Novel techniques and innovation in blood purification: a clinical update from Kidney Disease: Improving Global Outcomes

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Mortality in patients with end-stage renal disease (ESRD) remains unacceptably high. Emerging techniques and advances in dialysis technology have the potential to improve clinical outcomes in the ESRD population. This report summarizes the deliberations and recommendations of a conference sponsored by Kidney Disease: Improving Global Outcomes to address the following questions: (1) what is the appropriate frequency and duration of hemodialysis; (2) how should we optimize water quality and dialysate composition; and (3) what technical innovations in blood purification and bioengineering can result in better clinical outcomes? The conference report will augment our current understanding of clinical practice in blood purification and will pose several high-priority research questions.

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Kidney Disease: Improving Global Outcomes convened a Controversies Conference in Paris from 14 to 15 October 2011, titled 'Novel techniques and innovation in blood purification: How can we improve clinical outcomes in hemodialysis?' The conference, attended by 50 international experts, was designed to establish consensus and directions for optimal modes of blood purification. The plenary session presentations were followed by breakout group discussions to address three specific topic areas: (1) dialysis technique—frequency and duration; (2) dialysate composition and toxins; and (3) technical advances in dialysis. The breakout group deliberations were reported to the entire group, and a consensus-building process led to the clinical practice and research recommendations from the conference attendees, which are the substance of this report. The report was reviewed by all breakout group leaders, cochairs, and representatives of the Kidney Disease: Improving Global Outcomes Board of Directors. The conference agenda, selected presentations, and abstracts of the meeting are available on the Kidney Disease: Improving Global Outcomes website (http://www.kdigo.org/meetings_events/novel_tech.php).

The recent interest in novel techniques and innovation in blood purification was born out of the impasse in an effort to improve survival and quality of life of patients with end-stage renal disease (ESRD). Although there have been medical and technical advances, mortality rate of patients with ESRD remains unacceptably high at about 10–20% per year. To date, most medical interventions have failed to change the survival of ESRD patients.[1,2] It was suggested that the high mortality rate in ESRD was related to poor clearance of uremic toxins within the three-times-a-week paradigm. This hypothesis was tested in the Hemodialysis Study, a randomized controlled study that did not demonstrate a positive effect on patient

survival when dialysis dose was increased from a pretreatment Kt/V of 1.32 to 1.71.[3] Of equal importance is that the Hemodialysis Study did not demonstrate any overall benefit related to the use of high-flux versus low-flux dialyzers.[3] Recently, another randomized trial in Europe, the Membrane Permeability Outcome Study, was unable to show improved survival in all patients treated with high-flux membranes.[4] Although the provision of more intensive conventional hemodialysis has not reduced mortality, more frequent hemodialysis has demonstrated improvements in several clinical surrogate outcomes. Indeed, the Frequent Hemodialysis Network (FHN) Daily Dialysis and the Alberta Kidney Disease Network (AKDN) Trials have reported regression of left ventricular (LV) hypertrophy, improved blood pressure control, and better quality of life.[5–7] Other observational studies have suggested better survival (compared with conventional hemodialysis) with more frequent hemodialysis.[8,9] At the same time, use of convective techniques, such as hemodiafiltration (HDF), has increased and is now common in Europe and in other parts of the world. Survival advantage,[10] hemodynamic stability,[11] and enhanced clearance of small and middle molecules[12] have been reported with the use of HDF, but reports of larger controlled trials in Turkey and the Netherlands have not shown an overall survival advantage.[13,14]

With the increase in the worldwide chronic dialysis population and the growth of renal replacement therapy programs in large countries such as China and India, it has become evident that advances in technology and process are required to facilitate the widespread clinical application of renal replacement therapy. At present, most dialysis machines are not engineered to be used easily by patients. Improved flexibility of a dialysis platform for users with different levels of training and skills will likely transform the clinical landscape of ESRD care. Other novel technical advances in blood purification include application of nanotechnology,[15,16] the use of sorbents to remove uremic toxins and regenerate water for dialysis,[17] 'wearable kidneys,'[18,19] and the incorporation of renal cells as part of a bioartificial kidney.[15,20,21] The clinical applications of novel biomaterials[22] and therapeutic use of endothelial[23] or endothelial progenitor cells[24] may provide much needed innovation in vascular access devices (Figure 1).

HEMODIALYSIS TECHNIQUES: DURATION AND FREQUENCY

Nomenclature

More frequent dialysis than the standard three-times-a-week has been performed since the 1960s;[25–30] however, there is no uniform nomenclature to describe the different types of more frequent hemodialysis. Our group proposes that all hemodialysis prescriptions should be described by indicating both duration of the individual dialysis session and the frequency per week (Table 1).

Other frequencies can also be derived from this nomenclature, such as conventional indicates three times per week,

Table 1 | Descriptive nomenclature for hemodialysis frequency and duration

Conventional hemodialysis	3–5 h per session, three times per week
Short daily hemodialysis	Less than 3 h per session, six times per week
Standard daily hemodialysis	3–5 h per session, six times per week
Long daily hemodialysis	More than 5 h per session, six times per week

