Chapter 20

Advances in Hemodialysis Techniques

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1. Introduction

Hemodialysis (HD) is a technique that is used to achieve the extracorporeal removal of waste products such as urea and creatinine and excess water from the blood when the kidneys are in a state of renal failure. HD is the most prevalent modality of renal replacement therapy for patients with kidney failure followed by kidney transplantation and peritoneal dialysis.

Hemodialysis treatment is provided for critically ill patients with acute kidney injury as inpatient therapy. More commonly, HD is routinely provided for stable patients with end-stage renal failure (ESRF) as an outpatient therapy conducted in a dialysis outpatient facility, either a purpose built room in a hospital or a dedicated stand-alone clinic. Less frequently HD is done at home, where it can be self-initiated and managed or done jointly with the assistance of a trained helper who is usually a family member.

The principle of HD is the same as other methods of dialysis; it involves diffusion of solutes across a semipermeable membrane. HD utilizes counter current flow, where the dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit. Counter-current flow maintains the concentration gradient across the membrane at a maximum and increases the efficiency of the dialysis. Fluid removal (ultrafiltration) is achieved by altering the hydrostatic pressure of the dialysate compartment, causing free water and some dissolved solutes to move across the membrane along a created pressure gradient. Urea, creatinine and other waste products, potassium, and phosphate diffuse into the dialysis solution. However, concentrations of sodium and chloride in the dialysate solution are similar to those of normal plasma to prevent loss. Sodium bicarbonate is added into dialysate in a higher concentration than plasma to correct blood acidity. A small amount of glucose may also be added to dialysate solution [1].

This chapter will focus on the recent advances in HD techniques, and illustrate and compare the different HD modalities that can achieve a better quality of life than the conventional HD treatment.

2. Background

Conventional HD remains the main modality of renal replacement therapy for patients with end-stage renal disease (ESRD) worldwide [1-5]. The technique of conventional HD is based on the physiologic principle of "*diffusion*", which means clearance or removal of high concentration of uremic toxins (in the blood) to the lower concentration solution (dialysate) through a semi-permeable membrane (the dialyzer or filter) [6]. Conventional HD is usually conducted over four hour duration three times per week for stable patients with ESRD. The dialyzer or filter used is usually of low-flux type, and the filtered molecules are water-soluble small-size (molecular weight< 500 Dalton) compounds.

Conventional HD treatment had over many years improved the survival rate of patients with ESRD [2] (figure 1a, 1b). However, this basic modality of dialysis is far from replacing the function of the normal kidneys. In fact, conventional HD prescription provides only about 10% of the clearance power of the natural kidneys [7]. Although it is capable of removing excess water and small size uremic toxins, yet conventional HD is not capable of removing middle and large size (>500 Dalton) and protein-bound toxic molecules [8]. These middle- and large-size molecules, which cannot be cleared and could be harmful, include β_2-microglobulin (β_2-M), which is strongly associated with carpal tunnel syndrome and dialysis-related amyloidosis [9], and pro-inflammatory cytokines and severe vasoactive molecules such as p-cresol and uridine adenosine tetraphosphate (table 1). The accumulation and retention of all types and sizes of uremic compounds (and excess water), which have concentration-dependent toxicity, leads to increased morbidity and mortality. Furthermore, the unphysiologic pattern of conventional intermittent HD (three times per week) with rapid change in fluid volume and electrolytes and uremic solutes serum concentrations results in permanent disequilibrium of internal milieu and inter and intra-dialysis complications [10].

Conventional HD has been associated with frequent intradialysis complications (hypotension, sickness and cramps) and post-dialysis complaints of headache, fatigue and inability to concentrate and function, which may impair significantly the quality of life, result in poor compliance, inconsistency in achieving HD prescription and inadequacy of HD sessions. Inadequate HD is mainly due to poor compliance and non-adherence to HD regimens (e.g. fluid restriction, regular attendance of dialysis sessions and adherence to four hours session) and the clearance limitations of the conventional HD technique. It has been shown that skipping at least one dialysis session is associated with a 25%-30% increase in the risk of death [4]. Moreover, even patients attending regular HD sessions are at increased risk of death, heart attacks and hospital admissions (for myocardial infarction, congestive heart failure, dysrhythmia and stroke) on the day after the two-day interval between HD treatments each week than at other times [11]. Inade-

quate HD delivery also has cost implications as a consequence of increased hospitalization rate; days stay at hospital and inpatient expenditures [12].

