC) devices for peritonitis provide useful, rapid, and inexpensive screening test for diagnosing peritonitis and may be helpful for patients who live in rural areas or patients who have difficulty getting to their clinics.

A leukocyte esterase strip test such as Peri-Screen/Peri-Plex may provide a point of care test for peritonitis. Preliminary results from a European study show a sensitivity of 100% and a specificity of 96%, along with the ability to detect as few as 50 leukocytes/mm^3, this test can detect as few as 100 leukocytes/mm^3 (with a neutrophil count of not less than 50%) [132].

11.3.4 Patient-Directed Therapy

In some healthcare settings, delivery of PD has focused on achieving the small solute targets suggested in the 2006 International Society for Peritoneal Dialysis (ISPD) prescription guidelines without considering the impact of increasing dialysis exchanges or hours on a cycling machine on quality of life.

However, since 2006, those in need of dialysis have changed considerably with increasing multimorbidity associated with higher proportions of people with diabetes and/or in older age groups. At the Kidney Disease Improving Global Outcomes (KDIGO) Controversies Conference on Dialysis Initiation, Modality Choice & Prescription in January 2018, it was proposed that there should be a change in terminology from "adequate" to "goal-directed" dialysis defined as "using shared decision-making between the patient and care team to establish realistic care goals that will allow the patient to meet their own life goals and allow clinicians to provide individualized, high quality dialysis care."

This approach concurs with the findings from the Standardised Outcomes in Nephrology–PD initiative (https://songinitiative.org/projects/song-pd/), which

identified core outcomes for PD chosen by patients, caregivers, and healthcare professionals, namely PD infection, cardiovascular disease, mortality, PD failure, and life participation. There is no evidence that small solute clearance on its own directly affects these outcome measures, except in a small proportion of individuals in whom transfer from PD to HD has been attributed to insufficient small solute removal.

11.3.5 Enhancing Uptake and Maintaining Numbers on PD

Innovation is not limited to material invention. A revolution happening in the last decade of translating patient experience into patient insights calls for its inclusion as the new global standard for therapeutic and device approvals as well as reimbursement decisions. This must be considered as an innovation, not earlier even imagined.

Another real-life evidence of an "abstract" innovation is the implementation of a quality improvement process. This implementation at the University Hospitals Birmingham NHS Foundation Trust successfully increased the number of incident and prevalent PD patients. PD uptake increased from 37 to 84 patients per year, giving a PD penetration increase from 8.4% to 19.1% between April 2014 and January 2018. Catheter insertions increased from 94 to 185 per year. Peritonitis rates remained stable, and PD drop out to HD, reduced from 52% to 41% during the same period.

Changes introduced as part of the QI process can take time to develop, introduce, and embed. Pathway mapping, patient education, and utilization of lean methodology can positively impact PD growth. The multidisciplinary team focus on growing home therapies can in conjunction with peer educators offers a new approach to patient education and treatment decision-making.

Pivotal to this process of enabling a philosophy of informed patient choice, resulting in the growth of home therapies, is a clinical champion "Home Therapies Lead" clinician. Continued research and audit can identify the longer-term impact of the cultural shift within renal services on growth and maintenance of home-based dialysis and more specifically PD numbers.

A key change for future state mapping is to move from thinking about patient preference for modality of dialysis, to patient preference for location of dialysis. By implementing a rapid improvement process and embedding continuous quality improvement process, an increase in the incidence and prevalence of PD should become apparent [133].

11.3.6 What About Innovation in PD Solutions and Its Mostly Used Osmotic Agent (Glucose)?

Paradigmatic of such condition is the case of one of this chapter's authors (AA), who spent most of his academic and professional medical life in researching and developing new anti-diabetic treatments, with no contact with the nephrology/

dialysis world. He was not aware that glucose, administered intraperitoneally in relatively large amounts, was the main osmotic agent used in PD therapy. This came as a surprise particularly in consideration that diabetes is the leading cause of kidney failure; the obvious next question was: *is there a way to replace glucose as the base osmotic agent?*

One possibility to mitigate the potential metabolic side effects of glucose would be to formulate PD solution containing a mixture of different osmotic agents, allowing to reduce the concentration of the single one and possibly to take advantage of a combination of favorable pharmaco-metabolic properties that may address not only the main dialytic objective of a PD solution along with a better preservation of the peritoneal membrane, but also common comorbidities such as diabetes mellitus, a disease that dramatically increases the already high preexisting risk of cardiovascular disease (CVD)/deaths in PD patients.

PD patients are potentially exposed to a constant hyperinsulinemic state because of the continuous intraperitoneal load of glucose, the most potent insulin-secretagogue [134, 135]. On the other hand, the hyperinsulinemic state in diabetic PD patients is most likely linked to insulin dipeptidyl peptidase-4 inhibitors or glucagon-like peptide 1 analog treatment [136]. An emerging concept for the etiology of CVD and the atherometabolic risk of diabetic and non-diabetic IR individuals is organ-and/or pathway-specific insulin resistance (IR), also known as selective IR [137–139]. This is based on the observation that IR does not occur for all insulin signaling pathways, with the result that those pathways still responding to insulin normally may be overstimulated because either of the concomitant compensatory hyperinsulinemic condition experienced by non-diabetic IR subjects and during the earlier stages of type-2 diabetes or in type 1 and 2 diabetics treated with insulin. This clearly indicates that glucose and insulin are the main culprits of some of the pathological sequelae occurring in PD therapy.

If insulin cannot be replaced in diabetic PD patients, it should be possible to reduce its use by improving glycemic control intervening at two levels: replacing most of the glucose present in the PD solution with osmo-metabolic agents able to improve glucose uptake and/or disposal. Two of these osmo-metabolic agents are L-carnitine and D-xylitol [140]. In addition to their good safety profile and great chemical stability, these two naturally occurring compounds are not only involved in major metabolic pathways involved in glucose and lipid homeostasis, but they may also improve insulin sensitivity and glucose uptake/disposal by modulating mitochondrial acetyl-CoA levels (i.e., L-carnitine) and via transcriptional and post-transcriptional interventions (i.e., D-xylitol) [141–144].

A combination that is currently under clinical investigation foresees the use of D-xylitol, as the major osmo-metabolic agent, along with L-carnitine and less than 70 to 85% D-glucose present nowadays in commercially available PD solutions [145]. Furthermore, in vitro studies conducted with this glucose-sparing PD solution are very encouraging as they do not seem to induce fibrosis and angiogenic effects in human mesothelial and endothelial cells, respectively [146]. Even more interesting is the recent renaissance of metabolism and metabolic reprogramming in the field of fibrosis that may see the involvement of the same osmo-metabolic agent in combatting the mesothelial-to-mesenchymal transition (MMT) too. Indeed, one

of the above osmo-metabolic agents, L-carnitine, may be extremely competent in mitigating the hyperglycolytic phenotype, also known as the "Warburg effect," commonly present in MMT [147]. The well-recognized intervention of supra-physiological concentration of L-carnitine within mitochondria in lowering acetyl-CoA and, hence, reactivating pyruvate dehydrogenase [141] is as efficient as glycolytic inhibitors in inhibiting TGF-b1 induced MMT [148]. An important implication of this finding is that to slow down the progression of fibrosis, it is not necessary to inhibit glycolysis, which may carry serious side effects, but only requires an efficient coupling of glycolysis with the Krebs cycle.