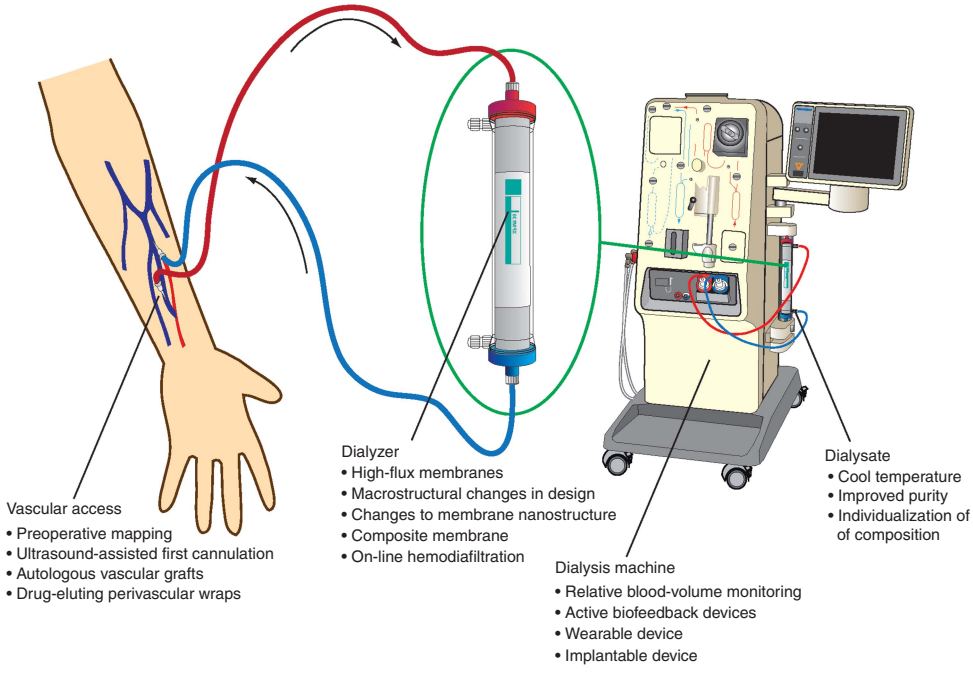

Figure 1 | Innovations in hemodialysis technology.

and the words short, standard, and long denote the length of an individual dialysis session. Other increased frequency lengths include every other day and four or five times per week hemodialysis. The location of the dialysis session should be indicated as in-center, self-care (for patient-assisted in-center hemodialysis), home-assisted (for staff-assisted home hemodialysis), and home (for patient provided home hemodialysis). The use of a standard nomenclature for describing the dialysis prescription should assist in comparative studies and in meta-analyses of different, more frequent hemodialysis prescriptions.

Potential benefits of more frequent hemodialysis—observational studies

As early as 1972, Bonomini *et al.*[27] noted that changing patients to short daily dialysis (3–4 h for 5 days per week) led to a resolution of severe anemia, polyneuropathy, insomnia, pruritus, restless leg syndrome, anorexia, amenorrhea, and impotence. Similar improvements in these and other areas, such as blood pressure control and LV hypertrophy, have been noted by many other investigators since that time in both Europe and North America.[31–34] Despite the enthusiasm for more frequent dialysis therapies, it was not until the 21st century that randomized trials were performed to assess the potential risks and benefits of more frequent hemodialysis modalities.

As late as 2006, a review of daily in-center hemodialysis was based on only 25 published manuscripts since 1989, which included information on five or more patients, followed up for at least 3 months, and were receiving a dialysis prescription of 1.5–3 h for 5–7 days per week.[35] A total of 14 cohorts with 268 unique patients were described in these publications, with only 1 randomized trial. There was a benefit of daily in-center hemodialysis in improving the control of hypertension, by either reducing the number of antihypertensive medications required and/or improving systolic and diastolic blood pressures. The findings for both serum albumin levels and quality of life were mixed, with 5 of 10 studies demonstrating an improvement in these parameters. Improvement in phosphate control, as determined by either lower serum phosphate levels or a decrease in the utilization of phosphate binders, was seen in only two of eight studies. Finally, there was no change in the rate of vascular access dysfunction in five of the seven reported studies.

Similarly, a review of nocturnal hemodialysis, published in 2005, identified only 10 manuscripts and 4 abstracts that reported on at least 1 of 4 outcomes of interest, had follow-up of at least 4 months, included a comparator group (case–control or pre/post within patient comparison), and provided a dialysis prescription of at least 5 nights per week and 6 h per session.[36] A total of 4 cohorts with 4–63 patients per cohort were found, with follow-up ranging from 6 weeks to 3.4 years; none of the studies were randomized trials. Daily nocturnal hemodialysis improved the control of hypertension, by both reducing the number of antihypertensive medications required and improving systolic and diastolic blood pressures. This therapy was shown to improve anemia, either by a reduction in erythropoietin dose or by an increase in hemoglobin levels. Improvement in phosphate control, as determined by either serum phosphate levels or a decrease in the utilization of phosphate binders, was seen in one of two studies. Analysis of more recent retrospective data has shown a survival benefit for patients who undergo more frequent home hemodialysis compared with in-center hemodialysis; however, these analyses are confounded by selection bias and lack of information on the socioeconomic and biochemical data adjustment.[9,37–39]

Potential benefits of more frequent hemodialysis—randomized trials

Several randomized studies have been performed with more frequent hemodialysis prescriptions, including the FHN studies in both short-daily[5] and long-nocturnal hemodialysis,[7] as well as the AKDN Trial of long-nocturnal hemodialysis.[6] Benefits of more frequent dialysis in all studies include improved control of hypertension (less antihypertensive medications prescribed and lower systolic and diastolic blood pressures)[5–7,40] and hyperphosphatemia (fewer phosphate binders prescribed and lower serum phosphorus levels).[5–7,41,42] In the FHN Daily and AKDN studies, there was a significant decline in LV mass (13.8 g (95% confidence intervals, -21.8 to -5.8 g) in the FHN Daily study and 15.3 g (95% confidence intervals, -29.6 to -1.0 g) in the AKDN study).[5,6,43] In the FHN Nocturnal study, however, there was a decrease in LV mass that was not statistically significant (-10.8 g; 95% confidence intervals, -23.7 to $+1.8$).[7] In the FHN Daily Trial, there was an improvement in the self-reported RAND Physical Health Composite, self-reported score in the more frequent hemodialysis (HD) group, but in the FHN Nocturnal study, there was a small nonsignificant increase in this score in both groups, perhaps related to the performance of hemodialysis at home in both groups.[5,7,44] In neither group, however, there were improvements noted in objective measures of physical performance.[44] Neither of the nocturnal studies showed a benefit in overall quality of life.[7,45] Finally, in contrast to the aforementioned observational, nonrandomized data, none of the more frequent dialysis prescriptions resulted in statistically significant improvements in the management of anemia,[5–7,46] depression,[5–7,47] cognitive function,[5,7] or nutrition (as measured by serum albumin levels).[5–7,48]