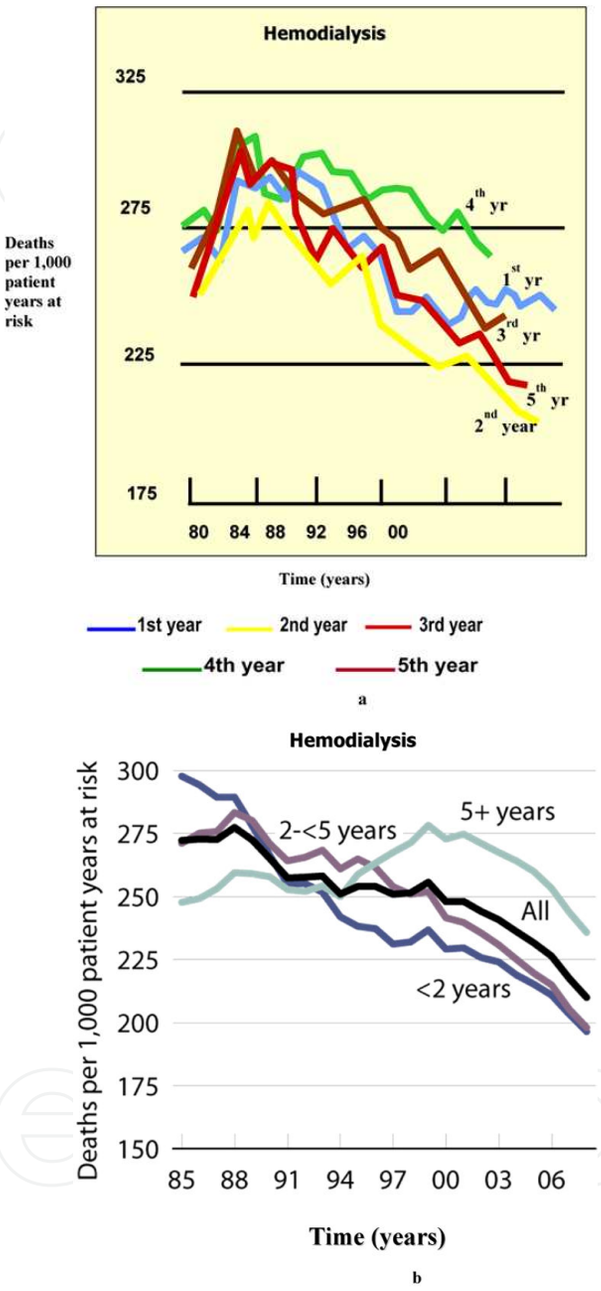

Figure 1. a: The undeniable clinical progress in hemodialysis reflected by the significant drop in mortality rates in incident ESRD patients from 1980-2010. *U.S. Renal Data System, the data supplied by the United States Renal Data System (USRDS): 2010 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010.* **b:** The undeniable clinical progress in hemodialysis reflected by the significant drop in mortality rates in incident ESRD patients from 1980-2010. *U.S. Renal Data System, the data supplied by the United States Renal Data System (USRDS): 2010 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2010*.