PD solution innovations such as pharmaco-metabolic intervention with a combination of osmo-metabolic agents in PD therapy may lead to beneficial effects both at systemic and peritoneal levels, improving the so-called global biocompatibility of PD.

11.3.7 Final Considerations for PD Innovations

Innovation must also be global. It is interesting to note and important to try understanding why a greater number of the innovations introduced in the PD space have actually been focused on further development of the Automated PD (APD). It seems like CAPD is the poor cousin of APD; however, sound evidence favoring APD therapy as superior to CAPD does not exist today. With innovation also focused on CAPD, expansion of assisted PD may become a perfect combination with CAPD: a simple, cheaper, and safe home dialysis option.

11.4 Future Perspectives

What can we expect from dialysis therapy in the years to come? Although there are different forms of innovation within the field, the idea of having smaller and portable dialysis devices, above all, brings hope and some excitement to the kidney community. The concept of portable dialysis is definitely not new; there are a few reports in medical literature from the 1970s and 1980s [149–151]. However, there is still a fine and little-known boundary between the dream, the myth, and effective developments in the area. Only recently, with the advent of miniaturization and nanotechnology, have we had actual innovative advances in order to possibly achieve a safe, economically viable and efficient treatment with portable devices in the near future [152, 153].

In this regard, the WAK (Wearable Artificial Kidney)–a wearable blood-based renal replacement device–is a potential innovative advance. It is a lightweight (<5 kg), battery-powered, that is used like a vest or belt (Fig. 11.4). Due to the potential risk for accidental disconnection, the WAK is more likely to be connected to an HD catheter instead of arteriovenous fistula (AVF) needles. The used dialysate

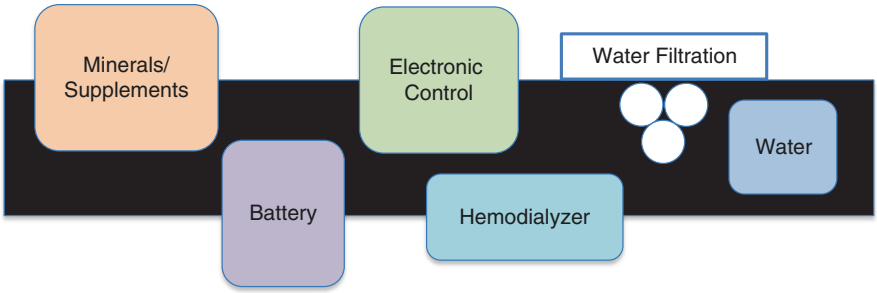

Fig. 11.4 The WAK (wearable artificial kidney). (Reproduced with permission from Salani et al. [154])

is regenerated using sorbent technology with the excess redirected through an ultrafiltration pump to a waste bag. The WAK pump has a double channel pulsatile counter phase flow, described in detail elsewhere [154–156].

A 2007 pilot landmark study by Davenport et al. showed some promising efficacy and safety results. Eight patients with end-stage kidney disease on regular HD were fitted with a WAK device for 4–8 h. Unfractionated heparin was administered to avoid coagulation, as it would be for conventional HD. Mean blood flow was 58.6 mL/min, with a dialysate flow of 47.1 mL/min, and the mean plasma creatinine clearance rate was 20.7 mL/min. There was no evidence of hemolysis, as well as no significant cardiovascular changes and no adverse changes in acid-base balance. Clotting of the vascular access occurred in two patients due to a decrease in the unfractioned heparin dose. As discussed above, AVF needle disconnection was an issue in this pilot study; one patient suffered a temporary disconnection due to his AVF needle becoming dislodged. The device's safety mechanisms ensured a quick interruption of the blood pump, avoiding blood loss, and the treatment continued with no clinical consequence to the patient [156].

A portable device also has been produced for PD; the AWAK (automated wearable artificial kidney–AWAK Technologies Pte, LTD). It is a tidal PD-based artificial kidney, battery operated, that uses regeneration of the dialysate in order to reduce fluid requirements. The system–composed of a disposable storage module, tubing set, and system controller–is even lighter (weight less than 2 kg) than the WAK and can be used like a bag [157] (Fig. 11.5). In the AWAK system, 1–1.5 L of dialysate is initially instilled into the peritoneal cavity, such as in conventional PD. Again, sorbents are used; a tidal volume of 0.5 L of equilibrated dialysate is then drained from the patient into the storage module and pumped through the sorbent cartridge for clearance. After filtration, supplementation (with glucose and electrolytes) and degassing of the spent dialysate, the regenerated dialysate returns to the peritoneal cavity. The tidal exchange lasts about 7–8 min, resulting in eight exchanges per hour. The sorbent cartridge can be utilized for 6–8 h, before being discarded and replaced–so the process can commence again [154, 157].

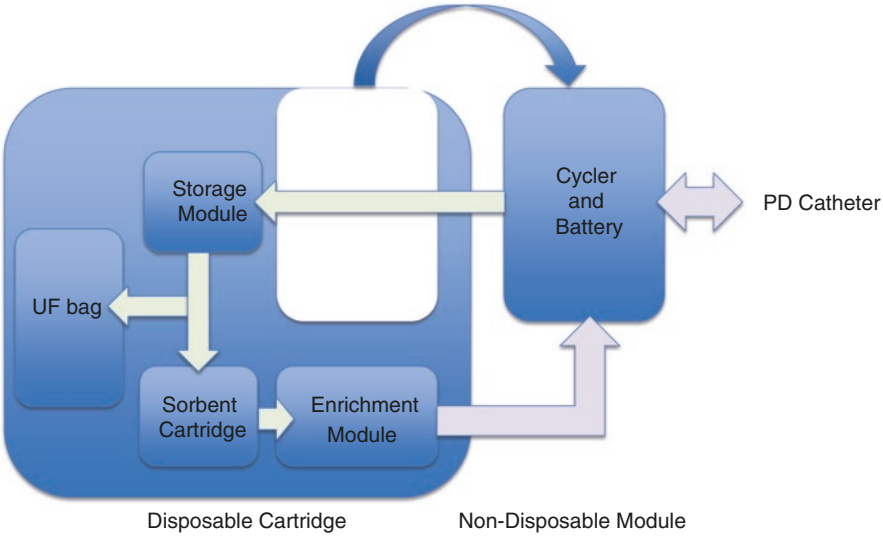

Fig. 11.5 The AWAK (automated wearable artificial kidney). (Reproduced with permission from Salani et al. [154])

A study conducted with 20 patients using the AWAK system reported a urea clearance of 31.5 mL/min. The AWAK was worn for 4–24 h, and the treatment was based on the tidal PD mode of dialysate delivery. Although no adverse event was reported, the consequences of the regenerated dialysate and the continuous fluid exchange and how this influence risk of peritonitis, membrane failure, hyperglycemia, and encapsulating peritoneal sclerosis are not yet fully understood [154, 158].

