



Frontiers in hemodialysis: Innovations and technological advances

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Abstract

As increasing demand for hemodialysis (HD) treatment incurs significant financial burden to healthcare systems and ecological burden as well, novel therapeutic approaches as well as innovations and technological advances are being sought that could lead to the development of purification devices such as dialyzers with improved characteristics and wearable technology. Novel knowledge such as the development of more accurate kinetic models, the development of novel HD membranes with the use of nanotechnology, novel manufacturing processes, and the latest technology in the science of materials have enabled novel solutions already marketed or on the verge of becoming commercially available. This collaborative article reviews the latest advances in HD as they were presented by the authors in a recent symposium titled “Frontiers in Haemodialysis,” held on 12th December 2019 at the Royal Society of Medicine in London.

KEYWORDS

bioartificial kidney, convection, expanded hemodialysis, graphene oxide membrane, hemodialysis, incremental, medium cut-off membrane, mixed matrix membrane, online hemodiafiltration, wearable artificial kidney

1 | INTRODUCTION

It is well known that amongst renal replacement therapies kidney transplantation is the one that confers the best quality of life and survival. Standard hemodialysis (HD) however

remains the most widely used treatment for patients with end-stage renal disease (ESRD), largely due to the rather limited availability of organs.¹ Despite its significant limitations, namely the rather poor quality of life it offers to the patients, poor clearance of middle and large molecular weight substances, high incidence of infections and cardiovascular



diseases as well as unacceptably high mortality among dialysis patients, and high cost,^{1,2} standard HD remains a unique treatment modality, offering a life sustaining treatment option for those with end-stage kidney failure, who are either waiting for or unable to receive a kidney transplant. Both the population of patients with ESRD and those on HD follows a constantly increasing trend internationally. Among 746 557 prevalent cases of ESRD in the United States on December 31, 2017, 62.7% were on HD, with the size of the prevalent HD population having increased by 84.1% between 2000 and 2017.² In Europe and worldwide there are approximately 350,000 and 3 million HD patients, respectively, and this is projected to reach 5.4 million worldwide by 2030,³ not including the significant number of patients who do not have access to HD treatment for financial reasons.

To overcome the above constraints of standard HD, research has focused over the last few years on efforts to develop a more individualized therapeutic approach as well as innovations and technological advances, which could lead to the development of purification devices such as novel dialyzers and wearable technology. These efforts have been lately promoted by State policies, such as the Kidney Health Initiative and public-private partnerships such as the KidneyX initiative.⁴ Novel knowledge such as the development of more accurate kinetic models, the development of novel HD membranes with the use of nanotechnology, novel manufacturing processes, and the latest technology in the science of materials have enabled novel solutions already marketed or on the verge of becoming commercially available.⁵ This collaborative article reviews some of the latest advances and innovations in hemodialysis treatment as they were presented in a recent symposium titled “Frontiers in Haemodialysis,” held on 12th December 2019 at the Royal Society of Medicine in London.

2 | INNOVATIONS IN HD MODALITIES

2.1 | Incremental HD: From empiricism to kinetic modeling

The optimal HD regimen for incident patients is not known. It is plausible that the routine practice of thrice weekly HD (3HD/wk) in incident patients with substantial residual kidney function (RKF) may be harmful, contributing to accelerated loss of RKF,⁶ and also poor quality of life, unnecessary expenditures, and potential risks for patients health. Although not a new concept, “incremental HD” has lately come back to the epicenter of the research interest in view of the novel concept of variable target model (VTM) of urea kinetic model (UKM) that was suggested recently by Casino and Basile,⁷ with expectations that it could lead to the application of HD in an individualized manner.