There are several caveats to these findings, including their generalizability, as patients in all three studies were significantly younger compared with the average hemodialysis patient, and more predominantly male patient.[49] There are also several significant differences between the FHN Nocturnal and AKDN trials. First, the FHN Nocturnal Trial included a larger proportion of incident patients ($\sim$50%) compared with the AKDN Trial. Second, the median duration of dialysis was higher in the AKDN Trial than in the FHN Nocturnal Trial. Although the AKDN Trial did not

report residual kidney function, the difference in both the percentage of incident patients and the mean duration of dialysis suggests that urine volume and renal solute clearances were likely to have been substantially higher in the FHN Nocturnal Trial, thus reducing the relative contribution of the nocturnal hemodialysis regimen to total solute and fluid removal. Third, the follow-up duration in the AKDN Trial was only 6 months compared with 12 months in the FHN Nocturnal Study. Although cardiac magnetic resonance imaging was used to measure LV mass in both trials, the calculation of LV mass excluded papillary muscle in the FHN Nocturnal Trial but included papillary muscle in the AKDN Trial.[7] Finally, it should be noted that none of the published trials are powered to detect the effect of frequent hemodialysis on clinical events.

Vascular access

In both the FHN studies, but not in the AKDN study, there was an increase in vascular access events in the more frequent arm of the study, although access survival was not affected in either of the trials.[5–7,50] Additional information regarding access type and specific access complications should be available in the future from both the FHN studies. In addition, the role of catheter use in home-hemodialysis patients needs to be better defined. Specifically, it is still unclear what the optimal management is for the patient with a current catheter who declines fistula placement, the patient with a current fistula or graft who refuses self-cannulation, or the magnitude of increased risk from either infection or air emboli with a catheter.

Feasibility

Many issues need to be further delineated regarding the feasibility of more frequent hemodialysis. First, there is great variability in the setup of the home hemodialysis unit in terms of staffing, equipment, training of patients, and home hemodialysis policies. Staffs need to ensure that patients adhere to their home dialysis protocols and that they follow infection control in the home setting. There is also variability in the provision of backup for the home hemodialysis patient. The special problems associated with the more frequent dialysis in patients managed at home include adherence, possible need for phosphorus replacement, and nutrition. The current experience mostly reflects the North American activity; more information is needed regarding the practice of more frequent dialysis therapies in Europe and the Asia-Pacific region. Best practices for all of these areas need to be combined to improve the standard of care received by patients receiving more frequent dialysis therapies.

Little information is available about the potential relative risks and benefits of different locations for more frequent dialysis. These locations include staff-assisted in-center dialysis, self-care in-center dialysis, and staff- or spouse-assisted and patient provided home hemodialysis. The choices available for an individual patient are likely to be dependent on local limitations. There are no data to inform on the risks and benefits of each of these locations.

There is also little information from randomized trials of costs associated with more frequent hemodialysis. It is clear that there is an upfront cost to training patients for home hemodialysis, which is balanced over time by decreased staffing costs. Less clear is the potential for savings for medications or hospitalizations.[51,52] None of the more frequent dialysis trials have shown a significant decrease in the use of erythropoietin in the more frequent arm of the trial.[5–7] We are unaware of the potential differences in costs of intravenous vitamin D analogs with more frequent hemodialysis. In addition, none of the randomized trials have been large enough to provide meaningful data on the potential for a decrease in hospitalizations. Finally, there are few data on patient costs to implement home hemodialysis, including home modifications for electricity, plumbing, and carpentry, as well as additional monthly costs for water to generate dialysate.[53] There is, therefore, a clear need to include economic analysis in any future studies of more frequent hemodialysis regardless of the location where it is delivered.

Home hemodialysis brings a unique set of burdens to the patient and the patient's spouse or dialysis helper.[54] There are variable rates of patient dropout reported in different regions of the world, but few hard data to help explain these. Some possible causes for variation include the degree of informatics support, the availability of support groups for dialysis patients, nurses and biomedical availability after hours, the type of home hemodialysis machine used, and the availability of respite in-center hemodialysis. Of equal importance is that frequent dialysis in the clinical setting presents logistic challenges such as local environment (comfort of chairs or beds), travel time, and costs. Table 2 lists the workgroup's recommendations for research in this area, and the section in this manuscript on 'Technical Advances in Dialysis' includes a discussion on potential new methods of delivering dialysis at home.

In summary, there is promising evidence suggesting the benefits of frequent hemodialysis. However, one must also consider the potential risks and barriers of implementing frequent hemodialysis in a wider spectrum of patients. This modality should be considered in patients who have LV hypertrophy (especially in patients with little residual kidney function), difficult-to-control hypertension, significant hyperphosphatemia, or sleep apnea. The risks of increased vascular access events need to be weighed against the benefits of more frequent dialysis in individual patients.

DIALYSATE COMPOSITION AND TOXINS

Dialysate composition and water purity

In many dialysis units worldwide, dialysate is prepared centrally and to standardized prescription, which can be modified to an extent by most dialysis machines. More recently, with an older and more complex group of patients on long-term hemodialysis, in an attempt to reduce

Table 2 | Research recommendations

- Observational data from registries providing additional information about the risks and benefits of more frequent hemodialysis. At a minimum, registries should collect prescription data that include the frequency of dialysis per week and the number of hours per hemodialysis session. Combining this data with laboratory information and patient outcome data, including hospitalizations, change in modality, and death, would provide much needed information on patient outcomes, even accounting for the potential selection bias of patients who are capable of choosing frequent hemodialysis.
- Clinical trials in more frequent hemodialysis could allow for meta-analyses of specific frequent modalities. It is also not known whether providing dialysis either four times a week or every other day would provide some or most of the benefits shown with six times per week dialysis, but at a lower cost.
- All studies should include careful baseline and periodic measurement of residual kidney function.
- Much work needs to be done to provide a less complex method for performing hemodialysis at home. Factors that are likely to limit the number of patients who perform home hemodialysis include the need to troubleshoot dialysis machines, the need for an appropriate partner at home, acceptance of a complex piece of machinery, avoiding hypotension, and avoiding access complications. More funding is needed to develop a simpler, more user-centric hemodialysis machine that will minimize the time needed for setup and take down, and further decrease the risks of having an adverse event while performing hemodialysis at home.

intradialytic and interdialytic complications and improve long-term outcomes, individualized prescriptions have been developed, evaluated, and used. In general, across all dialysate components, homeostasis is achieved best with 'middle-range' prescriptions.