Small Water Soluble Molecules (MW <500 Daltons)	Middle Molecules (MW >500 Daltons)	Protein-Bound Molecules (MW >500 Daltons)*
Sodium (23)	Adrenomedullin (6032) (potent hypotensive peptide)	Hippuric acid (insulin resistance and glucose intolerance)
Phosphorus (31)	AGE*	Homocystein (atherogenecity and thrombogenecity)
Potassium (35)	AOP*	Indoxyl sulfate (pro-inflammatory effect & endothelial dysfunction)
Urea (60)	Vitamin B12 (1355)	- *p*-cresylsulfate – *p*-cresol (endothelial and pro-inflammatory)
Creatinine (113)	Endothelin (4238) (strong vasoconstrictor)	Polyamines (inhibit erythroid colony growth in a dose-dependent way)
Uric acid (168)	PTH (9225)	
Glucose (180)	β_2-M (11800)	
	Leptin (16000)	
	Cytokines (15000-30000)	
	Immunoglobulin LC (28000 – 56000 Da)	
	Uridine adenosine tetraphosphate (very strong vasoconstrictive)	

Table 1. Examples of types and sizes of different uremic toxic molecules.

Patients managed with conventional HD are potentially exposed to hemodynamic instability, excessive intradialytic weight gain, anemia, mineral and bone metabolism disorder, inadequate nutrition, infection and sexual and psychosocial problems. The increased risks of fatal and non-fatal cardiovascular complications, which are the main cause of death in HD patients, continue to be much higher than in the general population. It has been reported that only 32% to 33% of patients on conventional HD survive to the fifth year of treatment [13]. In fact, the mortality rate in conventional HD ranges between 14-26% in Europe [14, 15] and 24% in USA [1, 2]. Actually, conventional HD does support life but has failed to restore the patient to full functional normality and longevity.

Quality management of dialysis patients is best achieved by implementation of "pre-dialysis care" [16], and care improvement at "post dialysis" stage [17]. Post-dialysis care should ensure strict control of infection [18, 19] and predominance of arterio-venous fistula (avoidance of indwelling catheters for vascular access) [20]. Furthermore, dialysis care should include (1) adequate control of body fluids (achievement of euvolemic status), where strict volume control has been shown to reduce both morbidity and mortality and dialysis ade-

quacy outcomes [21, 22], (2) mitigation of left ventricular hypertrophy and fibrosis, and (3) efficient removal of all types and different sizes of retained uremic toxic solutes that would result in inflammation and exacerbation of cardiovascular damage [20]. Actually, improvement in quality HD care should achieve optimum HD rather than adequate HD.

The aim of HD technique has, and will always be, to simulate or reproduce the physiologic process of glomerular ultrafiltration. Conventional HD, which is performed over 4 hour duration and conducted three times per week, does not fulfill this criterion [1]. The major deficiencies of this technique are limited solute clearance and volume control, which have been associated with poor quality of life [23] and unacceptable high rates of morbidity and mortality [2, 14, 15, 24, 25].

Over the past four decades it has been suggested that the accumulation of various 'uremic toxins', and in particular middle-size and protein-bound molecules, contribute to this increased mortality. These toxins include urea, phosphorus, parathyroid hormone (PTH), β_2-microglobulin, homocysteine, leptin and a variety of esoteric molecules such as advanced glycation end products, asymmetric dimethylarginine and advanced oxidation protein products [8, 26, 27]. Furthermore, the persistence of increased interdialytic weight gains and the limited ability of conventional HD to maintain adequate homeostasis, without frequent episodes of hypotension and increased risk for cardiovascular and all-cause mortality [28], results in failure of many HD patients to achieve adequate volume control and remain permanently volume overloaded [21]. This has been associated with increased prevalence of hypertension, left ventricular hypertrophy and increased cardiovascular mortality, as a major cause of death, among patients treated with conventional HD [21, 29].

Observational studies [30-35] and randomized controlled trials [36, 37] of improving the efficiency of hemodialysis, by increasing frequency and duration of HD treatment, demonstrated better clearance efficiency of uremic toxins and volume control, and improved quality of life. However, the recent innovations in HD technologies paved the way for better quality HD. These include higher specifications of HD machines, creation and improvement in dialysis membranes with different transport (clearance) capabilities of middle, large and even protein-bound molecules by using all the available membrane separation phenomena: diffusion, convection and adsorption, and quality improvement in the technology of water treatment plants, with almost nil presence of bacteria growth and endotoxin concentration. Based on different observational studies and randomized clinical trials and new innovations, this chapter illustrates the possible and available options of different advances in HD techniques, their influence on improving the adequacy of HD, the patient's quality of life and the reduction in morbidity and mortality rates.

