Chapter 1

# Introductory Chapter

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## 1. Introduction

Conventional hemodialysis (HD) treatment, which is the most prevalent dialysis modality and can be performed in hospital and at home, has been associated over the past 40 years with reduction in mortality rate [1], and in recent years, it has been associated with slight incremental improvement in survival rate [2]. However, its prescription remains far from being optimal in replacing the function of normal kidneys, and its unphysiologic clearance pattern and inability to remove all types and sizes of uremic toxins resulted in inter- and intradialytic complications, higher hospitalization rate, poor quality of life and an unacceptably high rate of cardiovascular and all-cause mortality [3–5]. The major HD-contributing factors to high mortality and morbidity rates are excess fluids (hypervolemia) and retention of middle and larger size uremic toxins.

Fluid retention in patients on dialysis has been associated with increased blood volume and cardiac output, which can result in increased blood pressure, left ventricular hypertrophy (increased left ventricular mass) and consequently heart failure [3, 6]. Fluid (and cumulative fluid) overload has been significantly associated with greater risk of mortality [7]. Moreover, removal of accumulating fluids with conventional HD has been accompanied with symptomatic hypotension. Frequent episodes of hypotension can lead to ischemic insults to myocardium (stunning), which can lead to functional and structural changes and result in systolic dysfunction and consequently heart failure [8, 9]. In addition, fast removal of fluids of more than 10 ml/kg/h can also lead to increase in cardiovascular and all-cause mortality [10]. Recent innovations in fluid management include assessment of fluid status by bioimpedance spectroscopy [11–13], which is a noninvasive method using a portable device, and by controlled modulation of ultrafiltration rate and dialysate sodium using biofeedback hemocontrol [14].

Conventional HD, using low-flux dialyzers, is capable of removing only small-size uremic toxins of molecular weight less than 500 Daltons (D) such as urea and creatinine. However, this modality of HD is not capable of clearing middle and larger size uremic toxins of more than

500 Daltons such as β2-microglobulin, myoglobin, pro-inflammatory cytokines and Kappa (κ) and Lambda (λ) free light chains (**Table 1**), in which all have potent toxic and pro-inflammatory effects [15]. Larger size uremic toxins, such as beta 2-microglobulin, and protein-bound molecules, such as indoxyl sulfate and *p*-cresol, cannot be removed, and their accumulation in the blood can lead to hemodialysis-related amyloidosis and endothelial inflammation and toxicity, which may explain, at least in part, the higher incidence of morbidity and mortality in patients treated with conventional HD.

In recent years, HD treatment witnessed significant improvements in HD machines, including designs, weight, mobility, multifunctional touch screens, performance of different modalities of dialysis, assessment of dialysis adequacy and ultrafiltration control [16]. The option of controlled ultrafiltration, for example, has been shown to safely remove excess fluids without exposing dialysis patients to frequent episodes of hypotension [14, 17]. This hemocontrol technique, which is based on an automatic slowdown of ultrafiltration rate, sodium transfer and the release of the vasoconstrictor arginine vasopressor [18], has been used to support patients with excessive fluid retention, especially those who lost their residual renal function and non-adherent to dialytic prescription, and are predisposed to frequent episodes of intradialytic hypotension [14]. The advancement technology of HD machines was accompanied by significant improvement in dialyzers compatibility and membrane permeability (including pore size, density and distribution, length of fibers and its reduced inner diameter), which include high-flux and medium-to-high cut-off membranes [19]. These innovations, together with the ability to provide ultrapure and online treated water by modern water treatment plants, did not only reduce inflammation, erythropoietin resistance and cost reductions [20], but also allowed the implementation of online hemofiltration (HF) and hemodiafiltration (HDF) treatments [21, 25] and the use of high-flux dialyzers. For example, middle size uremic toxins such

| **Small** (<500 Daltons) | **Medium** (500–15,000 Daltons) | **Large** (>15,000 Daltons) | **Protein-bound*** (Daltons) |
|---|---|---|---|
| Sodium (23) | Vitamin B12 (1355) | Cytokines (15,000–30,000) | Phenol (94) |
| Phosphorus (31) | Vancomycin (1448) | Myoglobin (17,000) | *p*-Cresol (108) |
| Potassium (35) | ANP (3100) | Kappa FLC (22,500) | Homocysteine (135) |
| Urea (60) | Endothelin (4300) | Complement factor D (27,000) | Indole-3-acetic acid (175) |
| Creatinine (113) | Insulin (5200) | FGF-23 (32,000) | Hippuric acid (179) |
| Uric acid (168) | PTH (9225) | α1-Microglobulin (33,000) | Carboxymethyl-lysine (204) |
| Glucose (180) | $\beta_2$-Microglobulin (11,800) | Erythropoietin (34,000) | Indoxyl sulfate (251) |
| | Resistin (12,500) | Lambda FLC (45,000) | Acrolein (56) |
| | Cholecystokinin (12,700) | Albumin (68,000) | |
| | Cystatin C (13,300) | AOP (various) | |
| | | AGEP (various) | |

Abbreviations: ANP, atrial natriuretic peptide; PTH, parathyroid hormone; FLC, free light chains immunoglobulin; FGF-23; fibroblast growth factor-23; AOP, advanced oxidation products; AGEP, advanced glycation end products.*Protein-bound molecules are small size solutes, but difficult to clear from circulation as they are protein-bound.