Another innovation–this one in earlier stages of research and with no clinical trial in humans so far–that arouses curiosity beyond hope to both patients and healthcare professionals is being developed by the Vanderbilt University Medical Center and the University of California, San Francisco: the IAK (Implantable Artificial Kidney). The device mimics a native kidney, incorporating tissue engineering and silicon nanotechnology, and is designed to be surgically implanted [154]. The IAK system closely replicates the nephron physiology through a combination of a high-efficiency filter (the HemoCartridge) and a bioreactor of cultured kidney tubule epithelial cells (the BioCartridge). Originally, the IAK does not require electrical pumps since it is meant to be connected to the arterial vasculature, allowing blood to be pumped by the force of the patient's own blood pressure. The ultrafiltrate produced in the HemoCartridge is processed by the BioCartridge, which returns water, salt, and glucose to the blood and concentrates toxins into a small amount of fluid similar to urine in a progressive manner (Fig. 11.6). Originally, the IAK does not require electrical pumps since it is meant to be connected to the arterial vasculature, allowing that the patient's blood pressure to pump blood through the filter [157].

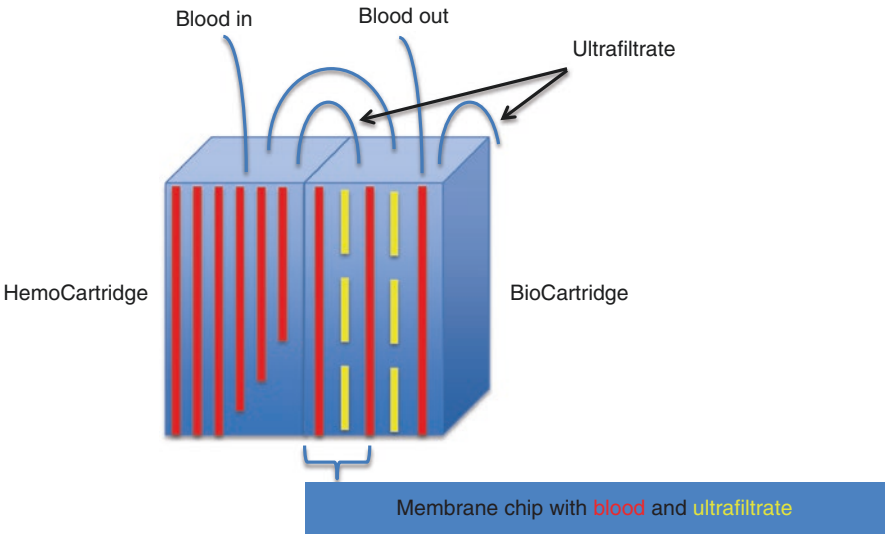

Fig. 11.6 The IAK (Implantable Artificial Kidney). (Reproduced with permission from Salani et al. [154])

In addition to research and development of the aforementioned portable (WAK and AWAK) and implantable devices (IAK), the nephrology community desires–and requires–innovations to turn dialysis more equitable and globally accessible. A few years ago, Kotanko et al. suggested a rather controversial, yet only theoretical, model in order to solve this issue. In summary, the authors proposed a model in which a healthy human being (called the "buddy") could somehow replace the function of a HD machine (Fig. 11.7). This concept, known as allo-hemodialysis (the Greek prefix "allo" means "other"), is a paradigm-breaking innovative model of renal replacement therapy. In allo-hemodialysis, blood from the "buddy" flows in counter-current direction to the patient's blood, functioning as the dialysate. Uremic toxins diffuse from the ill patient across the dialyzer membrane into the "dialysate" (which in this case is the "buddy's" blood). Then, the buddy's blood is transported back to the buddy, where solutes and fluid received from the ill patient will be finally excreted by the buddy's healthy kidneys [159, 160]. A 2019 cross-sectional survey conducted in Mexico aimed to investigate acceptance of allo-hemodialysis among caregivers and nephrology healthcare professionals. Although only 60% of the healthcare professional accepted it, this new technique was mainly accepted by caregivers–both related (87%) and non-related (90%) to kidney patients [161]. Despite several bioethics and clinical unresolved issues, allo-hemodialysis, among all potential innovation, maybe the only one that could truly make the renal replacement therapy significantly cheaper and consequently more accessible especially in the poorest settings, where dialysis is not universally available.

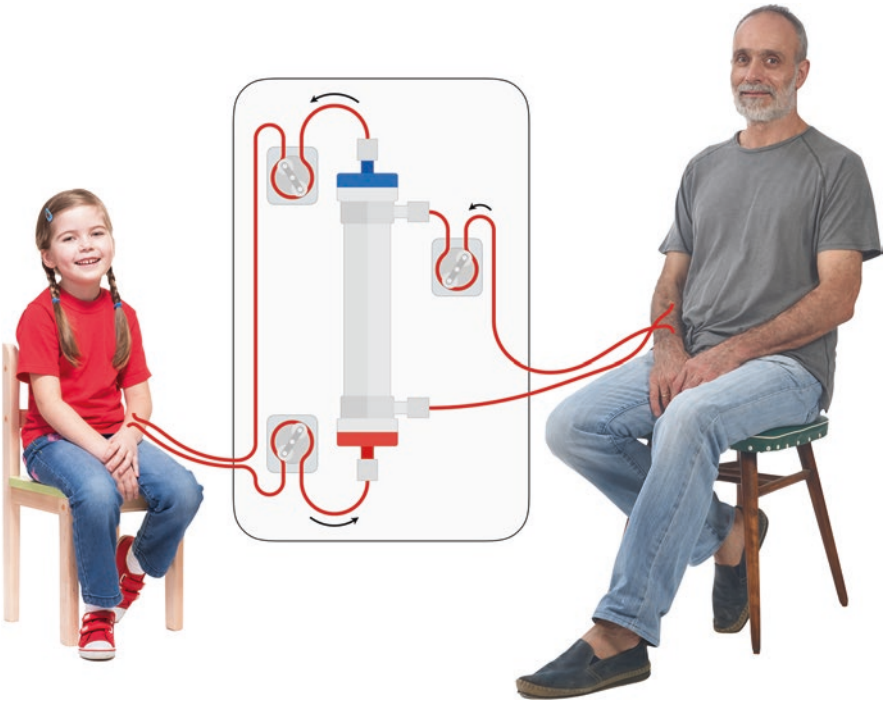

Fig. 11.7 Allo-hemodialysis model. The pediatric patient with kidney failure and the "buddy" (adult with healthy kidneys). The blood of the adult "buddy" is pumped through the dialysate compartment in countercurrent flow, serving as the dialysate. Ultrafiltration is due to speed differentials of the patient-sided pumps. (Reprinted with permission from Kotanko et al. [159, 160])

Despite all the promising research for innovations in dialysis therapy–at different stages of development, in fact–future perspectives for real breakthroughs may not lie in novel peritoneal or blood-based therapies. Otherwise, it would somehow be "more of the same" for the patient's experience and outcomes. Paradoxically, the future of dialysis may not be in dialysis therapy itself… rather, it may be related to paradigm-changing innovations that are based on demands and expectations of kidney disease patients, such as preventive (i.e., lifestyle education) or curative action on kidney disease (i.e., SGLT2i in diabetic kidney disease), or regenerative medicine to correct kidney injury, or xenotransplantation and/or biomedical engineering developing hybrid concept. Only time will tell us, and (hopefully) very soon what is the best pathway to follow.