In agreement with the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines,⁷ the term “incremental HD” implies that the dose and/or frequency of treatment can be lower at HD inception, in the presence of a substantial RKF, but should be progressively and timely increased to compensate for any subsequent reduction in RKF. Although clinical practice guidelines have not adopted so far an “incremental” approach to HD, this seems to contradict the well-established importance of RKF preservation in conservative therapy which, ironically, has been accepted by most of the peritoneal dialysis (PD) guidelines.⁸ Until recently, the application of incremental HD in clinical practice has been hindered by the arbitrary manner it had to be prescribed due to the lack of clear standards for incorporating RKF in the assessment of HD dose.⁹ The problem with the currently used UKM-based prescription is that, by overestimating the HD needs, in the presence of substantial RKF, it would require such high values for both the RKF and HD dose (Kt/V)¹⁰ that it would be difficult to prescribe less frequent treatments. The problem is not intrinsic to the UKM itself, but rather is generated by a misconception/misunderstanding: the equivalence between Kru and dialyzer urea clearance (Kd), correctly assumed by the UKM, only means that 1 mL/min of Kd clears the urea from the blood just as 1 mL/min of Kru does.^{11,12} By no means should such kinetic equivalence imply that 1 mL/min of Kd is clinically equivalent to 1 mL/min of urea clearance provided by the native kidneys.

VTM, which was suggested by Casino and Basile to set a paradigm shift in the incremental HD prescription,^{10,13,14} was developed on the scientifically validated ground of the UKM, which is the gold standard for assessing and prescribing dialysis.^{11,15} VTM gives more clinical weight to the RKF and allows less frequent HD treatments at lower RKF as opposed to the fixed target model, based on the wrong concept of the clinical equivalence between Kru and Kd^{10,13,14} (Figure 1). Despite increasing evidence derived from observational studies supporting the use of incremental HD,⁹ randomized clinical trials (RCTs) are lacking, and hence, urgently needed. The results of two RCTs on incremental HD based on the use of VTM, one in progress (IHDIP) and one about to start (REAL LIFE) (available at: www.era-edta.org/en/eudial),^{14,16} are awaited with great interest.

2.2 | High-volume convection

The age-old concept of uremia is defined as a retention syndrome of a range of uremic toxins, among which urea level is the relatively easiest to obtain surrogate parameter.¹⁷ Randomized trials in HD have demonstrated that simply focusing on urea reduction alone is unlikely to improve clinical endpoints.¹⁸ A range of putative toxins may be at play, several of which have been identified to have pathognomonic

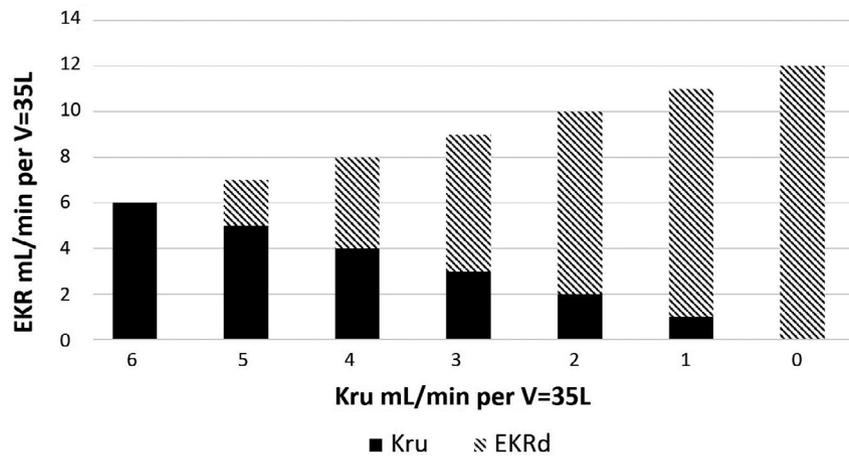


FIGURE 1 Variable target model (VTM) for incremental HD prescription. Total EKR is the total “equivalent renal clearance” (reference 14): it expresses a total clearance (dialytic + renal), that is, it is the sum of the contribution of dialyzer urea clearance (Kd) to EKR (EKRd) and of that of residual renal urea clearance (Kru). If Kru = 6 mL/min there is no need for HD (EKRd = 0); as Kru decreases EKRd increases linearly up to the value of 12 mL/min which is adequate for an anuric patient on a 3HD/wk schedule

