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Changing paradigms of renal replacement therapy in chronic kidney disease patients: ultrapure dialysis fluid and high-efficiency hemodiafiltration for all?

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Ultrapurity of dialysis fluid is important for the biocompatibility of renal replacement therapy systems. Penne and collaborators have assessed the microbiological quality of water and dialysis fluid in dialysis facilities. No side effects were noted in 97 patients who received 11,258 online hemodiafiltration sessions. This study confirms that ultrapure water and dialysis fluid may be easily produced and used for online hemodiafiltration.

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During the past decade, the microbiological quality of dialysis fluid has become a matter of major concern for hemodialysis patients.[1] Ultrapurity of dialysis fluid has emerged as a key component playing a major role in the overall biocompatibility of renal replacement therapy systems (Figure 1). Microbial contaminants (bacteria and/or derived byproducts) of dialysis fluid contribute to triggering and maintaining a low-grade inflammation in hemodialysis patients by inducing monocyte/macrophage activation and the subsequent release of proinflammatory cytokines (interleukin-1, interleukin-6, and tumor necrosis factor).[2] It is now well established that chronic inflammation is a key pathogenic actor in morbidity and mortality of hemodialysis patients. Inflammation represents the main link amplifying the expression of uremic toxicity and the severity of lesions in chronic kidney disease patients.[3] The pathogenic role of chronic microinflammation is multimodal: it enhances the progression of atherosclerosis and/or atheromatosis lesions; it amplifies the vascular and valvular calcifications associated with hyperphosphatemia; it worsens the malnutrition state, being responsible for protein energy wasting; it worsens the anemia by increasing the resistance to erythropoietin action and the production of hepcidin, which in turn reduces iron availability for erythropoiesis.[4] Prevention of chronic inflammation induced by dialysis fluid contamination should be considered the main driving force supporting the regular use of ultrapure dialysate in contemporary hemodialysis.[5,6] European regulatory authorities and the European Renal Association were the first to support this concept and implemented this new paradigm in the European Best Practice Guidelines.[7] Nowadays, ultrapurity of dialysis fluid is recognized worldwide as a necessary step for further improving overall dialysis quality. National guidelines (France, Dutch, Japanese), including the North American ones (from the Association for the Advancement of Medical Instrumentation), have incorporated this specific option in their latest issues.[8,9] Moreover, virtually all dialysis manufacturers are providing cold sterilization of the dialysis fluid by implementing a final ultrafilter in line on the dialysis machine.

In addition, two recent clinical randomized trials suggest that further improvement in hemodialysis patient outcomes could be achieved by an increase in middle-molecule removal. A *post hoc* analysis of the HEMO study assessing specifically the role of β_2-microglobulin (B2M) concentrations in mortality has clearly shown that high B2M concentrations were associated with an increased risk of death in hemodialysis patients.[10] The increase in the relative risk of death in the population studied was estimated to be 11% per 10 mg/l increase in predialysis B2M concentration for a threshold value of 27 mg/l. The Membrane Permeability Outcomes study has recently shown that mortality of hemodialysis patients was significantly reduced among high-risk patients (diabetics, hypoalbuminemic patients) with the use of a high-flux hemodialyzer.[11] The beneficial effect of high-flux membrane use was not observed in low-risk patients when they received an adequate dialysis dose equivalent for the two groups (Kt/V urea >1.2). Although this study did not primarily address the role of B2M in patient mortality, one might speculate that B2M concentrations were lower in the high-flux group. The potential beneficial impact of increased middle-molecule clearance is also highlighted by recent studies evaluating the effect of high-efficiency hemodiafiltration on dialysis-patient survival. By combining diffusive and enhanced convective clearances, online hemodiafiltration offers the most efficient renal replacement modality that maximizes middle-molecule clearance. Recent cohort studies have shown that the relative risk of mortality, accounting for dialysis dose and most comorbidities, was reduced by 35% in patients treated with high-efficiency hemodiafiltration.[12,13] In brief, these studies are in close agreement to suggest that combining the use of ultrapure dialysis fluid and enhancement

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Figure 1 | Dialysate ultrapurity produced by cold-sterilization process (ultrafiltration).

of middle-molecule clearance is significantly beneficial to patient outcomes.