Finally, the past and present of dialysis are filled with remarkable technical advances. Through history and looking to the future, we shall never forget the main driver of innovation: the patient. All efforts and progress are only meaningful when associated with superior outcomes, better patient perception and/or benefits for health systems. This is the only way to guarantee that innovation is a tangible reality that has the potential to change treatment paradigms and not just novelties restricted to private research or corporate interests.

References

1. Kelly CJ, Young AJ. Promoting innovation in healthcare. Future Healthc J. 2017;4:121–5.
2. Busink E, Canaud B, Schröder-Bäck P, et al. Chronic kidney disease: exploring value-based healthcare as a potential viable solution. Blood Purif. 2019;47:156–65.
3. Basile C, Davenport A, Mitra S, et al. Frontiers in hemodialysis: innovations and technological advances. Artif Organs. 2021;45:175–82.
4. Ronco C. Hemodiafiltration: technical and clinical issues. Blood Purif. 2015;40(Suppl 1): 2–11.
5. Granger Vallée A, Chenine L, Leray-Moragues H, et al. Online high-efficiency haemodiafiltration achieves higher serum free light chain removal than high-flux haemodialysis in multiple myeloma patients: preliminary quantitative study. Nephrol Dial Transplant. 2011;26:3627–33.
6. Bourguignon C, Chenine L, Bargnoux AS, et al. Hemodiafiltration improves free light chain removal and normalizes κ/λ ratio in hemodialysis patients. J Nephrol. 2016;29:251–7.
7. Pendón-Ruiz de Mier MV, Ojeda R, Álvarez-Lara MA, et al. Hemodiafiltration with ultrafiltrate regeneration reduces free light chains without albumin loss in multiple myeloma patients. BMC Nephrol. 2020;21:227.
8. Maduell F, Navarro V, Cruz MC, et al. Osteocalcin and myoglobin removal in on-line hemodiafiltration versus low- and high-flux hemodialysis. Am J Kidney Dis. 2002;40:582–9.
9. Roumelioti ME, Nolin T, Unruh ML, Argyropoulos C. Revisiting the middle molecule hypothesis of uremic toxicity: a systematic review of beta 2 microglobulin population kinetics and large scale modeling of hemodialysis trials in silico. PLoS One. 2016;11:e0153157.
10. Roumelioti ME, Trietley G, Nolin TD, et al. Beta-2 microglobulin clearance in high-flux dialysis and convective dialysis modalities: a meta-analysis of published studies. Nephrol Dial Transplant. 2018;33:1025–39.
11. Lornoy W, Becaus I, Billiouw JM, Sierens L, van Malderen P. Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. Am J Nephrol. 1998;18:105–8.
12. Lornoy W, Becaus I, Billiouw JM, Sierens L, Van Malderen P, D'Haenens P. On-line haemodiafiltration. Remarkable removal of beta2-microglobulin. Long-term clinical observations. Nephrol Dial Transplant. 2000;15(Suppl 1):49–54.
13. Wizemann V, Külz M, Techert F, Nederlof B. Efficacy of haemodiafiltration. Nephrol Dial Transplant. 2001;16(Suppl 4):27–30.
14. Rosner MH, Reis T, Husain-Syed F, et al. Classification of uremic toxins and their role in kidney failure. Clin J Am Soc Nephrol. 2021;16(12):1918–28.
15. Canaud B, Barbieri C, Marcelli D, et al. Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration. Kidney Int. 2015;88:1108–16.
16. Argyropoulos CP, Chen SS, Ng YH, et al. Rediscovering beta-2 microglobulin as a biomarker across the spectrum of kidney diseases. Front Med (Lausanne). 2017;4:73.
17. Cheung AK, Rocco MV, Yan G, et al. Serum beta-2 microglobulin levels predict mortality in dialysis patients: results of the HEMO study. J Am Soc Nephrol. 2006;17:546–55.
18. Canaud B, Morena M, Cristol JP, Krieter D. Beta2-microglobulin, a uremic toxin with a double meaning. Kidney Int. 2006;69:1297–9.
19. Drüeke TB, Massy ZA. Beta2-microglobulin. Semin Dial. 2009;22:378–80.
20. Shi F, Sun L, Kaptoge S. Association of beta-2-microglobulin and cardiovascular events and mortality: a systematic review and meta-analysis. Atherosclerosis. 2021;320:70–8.
21. Liabeuf S, Lenglet A, Desjardins L, et al. Plasma beta-2 microglobulin is associated with cardiovascular disease in uremic patients. Kidney Int. 2012;82:1297–303.
22. Kanda E, Muenz D, Bieber B, et al. Beta-2 microglobulin and all-cause mortality in the era of high-flux hemodialysis: results from the dialysis outcomes and practice patterns study. Clin Kidney J. 2021;14:1436–42.

23. Watanabe Y, Kawanishi H, Suzuki K, et al. Japanese society for dialysis therapy clinical guideline for “maintenance hemodialysis: hemodialysis prescriptions”. Ther Apher Dial. 2015;19(Suppl 1):67–92.
24. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. Nephrol Dial Transplant. 2013;28:542–50.
25. Ronco C, Marchionna N, Brendolan A, Neri M, Lorenzin A, Martínez Rueda AJ. Expanded haemodialysis: from operational mechanism to clinical results. Nephrol Dial Transplant. 2018;33:iii41–i7.
26. Lorenzin A, Neri M, Clark WR, et al. Modeling of internal filtration in theranova hemodialyzers. Contrib Nephrol. 2017;191:127–41.
27. Lorenzin A, Neri M, Lupi A, et al. Quantification of internal filtration in hollow fiber hemodialyzers with medium cut-off membrane. Blood Purif. 2018;46:196–204.
28. Kirsch AH, Lyko R, Nilsson LG, et al. Performance of hemodialysis with novel medium cut-off dialyzers. Nephrol Dial Transplant. 2017;32:165–72.
29. Maduell F, Rodas L, Broseta JJ, et al. Medium cut-off dialyzer versus eight hemodiafiltration dialyzers: comparison using a global removal score. Blood Purif. 2019;48:167–74.
30. Leypoldt JK, Storr M, Agar BU, et al. Intradialytic kinetics of middle molecules during hemodialysis and hemodiafiltration. Nephrol Dial Transplant. 2019;34:870–7.
31. Casino FG, Pedrini LA, Santoro A, et al. A simple approach for assessing equilibrated Kt/V beta 2-M on a routine basis. Nephrol Dial Transplant. 2010;25:3038–44.
32. Cornelis T, van der Sande FM, Eloot S, et al. Acute hemodynamic response and uremic toxin removal in conventional and extended hemodialysis and hemodiafiltration: a randomized crossover study. Am J Kidney Dis. 2014;64:247–56.
33. Collins AJ, Chan CT. Intensive hemodialysis: time to give the therapy greater consideration. Am J Kidney Dis. 2016;68:S1–s4.
34. Kraus MA, Fluck RJ, Weinhandl ED, et al. Intensive hemodialysis and health-related quality of life. Am J Kidney Dis. 2016;68:S33–s42.
35. McCullough PA, Chan CT, Weinhandl ED, Burkart JM, Bakris GL. Intensive hemodialysis, left ventricular hypertrophy, and cardiovascular disease. Am J Kidney Dis. 2016;68:S5–S14.
36. Bakris GL, Burkart JM, Weinhandl ED, McCullough PA, Kraus MA. Intensive hemodialysis, blood pressure, and antihypertensive medication use. Am J Kidney Dis. 2016;68:S15–23.
37. Mathew A, McLeggon JA, Mehta N, et al. Mortality and hospitalizations in intensive dialysis: a systematic review and meta-analysis. Can J Kidney Health Dis. 2018;5:2054358117749531.
38. Maduell F, Arias M, Durán CE, et al. Nocturnal, every-other-day, online haemodiafiltration: an effective therapeutic alternative. Nephrol Dial Transplant. 2012;27:1619–31.
39. Maduell F, Navarro V, Torregrosa E, et al. Change from three times a week on-line hemodiafiltration to short daily on-line hemodiafiltration. Kidney Int. 2003;64:305–13.
40. Maduell F, Ojeda R, Arias-Guillen M, et al. Eight-year experience with nocturnal, every-other-day. Online Haemodiafiltr Nephron. 2016;133:98–110.
41. Ward RA, Greene T, Hartmann B, Samtleben W. Resistance to intercompartmental mass transfer limits beta2-microglobulin removal by post-dilution hemodiafiltration. Kidney Int. 2006;69:1431–7.
42. Burton JO, Jefferies HJ, Selby NM, McIntyre CW. Hemodialysis-induced cardiac injury: determinants and associated outcomes. Clin J Am Soc Nephrol. 2009;4:914–20.
43. Flythe JE, Assimon MM, Wang L. Ultrafiltration rate scaling in hemodialysis patients. Semin Dial. 2017;30:282–3.
44. Flythe JE, Brunelli SM. The risks of high ultrafiltration rate in chronic hemodialysis: implications for patient care. Semin Dial. 2011;24:259–65.
45. Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with cardiovascular morbidity and mortality. Kidney Int. 2011;79:250–7.
46. Flythe JE, Xue H, Lynch KE, Curhan GC, Brunelli SM. Association of mortality risk with various definitions of intradialytic hypotension. J Am Soc Nephrol. 2015;26:724–34.
47. Canaud B, Kooman JP, Selby NM, et al. Dialysis-induced cardiovascular and multiorgan morbidity. Kidney Int Rep. 2020;5:1856–69.