significance.¹⁹ These toxins have variable pharmacokinetic behavior and are broadly classified into small, middle, and larger middle molecules, (typically smaller than albumin) and protein-bound toxins (larger than the size of albumin, at least in the bound state). Blood purification techniques may be augmented to remove the dialyzable middle (eg, beta-2 microglobulin) and larger middle molecules (eg, IL-6, light chains).¹⁸ The introduction of improved blood purification techniques of high-volume hemodiafiltration (HvHDF) and expanded HD (HDX) offer promise of improving blood purification and clinical outcomes in the treatment of uremia.

The introduction of highly permeable high flux membranes into routine 3HD/wk has paved the way for further advances in blood purification. With the use of high-volume online HDF (HvHDF) it is now technically feasible to add high-volume (>21 liters in postdilution mode) convection across highly permeable membranes using ultrapure dialysate, an option which promises improved purification in uremia. Clinical outcome benefit has been demonstrated in some HDF trials¹⁹ but not in others.^{4,20} The differences in outcome results could be partly due to the variable convective volumes achieved in different trial centers.^{4,21-23} Pooled individual participant analysis from HDF trials demonstrate that online HDF-reduced mortality risk, particularly pronounced in those receiving high convective volumes. The net convective dose delivered during online HDF treatment is affected by clinical (access type, patient body size, comorbidities, interdialytic weight gains), technical (dialysate to blood volume match), and treatment-related parameters (blood flow, time, needle gauge, dialyzer surface area, machine capabilities etc) and accounts for the varying outcomes in different trials.²⁴ As definitive outcome trials comparing high-volume HDF with standard high flux HD are lacking, the results of two large clinical trials that are currently underway, the H4RT ([https://](https://doi.org/10.1186/ISRCTN10997319)

doi.org/10.1186/ISRCTN10997319) and the CONVINCe study (<https://www.trialregister.nl/trial/6942>), aiming to recruit a combined total of 3350 participants, are long-awaited with high expectations.

3 | INNOVATIONS IN HD MEMBRANES

3.1 | Medium cutoff HD membranes

The advent of precision technologies in the membrane manufacturing process has allowed improved control on pore size distribution and its conformity. This has led to the introduction of medium cutoff HD (HDX) where improved clearance of middle and larger middle molecules may be achieved during a standard treatment with medium cutoff (MCO) membranes without the need for HDF technology and substitution fluid.²⁴ Studies with these new therapies have so far demonstrated technical feasibility and patient safety in clinical practice. However, clinical studies with HDX showing reduced inflammatory burden and calcification are limited by small sample sizes conducted in vitro settings.²⁵ Large observational studies show improved clearance of large middle molecules compared to standard high flux HD observed even at modest blood flow rates.²⁶ Improvements in membrane permeability and the quality of depuration offer a real promise in advancing the treatment of uremia in ESRD.

3.2 | Graphene oxide membranes

Historically dialyzers have been based on the use of polymeric membranes.²⁷ To overcome the inherent limitations of conventional polymeric HD membranes, namely the poor



clearance of middle and large molecular weight substances, high cost and poor patient outcomes, in recent times, novel materials based on two-dimensional molecular structure, have emerged as potential next-generation membrane materials. Among them, graphene oxide (GO)-based membranes (GOM) have been in the epicenter of the research over the last years. Their unique features, namely its high sorption capacity, functional access through covalent and noncovalent interactions, layered structure, amendable interlayer spacing, and expandable dimension, render GOM promising candidates as next-generation HD membranes.^{28,29} Resulting from their ability to function as a physicochemically tunable fine molecular and/or ion sieve, GOM can achieve selective permeability of specific ions and small molecules of different molecular weights via chemical modification,³⁰ a mechanism which is hoped to confer improved fluid control and solute transport.³¹