**Table 1.** Examples of different sizes (molecular weight-Daltons) of solutes and uremic toxins.

as β2-microglobulin has been shown to be efficiently removed by high-flux dialyzers, but the quantity of removal was much more efficiently done by online HDF [21, 25].

The HDF technique, which is based on physiologic principles of diffusion and convection and the need of large volume of fluid substitution (≥23 L/session or 55–75 L/week) [23, 24] together with higher blood flow rate (350 ml/min or more), is also based on the use of high-flux dialyzers. However, high-flux dialyzers are limited in their ability to remove larger-size uremic toxin such as κ and λ free light chains. The recent innovation of medium cut-off membranes [19], which has been shown to remove adequate concentrations of different and larger size uremic toxins, including myoglobin, pro-inflammatory cytokines and λ free light chains, are expected to support patients with retention of high contents of uremic toxins, erythropoietin-resistant anemia and malnutrition-inflammation syndrome, and possible positive impact on cardiovascular and all-cause mortality [15, 26, 28]. This type of dialyzer can be used on regular HD machine with usual blood flow rate (about 300 ml/min), dialysate flow rate (500 ml/min), conventional treated water (bacterial growth <100 U/ml and endotoxin <0.25 EU/ml) and without the need of fluid replacement [28]. Other types of improved dialyzers include membranes that are internally grafted with heparin, which have been used alone [29] and/or in conjunction with minimal systemic anticoagulation [30] or with citrate-containing dialysate [31] to dialyze patients at risk of bleeding and those who are in need of heparin-free HD. Furthermore, heparin-avoidance has also been successfully implemented using airless HD tubing. These tubing allow blood to flow in a circular and nonturbulent manner, where blood exposure to plastic is less than the conventional bloodlines [32].

Over recent years, there has been a significant improvement in the quality, modalities and techniques of PD and HD provided to patients with AKI and patients with chronic kidney disease (CKD) reached end-stage renal disease (ESRD). PD treatment has benefited from a better understanding of the molecular mechanisms involved in solute and water transport across the peritoneum, the advances in PD technology and in particular catheter placement, types of PD solutions, better connecting systems with significant reduction in peritonitis rate, and the improved technology of new generation of automated compact easy-to-use cyclers with remote monitoring and management [33]. This latter advanced technology allowed nephrologist and renal nurses in clinics to monitor PD patients at home and enable them to detect early technical problems, nonadherence to treatment and ability to remotely change the prescription [22, 27]. This proactive medical care can also reassure patients of continuous support by their clinical team [34]. Over many years, PD treatment has shown several beneficial clinical outcomes and numerous advantages over that of HD. These advantages include better survival during the first 1–2 years of therapy especially among nondiabetic and younger diabetic patients, better preservation of residual renal function and consequently better survival rate, delaying the need for vascular access, supporting patients with multiple vascular access failure, hemodynamic stability in older age group with cardiovascular disease, lower risk of infection with hepatitis B and C, better outcome after transplantation with lower incidence of acute kidney injury and delayed graft function, lower costs than HD and better quality of life (reviewed in [35]). PD, when there are no contraindications, has been considered an excellent initial choice and first treatment option.

Acute or temporary dialysis is needed in some patients with AKI, who cannot adequately benefit from conservative management, and/or in critically ill patients with severe AKI with

or without multiorgan failure in ICU. Both HD and PD modalities have been used to treat patients with AKI [36–39]. However, AKI patients with sepsis, multiorgan failure and on ventilators in ICU have benefited from modern specific HD machines that permit safe and reliable therapy, easy performance and monitoring and are capable of performing continuous renal replacement therapy (CRRT) with multiple modalities [40–42]. These well-developed techniques include sequential ultrafiltration, continuous venovenous HD, continuous venovenous HF and continuous venovenous HDF [43]. CRRT with HDF has been shown to provide better clinical outcomes than intermittent HD or sustained low efficiency HD (SLED) techniques [44] in providing fluid balance control, hemodynamic stability, early renal recovery and improvement in intracranial hypertension and brain edema [23, 39, 45, 46]. CRRT is also recommended in patients with fulminant hepatic failure and those in need for extracorporeal life support therapies [39, 47]. In patients with AKI and sepsis, the removal of inflammatory mediators (e.g., endotoxin and pro-inflammatory cytokines) by high cut-off membranes [48] and by specific adsorbers [49–51] has contributed to improved hemodynamic stability. More recently, specific dialyzers for the removal of excess carbon dioxide ($CO_2$) have contributed to reduce the need for endotracheal intubation [52, 53]. In addition, it has been found that the addition of extracorporeal $CO_2$ removal to therapy with CRRT and lung protective ventilation in patients with both adult respiratory distress syndrome and AKI was associated with a significant reduction in $PaCO_2$ and a significant increase in arterial pH [54].

This book, with its specifically selected chapters by distinguished authors, covers different aspects of dialytic modalities and related clinical scenarios. These chapters include an update on recent advances in dialysis therapies, body composition and its clinical outcome in maintenance HD patients, wide coverage of uremic toxins, high-efficiency HDF, cardiovascular disease in dialysis patients, cardiovascular risk factors in ESRD patients such as the impact of conventional dialysis *versus* online HDF, cardiovascular disease and allelic variants of the gene methylenetetrahydrofolate reductase in patients on HD, endotoxin-removal columns and other cytokine extracorporeal purification techniques, extracorporeal circuit patency in CRRT, RRT in burn patients, clinical application of bioimpedance spectroscopy in dialysis patients, lymphangiogenesis and peritoneal membrane failure during dialysis, and development of HD machines.

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