Sodium

Sodium has a critical role in the regulation of weight, extracellular fluid volume, blood pressure, and thirst. The sodium concentration in plasma water exceeds that in plasma by about 10 mmol/l, suggesting a large gradient driving sodium into the dialysate.[55] However, most of this apparent gradient is eliminated by the effect of negatively charged plasma proteins that reduce the diffusible sodium. Hence, the plasma sodium concentration is generally used instead of plasma 'water' sodium as the relevant concentration. This plasma sodium concentration may be a bit less, on average, compared with the diffusible, ionized sodium, and that the correlation between the diffusible sodium and the plasma sodium levels may differ a bit in individual patients.[55] Sodium removal during HD can occur through convection or diffusion. Current prescribing practices for chronic intermittent HD rely primarily on convective losses ($\sim$78%) and less on diffusive losses ($\sim$22%).[56] Hypothetically, a regular removal of 11 of ultrafiltered plasma water, considering a theoretical isotonic sodium concentration of 140 mmol/l in the ultrafiltrate, would be responsible for a removal of 140 mmol of sodium, equivalent to 8 g of sodium chloride ingestion in each interdialytic day.[57] The usual dialysate sodium level is between 135 and 145 mmol/l. In general, a high-sodium dialysate would be above 141 mmol/l, whereas below 137 mmol/l would be regarded as low sodium dialysate. The use of dialysate sodium that is markedly lower compared with the patient's serum sodium results in a rapid reduction in plasma osmolality and intravascular volume, leading to disequilibrium symptoms and hypotension;[57] however, when used at smaller gradients, sodium will not flux into the patient and, post dialysis, thirst is prevented without undesirable hemodynamic events. Dialysate sodium higher than serum sodium may help to maintain blood pressure with ultrafiltration, but leads to post-dialytic thirst, fluid-induced weight gain, and hypertension.[58] Creating a positive intradialytic sodium balance is effective in acutely reducing the incidence of intradialytic symptoms, but it also sustains a vicious cycle hampering the attainment of dry weight and predisposes the patient to an increased risk of intradialytic complications during the following dialysis session.[59] An isonatric hemodialysis may have a beneficial effect on blood pressure and dialysis tolerance. A biofeedback system using HDF with online (OL) regeneration of ultrafiltrate has been specially developed with an isonatric mode maintaining an equal serum sodium concentration between the start and the end of the dialysis session, combined with ultrafiltration and conductivity profiles.[60] A clinical trial is in progress to show these potential benefits with isonatric dialysis.[60]

Individualized therapy according to the set point, which implies alignment of dialysate and serum sodium, has been advocated.[58,61,62] Sodium profiling could be considered persistently symptomatic in patients because of intradialytic hypotension or disequilibrium symptoms.[63–65] However, evidence supporting these approaches is weak. Studies have been small, nonrandomized, short-termed, and limited to surrogate outcomes.[66,67] On first principles, the aim of a dialysis treatment should be to remove the quantity of sodium accumulated since the last session, but feasible and accurate methods to achieve that aim are currently unavailable. Alignment of the patient serum and dialysate sodium concentrations assists in achieving this goal. Avoiding sodium loading in hemodialysis patients is a cornerstone for blood pressure and fluid status management.[59]

Potassium

Hypokalemia and hyperkalemia may lead to potentially life-threatening cardiac arrhythmias. The usual dialysate potassium level is 2 mmol/l. Lowest mortality has been associated with the use of 3 mmol/l potassium.[68] Low dialysate concentrations, particularly those of 0 or 1 mmol/l, should be avoided. If used, extreme caution should be exercised because the rapid decline in plasma potassium concentration, which occurs in the early stages of a dialysis treatment, is arrhythmogenic. Hemodialysis is associated with the markers of cardiac electrophysiologic aberrancy, particularly in patients with underlying cardiovascular disease, and those markers are amplified by a low potassium bath.[69] Reducing the blood-to-bath potassium gradient during dialysis

mitigates the dialysis-associated electrophysiologic effects. However, the cardiac electrophysiologic markers appear to add little or nothing to the sudden death risk assessment and so are of dubious predictive value. A recent study by Gabutti *et al.*[70] showed a rapid decrease in the concentration of serum potassium during the initial stage of the dialysis following reduction of dialysate potassium translates into a decrease in systolic and mean blood pressure mediated by a decrease in peripheral resistance. The risk of intradialytic hypotension inversely correlates to the potassium concentration in the dialysate. The use of 1 mmol/l potassium dialysate in a chronic hemodialysis setting has been associated with an increased incidence of cardiac arrest.[71] Similar to sodium, potassium profiling has been suggested, but the evidence is weak. Studies by Redaelli *et al.*[72] and Santoro *et al.*[73] showed potential benefits of potassium modeling in reducing ventricular arrhythmias and complex arrhythmias, respectively. However, in the study by Redaelli *et al.*[72], the total drop in the serum potassium concentration was not different between the fixed and variable potassium dialysates, whereas the study by Santoro *et al.*[73] includes only a small number of 30 subjects. In contrast, longer dialysis sessions using a fixed potassium dialysate of 2 mmol/l can remove potassium at lower dialysate/plasma gradients.[74] Taken together, avoidance of high potassium concentration gradients between the dialysate and blood could have favorable hemodynamic consequences.[72]

Calcium

Lower dialysate calcium (1.25–1.5 mmol/l) may reduce the risk of hypercalcemia, but may lead to negative calcium balance, hyperparathyroidism, and intradialytic hypotension. Increased attention has been paid recently to integrating choice of dialysate calcium level into the understanding of calcium balance, which is determined by diffusive intradialytic fluxes, the dietary calcium content, and in the administration of calcium-containing phosphate binders, as well as by dosage of vitamin D analogs.[75] If hypokalemia is coexistent, then critical QTc prolongation may occur.