Kidambi et al fabricated large-area nanoporous atomically thin membranes, by transferring the graphene synthesized using scalable chemical vapor deposition (CVD) to polycarbonate track-etched supports, and then, created size-selective pores (≤ 1 nm) by using oxygen-plasma etching.²⁸ They established a rapid diffusion and size selectivity for the membranes, with 1-2 orders of magnitude improvement in the permeability of small molecules in the molecular weight cutoff range of 0-1000 Da as well as higher selectivity (15-20) for the separation of KCl with respect to Allura Red dye (≈ 1 nm, 496 Da) and vitamin B12 (≈ 1.5 nm, 1355 Da), as compared to the commercial state-of-the-art HD membranes. They also showed that an increase in permeability could be achieved by increasing the oxygen-plasma time.²⁸ Song et al showed that doping with nitrogen can even tune the graphene membranes' size-dependent permeability for hydrated ions and improve the ion selectivity by 1-3 orders of magnitude in comparison to that of a GOM.³² Abraham et al reported that the ion permeability rates decrease exponentially with decreasing sieve size by a simple control of GO

swelling.³³ Zhou et al showed further that GOM could offer precise electrical control over transport of water molecules, from ultrafast permeation to complete blocking.³⁴

Furthermore, evidence shows that GOM can also be advantageous with regards to biocompatibility and biodegradability.³⁵ Kurapati et al showed that enzymatic catalysis of GO made with natural horseradish peroxidase, and covalent functionalization with coumarin or catechol can ensure a better biodegradability than unmodified GO.³⁶

In summary, the unique characteristics of GOM have created expectations that with the use of GO-based HD membranes novel clinical possibilities could be achieved, such as more efficient HD, less need for the use of high water volumes, or less need for the use of anticoagulation. Although the potential cost benefits from the use of GOM in HD applications are not clear at present, the potential future development of GOM-based bioartificial or wearable HD devices is anticipated to have major impact on the logistics of HD treatment as it is applied worldwide, and hence, potentially major cost benefits to the healthcare systems. Further research of the features and the applicability of GOM for use in HD membranes is warranted.

3.3 | Mixed matrix membrane (MMM)

Over the last few years, the group of Stamatialis et al have proposed the MMM, a membrane with improved blood purification characteristics, including improved removal of albumin-bound uremic toxins, through the combination of filtration and adsorption mechanisms.³⁷ The membrane consists of an inner layer composed of polyethersulfone (PES) and polyvinylpyrrolidone (PVP) blend and an outer layer composed of activated carbon (AC) microparticles embedded in PES/PVP (Figure 2). The inner layer achieves the membrane transport selectivity and protects the patient blood from