In this context, the study of Penne and collaborators[14] (this issue) is very well taken and quite informative. The authors took advantage of their prospective randomized trial comparing the effects of conventional low-flux hemodialysis and highly efficient online hemodiafiltration on morbidity and mortality (all causes and cardiovascular events) in prevalent dialysis patients (the Convective Transport Study (CONTRAST))[15] to assess the microbiological quality of water and dialysis fluid in dialysis facilities that were enrolled in the study.[14] Ten dialysis facilities were selected for the microbiological audit of water and dialysis fluid. The water treatment systems relied on a pretreatment system and, in 90% of cases, on a double reverse osmosis system; in one center, the reverse osmosis system was coupled with a continuous electronic deionizer in series. A water distribution loop was installed in all the dialysis facilities and was disinfected with a median frequency of four times per week, in 70% of cases by heat and in 30% of cases with ozone. Three types of EC-certified online hemodiafiltration machines (Fresenius 4008/5008; Gambro AK100/200 ULTRA; Nikkiso DBB05) were used and were heat-disinfected after each run. Microbial monitoring of water (100% of centers) and dialysis fluid (80% of centers) including bacteriometry and endotoxin content was performed monthly over the 2-year period of follow-up. A highly sensitive method based on dialysis-fluid culture on poor media (R2A) with a median incubating period of 7 days was performed once monthly on average. Similarly, endotoxin content was determined monthly on dialysis-fluid samples with the use of limulus amebocyte lysate based on a chromogenic method (70%) and clot gel (30%). Of 3961 dialysis-fluid samples, 99.1% complied with ultrapurity standards as defined by European Best Practice Guidelines and Dutch guidelines (bacteriometry <10 CFU/l and endotoxin content $\leqslant 0.03$ EU/ml). No side effects or pyrogenic effects were noted in 97 patients who received 11,258 online hemodiafiltration sessions. Interestingly, high-efficiency online hemodiafiltration was easily implemented in all dialysis facilities and was well accepted by both patients and nursing staff.

In brief, this study confirms that ultrapure water and dialysis fluid may be easily produced on a large, nationwide scale and used in virtually all contemporary dialysis facilities. Relatively simple and compact technical solutions for water treatment have been developed for dialysis centers and could be mastered by specialized water and plumbing engineering manufacturers and bioengineers. The extra cost generated by this highly sophisticated new water treatment technology appears quite affordable and amortizable over the life duration of plant production of the water treatment system.

In addition, the study by Penne *et al.*[14] confirms that high-efficiency online hemodiafiltration may be easily implemented in dialysis facilities and used as routine renal replacement therapy for all chronic kidney disease patients. A high volume of substitution fluid, which is made possible with online production machines, was used in all patients to maximize dialysis-dose efficacy. The cold-sterilization process, using a final ultrafiltration of dialysis fluid, is safe, provided that the quality of the water feeding the dialysis machine is ensured, heat disinfection of the machine is performed after each treatment, and the ultrafilter is changed periodically.

The impact of highly efficient online hemodiafiltration and ultrapure dialysis on morbidity and mortality of dialysis patients is currently under investigation in the Dutch CONTRAST study. Another randomized study evaluating patient outcomes with high-flux hemodialysis versus high-efficiency hemodiafiltration is currently running in France.[16] The results of both these studies are expected to be reported within the next three to four years.

To conclude, the nephrology community is waiting for a definitive answer on the exact role of high convective clearances and middle-molecule toxins and the regular use of ultrapure dialysis fluid in chronic kidney disease patients' outcomes. In addition, the prospect of easy and permanent access to ultrapure dialysis fluid permits us to envisage the development of new dialysis machines with total automation of priming and rinsing procedures incorporating biofeedback control of volume. Ultrapure dialysis fluid should become a new standard for contemporary hemodialysis machines.

DISCLOSURE

The author declared no competing interests.

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