Higher dialysate calcium levels (1.5–1.75 mmol/l) may improve hemodynamic stability during dialysis, but may also increase the risk of hypercalcemia and vascular calcification. Alappan *et al.*[76] studied the addition of high-calcium (1.75 mmol/l) dialysate to a group of patients with intradialytic hypotension, who are also treated with cool dialysate and midodrine. They found that the addition of high-calcium dialysate in this context further improved hemodynamic stability in patients with intradialytic hypotension. However, this therapy did not reduce symptoms or interventions required for intradialytic hypotension. Hypercalcemia occurred in 22% of the patients.[76]

The association of dialysate calcium with vascular calcification has been studied in a trial evaluating three different concentrations of dialysate calcium at 1, 1.25, and 1.50 mmol/l, respectively.[77] These investigators found that dialysate calcium and acute changes in the serum-ionized calcium concentration, even within the physiological range, were associated with detectable changes of arterial stiffness and central pulse-wave profile. Ionized calcium decreased with a dialysate calcium concentration of 1.00 mmol/l and increased with a dialysate calcium concentration of 1.50 mmol/l, but did not change with a dialysate calcium concentration of 1.25 mmol/l. The percentage increase in carotid–femoral pulse-wave velocity and carotid–radial pulse-wave velocity was associated with an increase in the level of ionized calcium.[77] A recent study by Gotch *et al.*[75] concluded that in 320 dialysis patients, the dialysate calcium required for neutral calcium mass balance, wherein calcium removal during dialysis was equal to calcium accumulation between the dialyses, was <1.25 mmol/l and averaged about 1.00 mmol/l. Bosticardo G *et al.*[78] recently showed how the use of 1.25 mmol/l dialysate calcium concentration in patients with predialysis blood-ionized calcium in the normal range allows stable blood-ionized calcium levels over the dialysis sessions, and approximately neutral dialysis calcium mass balances. At the same time, the use of 1.5 mmol/l dialysate calcium significantly increases blood-ionized calcium levels during the session and induces a marked calcium gain, suggesting that 1.5 mmol/l dialysate calcium should be used with caution.

Basile *et al.*[79] studied the effect of three dialysate total calcium concentrations (2.5, 2.75, and 3.0 mmol/l) on parathyroid hormone and calcium balance in highly controlled single dialysis session studies using a crossover design. They found that dialysate total calcium concentration of 2.75 mmol/l might be preferable, because it is able to give a mildly positive total calcium mass balance while maintaining normal plasma water−ionized calcium levels, and not stimulating short-term parathyroid hormone secretion but long-term studies are needed to confirm the results.

Given that dialysate calcium is only one component in the total calcium balance, dietary calcium, calcium-containing phosphate binders, and the use of vitamin D or its analogs also need to be considered when dialysate calcium is prescribed. Studies of dialysate calcium in isolation do not provide a firm basis for clinical decision making.[80]

Glucose

Hemodialysate solutions often contain high concentrations of glucose (up to 200 mg/dl).[81] The historical reasons for the addition of glucose to the dialysate included the following: (1) enhancing ultrafiltration and (2) minimization of nutritional (caloric) losses during dialysis. Recent evidence suggests that exposure to high levels of glucose may be proinflammatory and their use should be re-examined.[81,82] Dialysate glucose concentrations of 100 mg/dl are likely to be safe. Higher values may predispose to the metabolic syndrome. Glucose-free dialysate may be beneficial metabolically and possibly less inflammatory. However, glucose-free dialysate may be associated with hypoglycemia, particularly in poorly nourished patients, insulin-requiring diabetics, or in acute hemodialysis settings.

Buffering

Bicarbonate dialysate is now the fluid of choice. Bicarbonate is the primary buffer that traditionally has been prescribed in the range of 33–38 mmol/l. The concentrate of acetate used is variable and contributes to the total buffering, with a range of 4–8 mmol/l, whereas 5–6 mmol/l is most widely used and appears to be safe, providing these sources of bicarbonate concentration are considered when the dialysate prescription is written. The aim of intradialytic buffering is to avoid post-dialysis alkalosis and acidosis before the next session. Net acidosis may lead to a catabolic state, and insulin resistance and bone loss. Net alkalosis may lead to reduced cerebral blood flow, cramps, and fatigue. Recent observational data have demonstrated that high dialysate bicarbonate (>35 mmol/l) may be associated with adverse outcomes. Modeling dialysate bicarbonate is of uncertain benefit, but lower bicarbonate may assist patients with intradialytic hypotension.[83] The benefits of using citrate as a buffer are uncertain. Gabutti *et al.*[84] found that citrate-based bicarbonate dialysate compared with acetate-based bicarbonate dialysate had a positive impact on dialysis efficiency, acid–base status, and hemodynamics in selected patients on hemodialysis. A recent study also showed that hemodialysis with acetate-free citrate containing dialysate may improve a patient's clinical status with intractable metabolic acidosis, hyporesponsiveness to erythropoiesis-stimulating agent, and malnutrition that were not normalized in hemodialysis with acetate-containing dialysate.[85] Cheng *et al.*[86] have studied a dialysate, with a citrate level of 1 mmol/l as generated by adding citrate to the conventional liquid 'bicarbonate concentrate' system. Significantly less thrombus formation in the venous air traps was detected in the citrated dialysate patients.