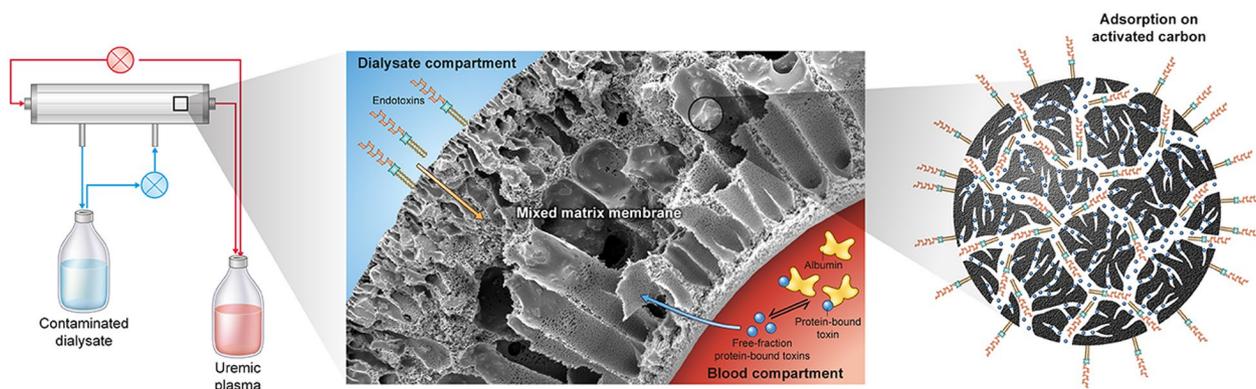


FIGURE 2 The application of mixed matrix membrane (MMM) for removal of protein-bound toxins from blood combined with removal of endotoxins from the dialysate. Reprinted from "Mixed matrix HD membrane for achieving endotoxin-free dialysate combined with high removal of uremic toxins from human plasma." Reprinted from ref. 38, with permission from Elsevier [Color figure can be viewed at wileyonlinelibrary.com]

contacting the adsorbent particles. The outer layer, composed of the AC particles, increases the concentration gradient of toxins between the blood and dialysate solution resulting in higher removal of the uremic solutes via adsorption toxins. In contrast to other sorption-based technologies, relatively small sorbent particles (between 20 and 40 microns) are incorporated into the MMM resulting in increased available surface area for toxin adsorption combined to low transmembrane pressure. Recent studies³⁸ showed that the dual layer hollow fiber MMMs can remove significantly more protein-bound toxins compared to benchmark membranes. Besides, the MMM can also be applied for removal of uremic toxins combined to achieving endotoxin-free dialysate and prevent transfer of endotoxins to the patients plasma *in vitro*. This may allow its application in areas of the world where purity and scarcity of water are limiting factors, as well as in therapies with low water consumption (portable/wearable artificial kidney (WAK) systems).

3.4 | Bioartificial kidney (BAK)

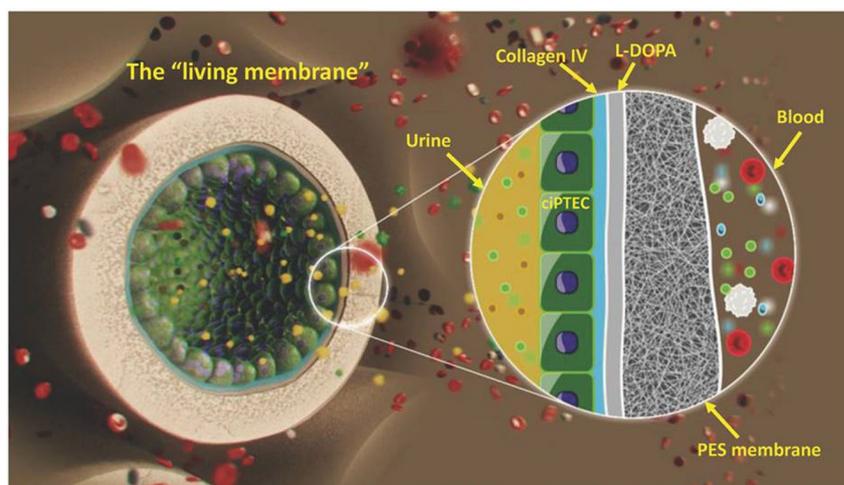
All active processes in the healthy kidney, including glomerular filtration (removal of small solutes) and proximal tubule secretion (of larger ones and protein-bound toxins), are performed by specialized cellular components. It would, therefore, seem applicable to try mimicking these active processes of the native kidney by engaging similar kidney cells on HD membranes. Aebischer et al was the first to demonstrate the feasibility of attaching and growing kidney epithelial cells on semipermeable hollow fiber membranes.³⁹ Later Humes and colleagues showed that combination of a bioreactor consisting of porcine primary renal cells with a conventional hemofilter could significantly increase the survival rate of patients with AKI, when compared to those treated with conventional RRT only.⁴⁰ An interim analysis of a follow-up phase IIb study showed a high survival rate in patients treated with a cell-free sham device leading to the suspension of the study.⁴¹