48. Lopot F, Válek A. Time-averaged concentration--time-averaged deviation: a new concept in mathematical assessment of dialysis adequacy. Nephrol Dial Transplant. 1988;3:846–8.
49. Lopot F, Nejedlý B, Sulková S. Physiology in daily hemodialysis in terms of the time average concentration/time average deviation concept. Hemodial Int. 2004;8:39–44.
50. Ledebo I. Does convective dialysis therapy applied daily approach renal blood purification? Kidney Int Suppl. 2001;78:S286–91.
51. Kliger AS. More intensive hemodialysis. Clin J Am Soc Nephrol. 2009;4(Suppl 1):S121–4.
52. Morfin JA, Fluck RJ, Weinhandl ED, Kansal S, McCullough PA, Komenda P. Intensive hemodialysis and treatment complications and tolerability. Am J Kidney Dis. 2016;68: S43–s50.
53. Canaud B, Chazot C, Koomans J, Collins A. Fluid and hemodynamic management in hemodialysis patients: challenges and opportunities. J Bras Nefrol. 2019;41(4):550–9.
54. Flythe JE. Turning the tide: improving fluid management in dialysis through technology. J Am Soc Nephrol. 2017;28:2260–2.
55. Flythe JE, Assimon MM, Overman RA. Target weight achievement and ultrafiltration rate thresholds: potential patient implications. BMC Nephrol. 2017;18:185.
56. McIntyre CW. Recurrent circulatory stress: the dark side of dialysis. Semin Dial. 2010;23:449–51.
57. London GM. Ultrafiltration intensification for achievement of dry weight and hypertension control is not always the therapeutic gold standard. J Nephrol. 2011;24:395–7.
58. Flythe JE, Chang TI, Gallagher MP, et al. Blood pressure and volume management in dialysis: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. Kidney Int. 2020;97:861–76.
59. Canaud B, Stephens MP, Nikam M, Etter M, Collins A. Multitargeted interventions to reduce dialysis-induced systemic stress. Clin Kidney J. 2021;14:i72–84.
60. Davies SJ. The elusive promise of bioimpedance in fluid management of patients undergoing dialysis. Clin J Am Soc Nephrol. 2020;15:597–9.
61. Onofriescu M, Hogas S, Voroneanu L, et al. Bioimpedance-guided fluid management in maintenance hemodialysis: a pilot randomized controlled trial. Am J Kidney Dis. 2014;64: 111–8.
62. Moissl U, Arias-Guillén M, Wabel P, et al. Bioimpedance-guided fluid management in hemodialysis patients. Clin J Am Soc Nephrol. 2013;8:1575–82.
63. Hur E, Usta M, Toz H, et al. Effect of fluid management guided by bioimpedance spectroscopy on cardiovascular parameters in hemodialysis patients: a randomized controlled trial. Am J Kidney Dis. 2013;61:957–65.
64. Zoccali C. Lung ultrasound in the management of fluid volume in dialysis patients: potential usefulness. Semin Dial. 2017;30:6–9.
65. Di Nicolo P, Magnoni G, Granata A. Lung ultrasound in hemodialysis: a card to be played? Blood Purif. 2017;44:1–7.
66. Loutradis C, Papadopoulos CE, Sachpekidis V, et al. Lung ultrasound-guided dry weight assessment and echocardiographic measures in hypertensive hemodialysis patients: a randomized controlled study. Am J Kidney Dis. 2020;75:11–20.
67. Zoccali C, Torino C, Mallamaci F, et al. A randomized multicenter trial on a lung ultrasound-guided treatment strategy in patients on chronic hemodialysis with high cardiovascular risk. Kidney Int. 2021;100:1325–33.
68. Antlanger M, Hecking M, Haidinger M, et al. Fluid overload in hemodialysis patients: a cross-sectional study to determine its association with cardiac biomarkers and nutritional status. BMC Nephrol. 2013;14:266.
69. Di Somma S, Navarin S, Giordano S, et al. The emerging role of biomarkers and bioimpedance in evaluating hydration status in patients with acute heart failure. Clin Chem Lab Med. 2012;50:2093–105.
70. Bargnoux AS, Morena M, Jaussent I, et al. A combined index of cardiac biomarkers as a risk factor for early cardiovascular mortality in hemodialysis patients. Clin Chem Lab Med. 2013;51:1865–74.