3. Adequacy of hemodialysis

The adequacy of HD is usually assessed and measured by Kt/V [38]. This represents the product of clearance (K) per time multiplied by the duration (t) and adjusted for body size by dividing this clearance by the distribution volume (V). Kt/V reflects the clearance of urea,

as a surrogate marker for the clearance of small, but not middle or large-sized, uremic toxins. The single-pool Kt/V overestimates the delivered dose of dialysis, because it fails to account for blood urea rebound after dialysis. A more accurate measure of the dialysis dose, the equilibrated Kt/V, corrects for urea rebound and is usually 0.15 to 0.20 lower than the single-pool Kt/V. Ideally, single-pool Kt/V should not be below 1.4, as lower values have been associated with increased morbidity and costs [12], and reduction in survival rate [39-41]. The efficacy of HD, where low flux dialyzers are usually used, is limited by its inability to clear from circulation the middle or large-size or protein-bound toxic molecules. Increasing the dose of dialysis or using high-flux dialyzer membrane can help in ensuring optimal values of Kt/V. However, the hemodialyis (HEMO) Study, which was a randomized clinical trial, did not alter survival or morbidity by increasing the dose of dialysis or using a high-flux dialyzer membrane [42].

Adequacy and efficiency of HD can be increased by avoiding intradialytic hypotension episodes and frequent interruption of the 4 hours HD session. This can be achieved, in part, by controlling intradialytic weight gain (<4%) by fluid intake and sodium restriction and lowering dialysate sodium concentration [43], and avoiding rapid ultrafiltration (not to exceed 10 ml/Kg/hr), where exceeding this limit has been associated with increased risk for cardiovascular and all-cause mortality [28, 29]. The adequacy and efficiency of HD can also be improved by increasing the blood [44-47] and dialysate [48, 49] flow rates and the dialyzer size and surface area [50, 51]. However, recent improvements in dialyzers technology, such as hollow fiber undulations, spacer yarns and changes in fiber packing density [52], have led to improvement in dialysate flow distribution through the dialysate compartment (with improved urea clearance) and reduced the need of increasing dialysate flow rate from 600 ml/min to 800 ml/min; an achievement with important economic impact allowing a significant reduction (25%) in water consumption [53].

4. Efficient hemodialysis

The efficiency of HD is largely dependent on arterial blood flow rate from a well-preserved and functioning vascular access [44-47]. The vascular access is the life-line for end-stage renal disease patients on regular hemodialysis. There are three major types of vascular access: arterio-venous fistula (AVF), arterio-venous graft (AVG) and central venous catheter (CVC). The type of vascular access is associated with patient outcome. Despite the recent improvement and advanced technology of catheters, temporary and permanent catheters have been associated with increased incidence of luminal thrombosis, central venous stenosis, inadequate blood flow rate, inadequate dialysis, increased risk of infection, increased risk of hospitalization, increased risk of death and high cost [54-61]. AVG has also been associated with bleeding, infection and graft failure. The KDIGO guidelines published in 2001 [62] defined the ideal vascular access as that which (a) delivers a flow rate adequate for the dialysis prescription, (b) has a long use-life, and (c) has a low rate of complications (infection, stenosis, thrombosis, aneurysm and limb ischemia). Although none of the major types of vascular access fulfills all of these criteria, the native AVF is the closest to this definition [62].

The "Fistula First Breakthrough Initiative" [63] was established in 2003, where a goal set to have 40% AVF use in prevalent US hemodialysis patients. This goal was achieved in 2005. The bar was subsequently raised to 66% AVF use, a level which was comparable to that achieved in several European countries [64]. The current USA prevalent AVF use rate by network is about 60% but incident AVF use rate by network is still below 20% [65]. DOPPS 4 of 2010 Study showed Australia, New Zealand and some European countries (France, Italy and Germany) have achieved more than 70% AVF use compared with Japan who achieved more than 90% [65].