In recent years, Stamatialis and coworkers have also focused on the development of a BAK device. This device consists of “living membranes” based on a monolayer of conditionally immortalized kidney proximal tubule cells (ciPTEC) cultured on polymeric membranes (Figure 3).^{42,43} The polymeric membrane, besides cell support, also serves as an immunoprotecting layer separating the kidney cells from the patients’ blood. A small scale BAK with matured cells representing clear epithelial characteristics with barrier and active transport function is successfully established.⁴⁴ Future work will focus on confirming its safety and efficacy in a relevant animal model of ESRD. In response to the need for close monitoring and regulation on such products involving biological components, the European Union, USA, Canada, and Japan have set up the Advanced Therapies Medicinal Products (ATMP) cluster—a cooperation forum in which international regulators share scientific and regulatory views on guidelines and product-related issues.⁴⁵

4 | WEARABLE HD DEVICES

Sorbents, by either absorbing toxins directly or exchanging them for other molecules could be used to recycle waste dialysate (Figure 4). Although carbon, silica, and zirconium can be used as absorbents as they can absorb many of the azotemic solutes which are retained in patients with chronic kidney disease, they do not effectively remove urea. As such an absorbent cartridge will need to contain either urease, an enzyme which converts urea to ammonia and carbon dioxide, or an alternative method of breaking down urea, such as electro-oxidation. As electro-oxidation may generate chlorine and/or chloramine, and involves the risk of small particles breaking off from the electrodes and passing into the dialysate, most investigators so far have opted to use urease to break down urea. This leads to the generation of ammonia, which has to then be removed by an ion exchanger, such as zirconium phosphate which exchanges ammonium

FIGURE 3 The BAK containing kidney proximal tubular cells cultured on polymeric hollow fibers. Reprinted from ref. 43, with permission from Wiley [Color figure can be viewed at wileyonlinelibrary.com]



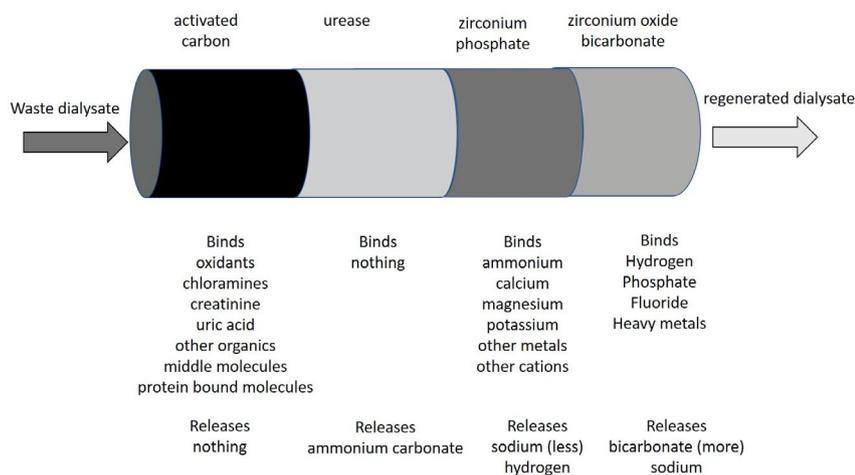


FIGURE 4 Schematic diagram of a sorbent system [Color figure can be viewed at wileyonlinelibrary.com]

ions for hydrogen and sodium. Zirconium phosphate is not only specific for ammonium, but will also take up calcium, magnesium, potassium, and other metal ions. Thus, any sorbent containing urease will require an ammonia sensor to alarm and inform the patients when the sorbent needs to be changed. As zirconium phosphate releases hydrogen ions, another ion exchanger is then required to take up hydrogen ions, thus zirconium oxide and zirconium bicarbonate can be added, which will take up hydrogen, but also phosphate, fluoride and heavy metals, and release bicarbonate and acetate. Thus, the final sorbent is not just a simple mixture of compounds, but an organized structured cartridge with differing amounts of sorbents and ion exchangers in sequence. For clinical use, there is a balance between the amount of sorbent, as the greater the amount of sorbent the greater the time between having to change the sorbent cartridge(s), but the greater the amount of sorbent, the greater the weight of the wet sorbent.