71. Chazot C, Vo-Van C, Zaoui E, et al. Fluid overload correction and cardiac history influence brain natriuretic peptide evolution in incident haemodialysis patients. Nephrol Dial Transplant. 2011;26:2630–4.
72. Kron S, Schneditz D, Leimbach T, Kron J. Feedback control of absolute blood volume: a new technical approach in hemodialysis. Hemodial Int. 2020;24:344–50.
73. Franssen CF, Dasselaar JJ, Sytsma P, Burgerhof JG, de Jong PE, Huisman RM. Automatic feedback control of relative blood volume changes during hemodialysis improves blood pressure stability during and after dialysis. Hemodial Int. 2005;9:383–92.
74. Selby NM, Lambie SH, Camici PG, Baker CS, McIntyre CW. Occurrence of regional left ventricular dysfunction in patients undergoing standard and biofeedback dialysis. Am J Kidney Dis. 2006;47:830–41.
75. Leung KCW, Quinn RR, Ravani P, Duff H, MacRae JM. Randomized crossover trial of blood volume monitoring-guided ultrafiltration biofeedback to reduce intradialytic hypotensive episodes with hemodialysis. Clin J Am Soc Nephrol. 2017;12:1831–40.
76. Selby NM, McIntyre CW. A systematic review of the clinical effects of reducing dialysate fluid temperature. Nephrol Dial Transplant. 2006;21:1883–98.
77. Mustafa RA, Bdair F, Akl EA, et al. Effect of lowering the dialysate temperature in chronic hemodialysis: a systematic review and meta-analysis. Clin J Am Soc Nephrol. 2016;11:442–57.
78. Roumelioti ME, Unruh ML. Lower dialysate temperature in hemodialysis: is it a cool idea? Clin J Am Soc Nephrol. 2015;10:1318–20.
79. Ságová M, Wojke R, Maierhofer A, Gross M, Canaud B, Gauly A. Automated individualization of dialysate sodium concentration reduces intradialytic plasma sodium changes in hemodialysis. Artif Organs. 2019;43:1002–13.
80. Kuhlmann U, Maierhofer A, Canaud B, Hoyer J, Gross M. Zero diffusive sodium balance in hemodialysis provided by an algorithm-based electrolyte balancing controller: a proof of principle clinical study. Artif Organs. 2019;43:150–8.
81. Ponce P, Pinto B, Wojke R, Maierhofer AP, Gauly A. Evaluation of intradialytic sodium shifts during sodium controlled hemodialysis. Int J Artif Organs. 2020;43:620–4.
82. Canaud B, Kooman J, Selby NM, et al. Sodium and water handling during hemodialysis: new pathophysiologic insights and management approaches for improving outcomes in end-stage kidney disease. Kidney Int. 2019;95:296–309.
83. USRDS. International Comparisons. USRDS Annual Data Report 2015.
84. Davenport A. Selecting patients for home haemodialysis modality. Contrib Nephrol. 2017;189:46–53.
85. Haroon S, Griva K, Davenport A. Factors affecting uptake of home hemodialysis among self-care dialysis unit patients. Hemodial Int. 2020;24:460–9.
86. Haroon S, Davenport A. Haemodialysis at home: review of current dialysis machines. Expert Rev Med Devices. 2018;15:337–47.
87. Wong J, Vilar E, Davenport A, Farrington K. Incremental haemodialysis. Nephrol Dial Transplant. 2015;30:1639–48.
88. Garofalo C, Borrelli S, De Stefano T, et al. Incremental dialysis in ESRD: systematic review and meta-analysis. J Nephrol. 2019;32:823–36.
89. Golper TA. Incremental dialysis: review of recent literature. Curr Opin Nephrol Hypertens. 2017;26:543–7.
90. Yan Y, Wang M, Zee J, et al. Twice-weekly hemodialysis and clinical outcomes in the China dialysis outcomes and practice patterns study. Kidney Int Rep. 2018;3:889–96.
91. Dai L, Lu C, Liu J, et al. Impact of twice- or three-times-weekly maintenance hemodialysis on patient outcomes: a multicenter randomized trial. Medicine (Baltimore). 2020;99:e20202.
92. Yan Y, Ramirez S, Anand S, Qian J, Zuo L. Twice-weekly hemodialysis in China: can it be a better option for initiation or maintenance dialysis therapy? Semin Dial. 2017;30:277–81.
93. Davenport A. Will incremental hemodialysis preserve residual function and improve patient survival? Semin Dial. 2015;28:16–9.

94. Li T, Wilcox CS, Lipkowitz MS, Gordon-Cappitelli J, Dragoi S. Rationale and strategies for preserving residual kidney function in dialysis patients. Am J Nephrol. 2019;50: 411–21.
95. Murea M. Precision medicine approach to dialysis including incremental and decremental dialysis regimens. Curr Opin Nephrol Hypertens. 2021;30:85–92.
96. Evenepoel P, Poesen R, Meijers B. The gut-kidney axis. Pediatr Nephrol. 2017;32:2005–14.
97. Meijers BK, Evenepoel P. The gut-kidney axis: indoxyl sulfate, p-cresyl sulfate and CKD progression. Nephrol Dial Transplant. 2011;26:759–61.
98. Yamaguchi J, Tanaka T, Inagi R. Effect of AST-120 in chronic kidney disease treatment: still a controversy? Nephron. 2017;135:201–6.
99. Lok CE, Foley R. Vascular access morbidity and mortality: trends of the last decade. Clin J Am Soc Nephrol. 2013;8:1213–9.
100. Lee T, Thamer M, Zhang Q, Zhang Y, Allon M. Vascular access type and clinical outcomes among elderly patients on hemodialysis. Clin J Am Soc Nephrol. 2017;12:1823–30.
101. Lee T, Allon M. Reassessing recommendations for choice of vascular access. Clin J Am Soc Nephrol. 2017;12:865–7.
102. Vachharajani TJ, Taliercio JJ, Anvari E. New devices and technologies for hemodialysis vascular access: a review. Am J Kidney Dis. 2021;78:116–24.
103. Lee KG, Chong TT, Goh N, et al. Outcomes of arteriovenous fistula creation, effect of preoperative vein mapping and predictors of fistula success in incident haemodialysis patients: a single-centre experience. Nephrology (Carlton). 2017;22:382–7.
104. Hui SH, Folsom R, Killewich LA, Michalek JE, Davies MG, Pounds LL. A comparison of preoperative and intraoperative vein mapping sizes for arteriovenous fistula creation. J Vasc Surg. 2018;67:1813–20.
105. Brown PW. Preoperative radiological assessment for vascular access. Eur J Vasc Endovasc Surg. 2006;31:64–9.
106. Georgiadis GS, Charalampidis DG, Argyriou C, Georgakarakos EI, Lazarides MK. The necessity for routine pre-operative ultrasound mapping before arteriovenous fistula creation: a meta-analysis. Eur J Vasc Endovasc Surg. 2015;49:600–5.
107. Wong CS, McNicholas N, Healy D, et al. A systematic review of preoperative duplex ultrasonography and arteriovenous fistula formation. J Vasc Surg. 2013;57:1129–33.
108. Franco G, Mallios A, Bourquelot P, Hebibi H, Jennings W, Boura B. Feasibility for arteriovenous fistula creation with ellipsys(®). J Vasc Access. 2020;21:701–4.
109. Hull J, Deitrick J, Groome K. Maturation for hemodialysis in the Ellipsys post-market registry. J Vasc Interv Radiol. 2020;31:1373–81.
110. Koo KSH, Monroe EJ, Reis J, Shivaram GM, Munshi R. Initial experience with the Ellipsys vascular access system for percutaneous arteriovenous fistula creation in adolescents: a case report. Radiol Case Rep. 2021;16:441–7.
111. Shahverdyan R, Beathard G, Mushtaq N, Litchfield TF, Nelson PR, Jennings WC. Comparison of outcomes of percutaneous arteriovenous fistulae creation by Ellipsys and Wavelinq devices. J Vasc Interv Radiol. 2020;31:1365–72.
112. Lawson JH, Glickman MH, Ilzecki M, et al. Bioengineered human acellular vessels for dialysis access in patients with end-stage renal disease: two phase 2 single-arm trials. Lancet. 2016;387:2026–34.
113. Lawson JH, Niklason LE, Roy-Chaudhury P. Challenges and novel therapies for vascular access in haemodialysis. Nat Rev Nephrol. 2020;16:586–602.
114. Niklason LE, Lawson JH. Bioengineered human blood vessels. Science. 2020; 370(6513):eaaw8682.
115. Song HG, Rumma RT, Ozaki CK, Edelman ER, Chen CS. Vascular tissue engineering: progress, challenges, and clinical promise. Cell Stem Cell. 2018;22:340–54.
116. Jaffer Y, Selby NM, Taal MW, Fluck RJ, McIntyre CW. A meta-analysis of hemodialysis catheter locking solutions in the prevention of catheter-related infection. Am J Kidney Dis. 2008;51:233–41.