5. Compatible hemodialysis

Dialyzer membranes used to be made primarily of cellulose (derived from cotton linter). The surface of such membranes was not very biocompatible, because exposed hydroxyl groups would activate complement in the blood passing by the membrane. More recently, membranes have been made from synthetic materials, using polymers such as polyarylethersulfone, polyamide, polyvinylpyrrolidone, polycarbonate, and polyacrylonitrile [66]. These synthetic membranes activate complement to a lesser degree than unsubstituted cellulose membranes. Synthetic membranes can be made in either low- or high-flux configuration, but most are high-flux. Nanotechnology is being used in some of the most recent high-flux membranes to create a uniform pore size. These recent innovations in the technology of dialysis membranes have resulted in improvement of their biocompatibility and anti-thrombotic effect, as well as in their hydraulic and perm selective properties [67].

The contact and interaction of blood with artificial surfaces within the extracorporeal circuit (dialyzer, needles, catheters, tubing, and the arterial and venous bubble traps) induces profound activation of plasmatic coagulation [68]. Further risk factors for clotting of the extracorporeal circuit include slow/turbulent blood flow, excessive ultrafiltration (due to hemoconcentration), high hematocrit, and blood transfusions into the extracorporeal circuit [69]. This non-physiological environment leads to activation of platelets, leukocytes, and the coagulation cascade, resulting in fouling of the membrane and ultimately in clotting of fibers and the whole hemodialyzer. As hemodialysis requires access to the circulatory system and the passage of blood in the blood lines and the dialyzer, anticoagulation is vital to maintain the in- and outflow of blood through the extracorporeal circuit and dialyzer without clotting. There have been different anticoagulants used to prevent thrombosis in the blood circuit. These include unfractionated heparin, low molecular-weight heparin, natural and synthetic heparinoids, direct thrombin inhibitors, prostanoids, saline flushes and citrate infusion or citrate based dialysate [70]. Heparin has been the most commonly used anticoagulant as it is generally well tolerated, easily administered, low cost, short biological half-life, and can be quickly reversed with protamine sulfate [69]. However, long-term use of heparin can expose hemodialysis patients to thrombocytopenia, hypertriglyceridemia, osteoporosis, hypersensitivity, alopecia, metabolic disturbances, and hypotension [70]. Furthermore, there are some patients at high risk of bleeding, where heparin cannot be used. The recent improvement and innovation in dialysis membranes have yielded high-flux membranes graft-

ed with unfractionated heparin that can be used to avoid or reduce the exposure to systemic heparin [71].

6. High-flux hemodialysis

The creation of larger pore size semipermeable membranes in compact cartridges (high-flux dialyzers), with variable sizes of these pores, enhanced their ability to remove small solutes and 'middle molecules' [66]. High-flux dialyzers allow the passage and removal of retained solutes of higher molecular weight than do low-flux membranes. Dialyzers are considered as high-flux type if their ultrafiltration coefficient (KUF) exceeds 15 ml/h/mmHg and their ability to clear β_2-M exceeds 20 ml/min (low-flux dialyzer clears KUF <15 ml/h/mmHg and β_2-M < 10 ml/min) [50]. However, the fluids (dialysate and water) used with these high-flux dialyzers should be sterile non-pyrogenic and endotoxin free in order to avoid reverse filtration of endotoxins and blood contamination [72]. Microbiological contamination of water is a serious health concern for patients on dialysis. Therefore, it is essential to regularly monitor both bacteria and endotoxin levels in the water used for dialysis especially with high-flux dialyzers and for patients treated with online hemofiltration or hemodiafiltration.