Water purity and quality

Quality standards for water and concentrates used to produce dialysate are well established.[80,87] The European Renal Association standard stipulates that microbiological contamination of the delivered water should comply with the recommendations of the European Pharmacopoeia bacterial count of -100 colony-forming unit/ml and endotoxin content of -0.25 endotoxin unit/ml. All convective methods require ultrapure water (endotoxin level <0.03 EU/ml). Regular monitoring of water quality, preferably monthly, should be performed. Ultrapure dialysate is defined as a bacterial count <0.1 colony-forming unit/ml and an endotoxin level <0.03 endotoxin units/ml.[80] This endotoxin level is the sensitivity threshold for the simplest of the limulus amoebocyte lysate assays. Recently, Europe, the United States, and Japan endorsed the upgrading of water and dialysate quality for all dialysis modalities. Guidelines supporting the regular use of ultrapure dialysis fluid for all hemodialysis modalities have been produced.[88] To have such a high grade of microbiological purity in the dialysis fluid, several prerequisites have been identified: (1) an adequate water treatment and distribution system; (2) cold sterilizing ultrafilters on the inlet dialysis fluid circuit of the dialysis machines; (3) sensitive assays for microbiological monitoring with protocols of hygienic rules for disinfecting water and dialysate pathways; and (4) a broad-based quality-control and assurance process.[88]

Bacterial products, such as endotoxins, fragments of endotoxin, peptidoglycans, and fragments of bacterial DNA, can cross the pores into the bloodstream. These are all potent inducers of cytokines and stimulators of the acute-phase response contributing to chronic inflammation.[89,90] Recently, circulating endotoxins have been shown to have potential impact on survival in patients undergoing peritoneal dialysis or hemodialysis.[91,92] The introduction of ultrafiltered dialysate was associated with a significant reduction in plasma β2-microglobulin concentration and a significant improvement in nutritional status, assessed by plasma albumin concentration and creatinine generation rate as a marker of muscle mass.[93]

In summary, given the limited amount of evidence supporting the various strategies in titrating dialysate concentrations in patients receiving three-times-a-week hemodialysis, we suggest several dialysate strategies that need to be tested in randomized controlled trials. Potential questions that could be addressed include the following: (1) the use of individualizing dialysate sodium (relative to sodium set point) versus standard care, (2) minimization of potassium gradient, and (3) customization of dialysate calcium according to calcium-balance measurements.

TECHNICAL ADVANCES IN DIALYSIS

Can improvements in dialyzer technology increase uremic toxin clearance?

Dialyzer technology has evolved to allow production of high-flux membranes, with both increased water (ultrafiltration coefficient >20 ml/h/mm Hg) and solute removal.[94] Small solute clearances can be increased by fiber surface undulations and internal constriction, or other designs to create an internal vortex flow.[95,96] Larger solute clearances can be achieved by increased internal diafiltration by creating oscillations in the transmembrane pressure,[97] creating resistance to blood flow within the dialyser, either by reducing the internal diameter of the fibers or by increasing the dialyser length.[94] Although nanotechnology-produced dialyzer membranes have both increased solute removal mass and enlarged the spectrum of solutes cleared, many are predominantly intracellular or bound to plasma proteins. As such, the rate-limiting step is often the movement from intracellular sites to the plasma water or the rate of dissociation from plasma proteins. As such, the clearance of such solutes is time-dependent and can potentially be overcome by longer and more frequent dialysis sessions.[98]

Despite these advances, current dialysis strategies only remove a fraction of the spectrum of putative uremic toxins largely because of these being bound to the protein.[99] Further increases in membrane pore size with high-permeability dialyzers not only increase larger solute clearances, including

free plasma light chains, peptides, and small proteins, but also result in albumin losses.[100] Although removal of protein-bound toxins is increased with these high-permeability membranes, this is proportional to protein losses.[101] Alternative strategies to increase removal of larger and protein-bound uremic toxins[102] include alteration of the dialyzer surface characteristic to increase adsorption[103] and the construction of composite membranes containing carbon particles or specific sorbents to also increase adsorption of toxins.[104] Further work is required to clarify the toxicity of individual uremic retention products[102] to determine whether groups or classes should be preferentially targeted. As some of the putative uremic toxins are derived from gastrointestinal bacterial metabolism, strategies aimed to change gastrointestinal bacterial flora may be an effective alternative strategy.

Do advances in hemodialysis machine technology translate to improved patient outcomes?

Intradialytic hypotension is the commonest complication in routine outpatient hemodialysis practice,[105] and reduction in myocardial perfusion during hemodialysis has been associated with increased mortality risk.[106] Repetitive episodes of hypotension also risk cerebral ischemic damage and may also potentially cause ischemia to other perfusion-dependent organs, including the pancreas and the gut. Maintenance of the initial body temperature at the commencement of dialysis will minimize intradialytic instability and complications, but in those patients who develop significant intradialytic hypotension, lowering the dialysate temperature may be beneficial.[107] Cool-temperature dialysate typically uses 35 °C. Deliberate cooling of the dialysate was shown to reduce intradialytic hypotension[108,109] and diminishes cardiac stunning compared with isothermic dialysis[110] and risk of hypotension.[111]

Reduction in plasma water due to ultrafiltration increases hematocrit and blood density, which can be monitored using changes in optical or ultrasonic properties during treatment, as is used in relative blood volume monitoring (rBVM). If the rate of plasma water removal exceeds the compensatory refilling rate, then the slope in rBVM becomes steeper.[112] However, multicenter trials have failed to show a reduction in intradialytic hypotension with the use of rBVM.[113] Similarly, passive biofeedback systems that stopped ultrafiltration at a preset rBVM or rate of decline, failed to prevent intradialytic hypotension because of patient intratreatment variability[114] and lack of correlation between the nadir rBVM and hypotension.[115] More recently, active biofeedback devices have been introduced that vary the ultrafiltrate rate and dialysate sodium concentration according to the response in rBVM. Although the use of these devices has been reported in single-center studies, to reduce serious intradialytic hypotension,[116,117] they did not prevent hypotension. As hematocrit differs between capillaries and the capacitance arteriovenous (AV) system,[118] small capillaries constrict first in response to ultrafiltration, thus returning a relatively lower hematocrit blood to the central vessels. As such, the change in rBVM lags behind these compensatory changes in ultrafiltration.[119] It is not known whether repetitive intradialytic hypotension adversely affects cardiac and cerebrovascular disease, or residual renal function, or whether patients with preexisting vascular disease are more prone to intradialytic hypotension.[120]

Is OL-HDF the future for standard three-times-a-week therapy?