117. Abdul Salim S, Masoud AT, Thongprayoon C, et al. Systematic review and meta-analysis of antibiotic and antimicrobial lock solutions for prevention of hemodialysis catheter-related infections. ASAIO J. 2021;67:1079–86.
118. Chen CH, Chen YM, Yang Y, Chang YJ, Lin LJ, Yen HC. Re-evaluating the protective effect of hemodialysis catheter locking solutions in hemodialysis patients. J Clin Med. 2019;8(3):412.
119. Sheng KX, Zhang P, Li JW, et al. Comparative efficacy and safety of lock solutions for the prevention of catheter-related complications including infectious and bleeding events in adult haemodialysis patients: a systematic review and network meta-analysis. Clin Microbiol Infect. 2020;26:545–52.
120. Perl J, Dember LM, Bargman JM, et al. The use of a multidimensional measure of dialysis adequacy-moving beyond small solute kinetics. Clin J Am Soc Nephrol. 2017;12:839–47.
121. Pizzarelli F, Basile C. Do we have to rely on metric-based quality improvement strategies for the management of ESKD? Nephrol Dial Transplant. 2021;37(3):397–9.
122. Kliger AS. Quality measures for dialysis: time for a balanced scorecard. Clin J Am Soc Nephrol. 2016;11:363–8.
123. Garbelli M, Ion Titapiccolo J, Bellocchio F, Stuard S, Brancaccio D, Neri L. Leveraging digital transformation to empower clinical governance: enhancement in intermediate clinical endpoints and patients' survival after implementation of a continuous quality improvement program in a large dialysis network. Nephrol Dial Transplant. 2021;37(3):469–76.
124. Moncrief J, Popovich RP. Continuous ambulatory peritoneal dialysis (CAPD)—worldwide experience. In: Peritoneal dialysis. 1st ed. Dordrecht: Springer; 1981. p. 178–212.
125. Moncrief JW, Popovich RP, Nolph KD, Rubin J. Additional experience with continuous ambulatory peritoneal dialysis (CAPD). Trans Am Soc Artif Intern Organs. 1978;24(4):76–83.
126. Oreopoulos DG, Robson M, Izatt S, Clayton SL, DeVeber GA. A simple and safe technique for continuous ambulatory peritoneal dialysis (CAPD). Trans Am Soc Artif Intern Organs. 1979;24:484–9.
127. Di Paolo N, Petrini G, Garosi G, Buoncristiani U, Brardi S, Monaci G. A new self-locating peritoneal catheter. Perit Dial Int. 1996;16(6):623–7. PMID: 8981532.
128. Di Paolo N, Capotondo L, Sansoni E, Romolini V, Simola M, Gaggiotti E, Bercia R, Buoncristiani U, Canto P, Concetti M, De Vecchi A, Fatuzzo P, Giannattasio M, La Rosa R, Lopez T, Lo Piccolo G, Melandri M, Vezzoli G, Orazi E, Pacitti A, Ramello A, Russo F, Napoli M, Tessarin MC. The self-locating catheter: clinical experience and follow-up. Perit Dial Int. 2004;24(4):359–64. PMID: 15335150.
129. Stonelake S, Baharani J, Thomas M, Adkins R, Hollingsworth L, Wilmink T. Outcomes of the weighted peritoneal dialysis catheter in patients at risk of percutaneous catheter failure. Perit Dial Int. 2019;39(2):142–6; Epub 2018 Nov 25. PMID: 30478139. https://doi.org/10.3747/pdi.2017.00233.
130. Al-Hwiesh A, et al. A novel three cuff peritoneal dialysis catheter with low entry technique: three years single center experience. Urol Nephrol Open Access J. 2017;4(5):150–6. https://doi.org/10.15406/unoaj.2017.04.0014.
131. Hess S, Dubach M, Meboldt M, Foggensteiner L. Evaluating patient safety and ease of use of a novel connection-assist device for peritoneal dialysis. Patient Prefer Adherence. 2019;13:1785–90; PMID: 31754299; PMCID:PMC6825503. https://doi.org/10.2147/PPA.S218663.
132. Goodlad C, George S, Sandoval S, Mepham S, Parekh G, Eberl M, Topley N, Davenport A. Measurement of innate immune response biomarkers in peritoneal dialysis effluent using a rapid diagnostic point-of-care device as a diagnostic indicator of peritonitis. Kidney Int. 2020;97(6):1253–9; Epub 2020 Mar 6. PMID: 32359809. https://doi.org/10.1016/j.kint.2020.01.044.
133. Baharani J, et al. A quality improvement process to increase and sustain a peritoneal dialysis program in the United Kingdom. Blood Purif. 2022;1–9.