Conventional and high efficiency HD techniques, using low-flux dialyzers, are incapable of removing larger sized uremic toxins and/or protein-bound toxic molecules of > 500 Dalton (table 1). This would result in their accumulation in circulation where they can exert concentration-dependent toxicity, particularly on endothelium and cardiovascular system. Examples of these molecules include uridine adenosine tetraphosphate and endothelin [27], which exert vasoconstrictive effect, indoxyl sulfate and p-cresylsulfate – p-cresol, which has pro-inflammatory effect and cause endothelial dysfunction together with the pro-inflammatory cytokines, and has been associated with increased cardiovascular mortality [73]. Other retained molecules which are known to cause harmful effects include β_2-M, immunoglobulin light chains, parathyroid hormone, advanced glycation end products [74] and advanced oxidation products [27, 75, 76].

Beta 2-microglobulin, which is considered a surrogate marker of middle molecules, is strongly associated with carpal tunnel syndrome and dialysis-related amyloidosis [77]. Different studies have documented the efficiency of high-flux dialyzers in removing β_2-M from the circulation of patients on dialysis, which has been associated with clinical and radiological improvement of carpal tunnel syndrome and dialysis-related amyloidosis [78]. In addition, high-flux HD has been shown to be superior to peritoneal dialysis in clearing β_2-M and the protein-bound middle molecule p-cresol [71]. Furthermore, observational studies have documented the improvement of survival rates of patients on high-flux-dialyzers when compared with those on low-flux dialyzers [9, 79-82]. These findings have been confirmed by two large randomized clinical trials: the HEMO study and the MPO study. In the entire cohort in the HEMO Study the high-flux arm had no significant effect on the all-cause mortality rate or any of the four arm secondary outcomes. However, the high-flux HD provided significantly less cardiac and cerebrovascular mortality rates after 3.7 years HD than low-

flux HD [42, 83, 84]. The Membrane Permeability Outcome (MPO) study, which was conducted in Europe, showed higher survival rate in high-flux HD patients with low serum albumin (≤ 4 g/dl) and diabetic patients [85]. Following these two major studies, the European Best Practice Guidelines have recommended the use of high-flux dialyzers in patients at high risk (serum albumin < 4 g/dl) and even in low-risk patients [86]. Ever since, high-flux dialysis has surpassed low-flux use worldwide [87].

7. Super high-flux hemodialysis

New 'super high-flux' membranes for hemodialysis have been developed with a high cut-off pore size allowing efficient removal of middle and large size uremic toxin molecules that cannot be removed by conventional dialysis membranes. The recent availability of a new generation of hemodialysis membranes with molecular weight cut-offs closer to that of the native kidney (65000 Dalton) has led to great benefits in several different clinical settings. These membranes have shown efficient removal of myoglobin in patients with rhabdomyolysis [88], efficient and direct removal of free light chains and other plasma components [89], and greater clearance of inflammatory cytokines than conventional high-flux membranes [90]. They also have a positive impact on restoration of immune cell function, attenuation of hemodynamic instability and decrease in plasma interleukin-6 levels in septic patients with acute kidney injury [91]. However, albumin loss may be a disadvantage of these membranes, though albumin losses can be replaced by infusion of human albumin solution [90].

8. Adsorption hemodialysis

Despite the efficiency of removing middle-size uremic toxin molecules by high-flux HD, yet this technique is still incapable of removing larger-size and, more importantly, the protein-bound uremic toxins. Protein-bound uremic toxins are, in fact, small in size but become larger molecular weight compounds (50,000 – 200,000 Dalton) once are bound to different types of proteins depending on their binding affinity. Protein-bound uremic toxins have been potentially involved in important uremia co-morbidities such as itching and altered immune response caused by the retained and deposited free molecules (κ-type and λ-type) of the immunoglobulin light chain in internal organs [92-95].

Removing protein-bound uremic toxins from the blood by means of diffusion and convection is virtually impracticable. The technology of dialysis membranes have yielded thicker type of membranes (more than conventional 1 micron thickness) that have a great affinity to stick larger size molecules to their surfaces, hence known as adsorptive membranes [96]. Adsorption can occur at the outer surface of the membrane when molecules cannot pass through the pores of the membrane and/or within the inner membrane matrix when the molecules can permeate the membrane [97]. Synthetic membrane micro porous zeolite silica lite (MFI) has been shown to be quite effective in adsorbing high levels of the protein-bound

solute P-cresol [98], which is not eliminated efficiently by conventional HD. Furthermore, the synthetic thick polymethylmethacrylate (PMMA) membranes (30 micron thickness), which have good solute permeability and a high degree of biocompatibility, do have high adsorptive capacity reaching up to 160,000 Dalton [99].