OL-HDF is defined as a combination of diffusive and convective solute transport using a high-flux membrane with an effective ultrafiltration rate of at least 20% of the blood-flow rate in combination with OL-generated sterile and nonpyrogenic solution for fluid substitution.

Compared with standard conventional HD, the documented advantages of OL-HDF include a higher removal rate of higher molecular weight solutes, including phosphate, β2-microglobulin, and some protein-bound uremic compounds, which may translate into sustained lower serum β2-microglobulin and phosphate levels.[121–123] In many but not all studies, OL-HDF was further associated with a lower incidence of intradialytic hypotension, improvements in erythropoietin responsiveness, and nutritional status, as well as prevention of inflammation and better preservation of residual renal function.[11,124,125] These effects may be due to HDF itself or secondary to improved dialysate purity and cooling because of high-volume fluid infusion.

Despite these potential benefits, HDF has not found widespread adoption. Reasons for the reluctance in applying HDF to a larger patient population are multiple and include a lack of convincing cost-saving potential, safety concerns using a large volume of OL-prepared substitution fluid, and (in the United States at least) regulatory issues preventing OL fluid preparation. In addition, vascular access may be inadequate to match minimum blood-flow requirements, staff needs to be specifically educated, and OL-HDF machines are more expensive.

The main reason may be a lack of convincing evidence of a survival benefit compared with standard conventional HD. Several large, randomized controlled studies comparing HDF with standard conventional high- or low-flux HD are currently ongoing or have been concluded recently, such as the CONTRAST Study.[13,14] Although no overall significant survival difference between OL-HDF and either low- or high-flux HD was observed in either of these two studies, secondary on-treatment analyses in both studies indicate that higher delivered convective volumes ($>$17–22 l per session) are independently associated with a reduced all-cause mortality risk.

In the future, an international consensus definition of target ultrafiltration volume, as surrogate of convective dose, is needed to objectively assess the potential impact of convective therapies. Furthermore, in the absence of a general survival advantage with HDF, target populations that benefit mostly from this treatment form need to be defined, and

potential long-term side effects of OL-HDF, such as chronic nutrient depletion,[126] need to be elucidated.

Is the wearable dialysis device technically feasible and a reality?

Wearable or implantable devices would potentially allow patients to benefit from longer treatment durations with greater solute clearance and improved volume balance. However, wearable devices also have to maintain electrolyte and acid–base homeostasis. Although several groups have developed wearable devices on the basis of peritoneal dialysis with regeneration of spent dialysate using carbon and other sorbents, definitive clinical trials remain awaited.[127,128] The development of a truly wearable hemodialysis device has been a goal since the 1970s, and despite many attempts there has only been one recent 'proof-of-concept' clinical trial,[129] which showed that such a device would be predicted to achieve greater small- and middle-sized, water-soluble solute and protein-bound toxin clearances compared with the standard three-times-a-week conventional hemodialysis.[97] However, many hurdles have to be overcome before a proof-of-concept device can be brought to clinical practice.

Implantable devices depend upon a membrane mimicking glomerular filtration, producing an ultrafiltrate, which then has to be processed, reabsorbing the majority of water and electrolytes on one hand and excreting a concentrated waste on the other. Until now, these devices are restricted to laboratory testing or early-phase animal trials.[130] Any wearable dialysis device should currently be considered as a complementary and challenging tool, but with uncertain position in clinical CKD management.

Status of the implantable bioartificial kidney

The bioartificial kidney aims to combine the glomerular membrane-sieving function with the tubular metabolic and endocrine function of the nephron.[131] One component of the bioartificial kidney, the renal tubular cells containing the renal assist device, has been applied in two exploratory pilot trials in patients with acute kidney injury and multiorgan failure. The renal assist device is based on a standard hemofiltration cartridge containing renal tubular cells grown along the lumen side of the hollow fibers. The renal assist device is connected in series to a conventional hemofilter in an extracorporeal blood circuit. One pilot trial, designed to demonstrate safety and clinical efficacy of the device, was suspended after an interim analysis because of an unanticipated high survival rate of the sham device arm of the study, which may have been related to the use of citrate as an anticoagulant in the placebo arm, compared with heparin in the active arm.[132] Proof-of-concept, demonstration of durability and efficacy, long-term feasibility, cost and clinical benefits, as well as exclusion of potential immunogenicity will be required before these devices can be applied on humans. Pluripotential stem cells have been shown to accelerate renal recovery from acute kidney injury in animal models,[133] and have been seeded on extracorporeal bioreactors, but remain experimental, as concerns have been raised about interstitial fibrosis in the longer term. Currently, cell-based technologies have been unable as yet to recreate a human glomerulus, let alone a nephron unit.

Are there technical/clinical tools to improve the present vascular access outcome?