Both wearable peritoneal and hemodialysis devices, by regenerating dialysate potentially offer environmental advantages in terms of reducing transportation of dialysate consumables, water consumption and reducing the amount of nonrecyclable waste. Both treatments, however, have technical problems to overcome, such as prevention of access infections and thrombosis, appropriate circuit design in order to minimize protein deposition, remove microbubbles, and effectively maintain solute clearance as well as a replenish the dialysate once it has been through the sorbents.

Although sorbent-based HD treatments were developed for HD and used in clinical practice, they were withdrawn in the late 1980s, and although newer devices were developed, they have not been yet commercialized.^{46,47} Currently all wearable or portable HD devices remain in the experimental stage. Two devices have undergone clinical trials. The AWAK Peritoneal Dialysis (AWAK PD) (AWAK Technologies, Singapore) uses a standard single lumen peritoneal dialysis catheter, and uses a relatively high flow of peritoneal dialysate with a tidal dwell prescription.⁴⁸ As dialysate flow is

intermittent, the device requires a storage compartment in addition to the sorbent cartridge. The device has a de-bubbling unit to remove carbon dioxide generated by urease conversion of urea to ammonia and carbon dioxide and an ammonia sensor to determine when the sorbent cartridge should be changed. As glucose and bicarbonate concentrations will be lower in the waste dialysate, then, after passing through the sorbent cartridge the regenerated dialysate will then need to be refreshed by the addition of glucose and bicarbonate. This device has been successfully used in 14 patients for between 3.5 and 6 hours.⁴⁹ In this short period of time, clearance of urea, creatinine, and potassium were demonstrated, but 71% complained of abdominal pain and 36% abdominal bloating, and dialysate fibrin was observed in 36%. Currently the device requires drainage of peritoneal fluid, and then, restarting each time the sorbent cartridge is exchanged. The second device, the wearable artificial kidney (WAK) (Blood Purification Technologies Inc, Los Angeles, CA, USA) uses a dual lumen central venous catheter for blood access, and a specially devised dual chamber battery operated mini-pump that pumps blood and dialysate in opposite directions.⁴⁸ Waste dialysate is pumped through a series of sorbent cartridges, and microbubbles of carbon dioxide generated by urease conversion of urea is vented through gas permeable plastic dialysate circuit tubing. In addition to refreshing the regenerated dialysate with separate infusions of bicarbonate and electrolytes through additional mini-pumps, there is an additional mini-pump for unfractionated heparin to prevent clotting in the circuit. As with any extracorporeal device, the WAK has numerous alarms designed to detect any blood or dialysate leak, in addition to sensors for ammonia. This device was initially successfully trialed to treat patients for up to 6 hours, and then, for up to 24 hours. So far, the device has been shown to be safe, and effectively clear both small and middle-sized solutes and control acid-base, with no posttreatment fatigue. Although sorbents lasted more than 24 hours, microbubbles were noted in the dialysate compartment and further work will be required to improve removal.

5 | CONCLUSIONS

The recent advances and innovation in the field of HD, some of which have been presented at the recent meeting “Frontiers in Haemodialysis 2019” and reviewed herein, create expectations for the development in the near future of novel HD products and modalities as well as more individualized approaches to HD prescribing, that could lead to a longer survival and improved quality of life for the patients, and a more sustainable use of resources within the healthcare systems. Whether the upcoming advances in blood purification techniques can result in significant clinical and patient reported symptom benefits remains to be shown in the years to come.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest with the contents of this article.

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