Recent studies have shown a variety of efficient clinical implications for adsorption HD. The use of PMMA membranes has been shown to ameliorate the severity and frequency of pruritis [95] in HD patients due to adsorption of a 160,000 Dalton molecular weight molecule with stimulatory effect on mast cells [100]. PMMA membranes also efficiently adsorb β_2-M (representative of middle molecules), where they have been shown to improve carpal tunnel syndrome or total joint pain score in HD patients [99]. In addition, patients dialyzed with PMMA membrane have lower need for erythropoietin due to the elimination of an inhibitor of erythropoesis retrieved in the dialysate [101]. Furthermore, the free molecules (κ-type and λ-type) of the immunoglobulin light chain (Bence Jones protein), which accumulate at high levels in the blood of HD patients [102] may lead to various protein deposits in the internal organs and act as inhibitors of leukocyte and immune function in dialysis patients. These molecules, which usually exist as dimmers (56,000 Dalton) and not removed by high-flux HD, are significantly removed by HD with PMMA membrane [103] in patients with primary amyloidosis [104] and in patients on HD resulting in reduction in pain and frequency in analgesic treatment [105]. In addition, PMMA (BK-F) membranes have been shown to be quite effective in removing soluble CD40 from circulation of patients on HD. Soluble CD40, which mostly coexists as dimeric and even higher oligomerized forms of 50,000 and 150,000 Dalton, respectively [106], acts as natural antagonist of the CD40/CD40L contact [92, 106, 107] and have been associated with a lack of response to hepatitis B vaccination. The efficient removal of these molecules by PMMA membranes have been associated with improved response to hepatitis B immunization [94].

Finally, adsorption techniques have been used successfully, in conjunction with plasma filtration and hemofiltration, in clearing efficiently pro-inflammatory mediators in experimental animals [108] and in humans with acute kidney injury and sepsis [109]. This is known as "coupled plasma filtration adsorption" (CPFA) technique, where the treatment consists of the separation of plasma from the whole blood, using a plasma filter with high cutoff membrane of 800,000 Dalton, coupled with adsorption of the inflammatory mediators and cytokines from plasma, using a cartridge contains hydrophobic resins, followed by hemofiltration using a hemofilter.

9. Frequent hemodialysis

A significant improvement in efficiency of HD can be achieved by increasing the duration and frequency of dialysis sessions [110]. Different studies have confirmed that dialysis duration of less than 4 hours was associated with increased mortality rate by up to 42% [24, 25, 29]. By contrast, increasing the duration of dialysis, independent of blood or dialysate flow rates, to 8 hours has been associated with significant improvement in clear-

ance of urea, creatinine, phosphorus, uric acid and even β_2-M, but not much of protein-bound toxic molecules [29, 111, 112].

Another approach to improve the efficiency of HD is by increasing the frequency of HD sessions. This can be achieved by avoiding the two days weekend gap and implementation of in-center every other day dialysis [11, 113]. A recent study of analyzing records of 32,000 people receiving dialysis three times a week from 2005 through 2008 found a 22% greater risk of death on the day after a long break, compared with other days. In particular, stroke and heart-related hospitalizations more than doubled on the days after the long break [11]. The efficiency of HD can also be improved by short daily dialysis [30, 34, 36, 111, 114], long slow nocturnal dialysis [32, 33] or home daily or nocturnal HD [35, 51], instead of three HD sessions per week.