Clinical tools. Vascular access management is a way of improving hemodialysis outcomes. Currently, AV vascular accesses are unsatisfactory because of thrombosis or insufficient maturation. There was consent that vascular access outcomes may be improved by unifying vascular access pathways across centers and countries, and by increasing the number of surgeons and dialysis physicians with expertise in the field of access creation and management to establish best clinical practice.[134,135] Despite a lack of supportive studies, it was generally felt that preoperative vascular mapping and examination of vessel size are useful adjuncts and should be better promoted among dialysis physicians. There was general consensus that adequate maturation time up to 4 weeks should be allowed before first puncture. At 4 weeks after access placement, there should be an assessment for the degree of maturation and care pathways established in case of inadequate fistula-flow development.[134] So far, there have been no established medical therapies for the enhancement of maturation and prevention of fistula stenosis. It was agreed that cannulation skills and expertise are of utmost importance and are required for both dialysis physicians and nurses.

The role of ultrasound-assisted first cannulation was debated at the conference and it was concluded that this question should be addressed by clinical studies. It was pointed out that vascular access blood-flow rate may negatively affect cardiac function as well as access survival due to turbulence-induced intima proliferation. Further studies in these areas are eagerly awaited.

Emerging technical/medical tools. Pharmacologic treatments to improve vascular access outcome include use of aspirin and other antiplatelet drugs. Extended-release dipyridamole plus low-dose aspirin prolongs primary unassisted graft patency of newly created hemodialysis AV grafts.[136] However, the beneficial effects of anticoagulants and antiplatelet drugs may be counteracted by an increased bleeding tendency and mortality risk.[137]

There have been a number of different approaches adopted to improve AV graft patency, ranging from newer nanotechnology-manufactured synthetic grafts, using newer polymer materials and designs, to tissue-engineered grafts. Several of them are now entering clinical trials, and preliminary data to date from completely autologous vascular grafts grown in culture were reported to have a fourfold reduction in graft event rate in a small cohort of 15 patients followed up over a period of 3 months to 3 years.[138] Longer term follow-up, with greater patient recruitment, is required to assess outcomes of this promising approach weighed against the long time period for culture tissue and high cost. This and

other tissue engineering approaches appear to be fascinating and promising approaches for improving vascular access creation and patency.

Other approaches include local drug delivery, such as drug-eluting perivascular wraps. A recent study of paclitaxel-eluting perivascular wrap was suspended because of an increased rate of local infection. An initial phase II study with Sirolimus-eluting wraps showed primary unassisted AV graft patency of 75% and 38% at 1 and 2 years, respectively.[139]

SUMMARY

Despite more than 5 decades of chronic dialysis, 5-year survival remains lower than that for many solid-organ malignancies and provides a very strong stimulus to explore new innovations and techniques in blood purification. Over this period, numerous technological advances have helped to improve dialysis delivery and allow the treatment of high-risk patients. The individualization of dialysis prescription and dialysate composition with optimization of water quality may improve intradialytic morbidity, and perhaps mortality, when coupled with improved clinical practices and quality-control processes. Novel approaches to increase dialysis dose delivery and fluid and toxin removal by augmentation of frequency and/or duration of hemodialysis, in combination with convective or adsorptive techniques, represent a promising strategy, which warrant further testing in definitive randomized controlled trials.

Although technological advances have made it possible to successfully treat an increasing number of older, high-risk hemodialysis patients, technology alone will never replace clinical judgment and skills. Improved clinical practice, adopting best practices, strict quality-control processes, and individualized treatment regimens will represent the key to success in improving hemodialysis outcomes.

DISCLOSURE

AC has received honoraria from Amgen, FMC, Abbott, and Roche. MKK has received speaker honoraria from Abbott, Baxter, Gambro, Genzyme, Fresenius, Sanofi-Aventis, and Shire. CTC is a member of the Baxter Scientific Advisory Board. MVR is a consultant for DaVita and Amgen. PKTL received speaker honoraria from Baxter, FMC, and Roche, and is a member of Baxter Trial Advisory Board. NWL owns Fresenius stock and has served on Affymax and Roche Advisory Boards. DCW has received honoraria from Amgen, FMC, Abbott, and Shire, and research funding from Abbott, Roche, and Genzyme. All the other authors declared no competing interests.

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APPENDIX

Conference Participants

Gavin J. Becker, Australia; Peter J. Blankestijn, The Netherlands; Bernard Canaud, France; Christopher T. Chan, Canada; Alan Collins, United States; Bruce A. Cooper, Australia; Adrian Covic, Romania; Jonathan. Craig, Australia; Bruce Culleton, United States; Andrew Davenport, United Kingdom; Thomas Depner, United States; William Fissell, United States; Marc Goldstein, Canada; David A Goodkin, United States; Frank Gotch, United States; Roger Greenwood, United Kingdom; Victor Gura, United States; David Harris, Australia; Jörgen Hegbrant, Sweden; H. David Humes, United States; T. Alp Ikizler, United States; Michel Jadoul, Belgium; Kitty Jager, The Netherlands; Vanita Jassal, Canada; Bertram L. Kasiske, United States; Hideki Kawanishi, Japan; Peter Kerr, Australia; Martin K. Kuhlmann, Germany; Eduardo Lacson, United States; Ingrid Ledebo, Sweden; Edward Leonard, United States; Nathan W. Levin, United States; Philip K.T. Li, Hong Kong; Robert M. Lindsay, Canada; Francesco Locatelli, Italy; Alejandro Martin-Malo, Spain; Todd McAllister, United States; William McClellan, United States; Louise Moist, Canada; Ezio Movilli, Italy; Norma J. Ofsthun, United States; Ercan Ok, Turkey; Robert Pauly, Canada; Luciano A. Pedrini, Italy; Ronald L. Pisoni, United States; Viatcheslav Rakov, Switzerland; Brian Rayner, South Africa; Miguel Riella, Brazil; Michael V. Rocco, United States; Prabir Roy-Chaudhury, United States; Antonio Santoro, Italy; Rukshana Shroff, United Kingdom; Paul Stevens, United Kingdom; Ciro Tetta, Germany; Robert Toto, United States; Yusuke Tsukamoto, Japan; Ashish Upadhyay, United States; Raymond Vanholder, Belgium; Christoph Wanner, Germany; David Wheeler, United Kingdom.