134. Delarue J, Maingourd C. Acute metabolic effects of dialysis fluids during CAPD. Am J Kidney Dis. 2001;37(1 Suppl 2):S103–7. https://doi.org/10.1053/ajkd.2001.20762.
135. Selby NM, Fialova J, Burton JO, McIntyre CW. The haemodynamic and metabolic effects of hypertonic-glucose and amino-acid-based peritoneal dialysis fluids. Nephrol Dial Transplant. 2007;22(3):870–9. https://doi.org/10.1093/ndt/gfl654.
136. Rhee CM, Leung AM, Kovesdy CP, Lynch KE, Brent GA, Kalantar-Zadeh K. Updates on the management of diabetes in dialysis patients. Semin Dial. 2014;27(2):135–45.
137. Kubota T, Kubota N, Kadowaki T. Imbalanced insulin actions in obesity and type 2 diabetes: key mouse models of insulin signaling pathway. Cell Metab. 2017;25(4):797–810. https://doi.org/10.1016/j.cmet.2017.03.004.
138. King GL, Park K, Li Q. Selective insulin resistance and the development of cardiovascular diseases in diabetes: the 2015 edwin bierman award lecture. Diabetes. 2016;65(6):1462–71.
139. Lambie M, Bonomini M, Davies SJ, Accili D, Arduini A, Zammit V. Insulin resistance in cardiovascular disease, uremia, and peritoneal dialysis. Trends Endocrinol Metab. 2021;32(9):721–30. https://doi.org/10.1016/j.tem.2021.06.001.
140. Bonomini M, Masola V, Procino G, Zammit V, Divino-Filho JC, Arduini A, Gambaro G. How to improve the biocompatibility of peritoneal dialysis solutions (without jeopardizing the patient's health). Int J Mol Sci. 2021;22(15):7955. https://doi.org/10.3390/ijms22157955.
141. Arduini A, Bonomini M, Savica V, Amato A, Zammit V. Carnitine in metabolic disease: potential for pharmacological intervention. Pharmacol Ther. 2008;120(2):149–56. https://doi.org/10.1016/j.pharmthera.2008.08.008.
142. Bonomini M, Di Liberato L, Del Rosso G, Stingone A, Marinangeli G, Consoli A, Bertoli S, De Vecchi A, Bosi E, Russo R, Corciulo R, Gesualdo L, Giorgino F, Cerasoli P, Di Castelnuovo A, Monaco MP, Shockley T, Rossi C, Arduini A. Effect of an L-carnitine-containing peritoneal dialysate on insulin sensitivity in patients treated with CAPD: a 4-month, prospective, multicenter randomized trial. Am J Kidney Dis. 2013;62(5):929–38. https://doi.org/10.1053/j.ajkd.2013.04.007.
143. Arden C, Tudhope SJ, Petrie JL, Al-Oanzi ZH, Cullen KS, Lange AJ, Towle HC, Agius L. Fructose 2,6-bisphosphate is essential for glucose-regulated gene transcription of glucose-6-phosphatase and other ChREBP target genes in hepatocytes. Biochem J. 2012;443(1):111–23. https://doi.org/10.1042/BJ20111280.
144. Kishore P, Kehlenbrink S, Hu M, Zhang K, Gutierrez-Juarez R, Koppaka S, El-Maghrabi MR, Hawkins M. Xylitol prevents NEFA-induced insulin resistance in rats. Diabetologia. 2012;55(6):1808–12; Epub 2012 Mar 30. PMID: 22460760; PMCID: PMC3606878. https://doi.org/10.1007/s00125-012-2527-z.
145. Rago C, Lombardi T, Di Fulvio G, Di Liberato L, Arduini A, Divino-Filho JC, Bonomini M. A new peritoneal dialysis solution containing l-carnitine and xylitol for patients on continuous ambulatory peritoneal dialysis: first clinical experience. Toxins (Basel). 2021;13(3):174; PMID: 33668249; PMCID: PMC7996173. https://doi.org/10.3390/toxins13030174.
146. Masola V, Bonomini M, Onisto M, Ferraro PM, Arduini A, Gambaro G. Biological effects of xylocore, a glucose sparing pd solution, on mesothelial cells: focus on mesothelial-mesenchymal transition, inflammation and angiogenesis. Nutrients. 2021;13(7):2282. https://doi.org/10.3390/nu13072282.
147. Henderson J, O'Reilly S. The emerging role of metabolism in fibrosis. Trends Endocrinol Metab. 2021;32(8):639–53; Epub 2021 May 20. PMID: 34024695. https://doi.org/10.1016/j.tem.2021.05.003.
148. Masola V, Arduini A, Bonomini M, Gambaro G, Zaza G. Dichloroacetate and l-carnitine reduced tgf-beta-induced mesothelial-to-mesenchymal transition. Nephrol Dial Transplant. 2020;35(Supp 3):P1142.
149. Murisasco A, Reynier JP, Ragon A, Boobes Y, Baz M, Durand C, Bertocchio P, Agenet C, el Mehdi M. Continuous arterio-venous hemofiltration in a wearable device to treat end-stage renal disease. ASAIO Trans. 1986;32(1):567–71; PMID: 3778771. https://doi.org/10.1097/00002480-198609000-00040.

150. Shettigar UR, Kablitz C, Stephen R, Kolff WJ. A portable hemodialysis/hemofiltration system independent of dialysate and infusion fluid. Artif Organs. 1983;7(2):254–6. PMID: 6870603.
151. Stephens RL, Jacobsen SC, Atkin-thor E, Kolff W. Portable/wearable artificial kidney (WAK)–initial evaluation. Proc Eur Dial Transplant Assoc. 1976;12:511–8. PMID: 935129.
152. Ronco C, Davenport A, Gura V. A wearable artificial kidney: dream or reality? Nat Clin Pract Nephrol. 2008;4(11):604–5; Epub 2008 Sep 9. PMID: 18779855. https://doi.org/10.1038/ncpneph0929.
153. Salani M, Golper T. Avanços no rim artificial portátil e no rim bioartificial implantável. In: Moura-Neto JA, editor. Terapia Renal Substitutiva 2–Controvérsias e Tendências. São Paulo: Livraria Balieiro; 2019. p. 33–40.
154. Salani M, Golper T. Developments in implantable and wearable artificial kidneys. In: Fadem SZ, Moura-Neto JA, editors. Issues in kidney disease–dialysis. Hauppage. New York: Nova Science; 2021.
155. Gura V, Macy AS, Beizai M, Ezon C, Golper TA. Technical breakthroughs in the wearable artificial kidney (WAK). Clin J Am Soc Nephrol. 2009;4(9):1441–8; Epub 2009 Aug 20. PMID: 19696219; PMCID: PMC2736696. https://doi.org/10.2215/CJN.02790409.
156. Davenport A, Gura V, Ronco C, Beizai M, Ezon C, Rambod E. A wearable haemodialysis device for patients with end-stage renal failure: a pilot study. Lancet. 2007;370(9604):2005–10. PMID: 18083402. https://doi.org/10.1016/S0140-6736(07)61864-9.
157. Salani M, Roy S, Fissell WH 4th. Innovations in wearable and implantable artificial kidneys. Am J Kidney Dis. 2018;72(5):745–51; Epub 2018 Aug 23. PMID: 30146422. https://doi.org/10.1053/j.ajkd.2018.06.005.
158. Lee DB, Roberts M, Lee DBN, Roberts M. A peritoneal-based automated wearable artificial kidney. Clin Exp Nephrol. 2008;12(3):171–80.
159. Kotanko P, Maheshwari V, Pecoits-Filho R, Thijssen S. Alo-hemodiálise–um conceito novo na terapia renal substitutiva. In: Moura-Neto JA, editor. Terapia Renal Substitutiva 2–Controvérsias e Tendências. São Paulo: Livraria Balieiro; 2019. p. 25–32.
160. Kotanko P, Maheshwari V, Thijssen S, Zhang A, Dong A, Jor J. Allo-hemodialysis: a novel treatment option for patients with acute and chronic kidney failure in limited resource settings [Abstract]. Kidney Int Rep. 2019;4:S346.
161. Campos I, Arellano J, Gomez V, Quiroz J, Mariscal LA. Renal replacement therapy preferences survey: is Allo-hemodialysis an acceptable option for patient caregivers and health care professionals? Blood Purif. 2020;49(1–2):197–201; Epub 2019 Dec 18. PMID: 31851978. https://doi.org/10.1159/000504241.