Home, and in particular nocturnal, HD is probably the most convenient and efficient modality of HD. It can be performed on daily basis or at night at most suitable times, where the patient on nocturnal HD dialyzes for about twice the time (approximately eight hours per session) of conventional in-center HD sessions. This ensures a better chance that the patient will not be under-dialyzed; therefore, more toxins and fluids may be removed. Because this process occurs more slowly, there is less of a chance of cramping and hypotension episodes during dialysis [35]. Unlike conventional HD, patients on nocturnal HD do not report the "washed out" feeling after longer dialysis (no need to take a nap after treatment). Different studies have repeatedly confirmed the strong positive impact of nocturnal or more frequent dialysis on ultrafiltration rate (much better control of fluid excess), clearance of uremic toxins and adequacy of dialysis [36]. The better ultrafiltration rate has been associated with better control of blood pressure [33, 36, 37], where the majority of dialysis patients discontinued antihypertensive medications after 6-12 months of daily/nocturnal dialysis [30, 115]. Increasing dialysis frequency, and in particular nocturnal HD, has also been linked to significant improvement in renal anemia [31, 116] and reduction in erythropoietin dosage and iron supplements [115], significant reduction in left ventricular mass index [33, 36, 117], improvement in mineral metabolism and significant reduction in phosphorus binders [33, 36, 37, 114], improvement in nutritional status [30, 118], enhanced quality of life [33, 36, 119] and increased cumulative survival rate [34]. Moreover, patients on nocturnal HD have a similar survival rate as that in deceased kidney transplant recipients [120].

Despite its great benefits (Table 2), the implementation of daily/nocturnal HD has not gained much attraction among patients, treating physicians and decision makers. Kjellstrand et al [34] contributed the slow and difficult introduction of daily dialysis to multiple factors including logistic problems, conservatism by physicians and nurses, patient worries and worries about expenses by governments and administrators, which is expected to be a major obstacle. However, the clinical and quality of life improvement brought by daily/nocturnal HD has been associated with dose reduction in different pharmaceutical medications (antihypertensive medications, phosphorus binders and erythropoetin dosage and iron supplements), extended use of dialyzers and tubing and decreased waste production and transportation upon implementation of home HD, and significant reduction in hospitalization and morbidity (and mortality) rates, all of which may result in reduction in manage-

ment costs and total annual expenses [32, 119]. A recent economic assessment model for in-center, conventional home and more frequent home HD has shown that home-based conventional and more frequent HD are similar in cost to in-center HD in the first year but can be less costly than in-center HD from the second year onward [121]. The higher cost for more frequent home HD in first year is mainly due to higher consumables usage due to dialysis frequency. Frequent home HD (and conventional home HD), however, have been associated with much lower hospitalization costs than for in-center HD treated patients in first and subsequent years.

1	Improved uremic toxins and fluid removal
2	Less cramping and no "washout" feeling
3	Less hypotension episodes, better blood pressure control, less antihypertensive drugs
4	Improvement in anemia, reduction in EPO dose and iron supplements
5	Reduction in left ventricular mass index
6	Improvement in mineral metabolism and reduction in phosphorus binders
7	Improvement in nutritional status
8	Enhanced quality of life
9	Reduction in hospitalization rates and costs
10	Increased cumulative survival rate

Table 2. Benefits of Frequent (Daily/Nocturnal) Hemodialysis

10. Hemofiltration and hemodiafiltration

Attempts to increase the intensity or "dose" of HD with higher blood and dialysate flow rates, larger and adsorptive membranes and longer and more frequent dialysis sessions have improved the adequacy of HD, but failed to bring about the desired improvement in outcome [36, 37, 42, 83-85]. Recent innovations in the HD techniques have resulted in advancements in specifications of HD machines, HD medical devices, sterile ultrapure solutions and high quality water treatment plants [122]. These advancements have largely contributed to the ability to reconsider the implementation of the other physiologic principle of "convection" [123, 124]. This means that larger size uremic toxins can be dragged and removed from blood by filtering large volume of fluid pushed under high hydrostatic pressure through a larger pore size membrane (high cut-off membrane/high-flux dialyzer). This technique is known as "hemofiltration". Fluid balance is maintained by infusion of replacement solutions, which can be administered before the filter (pre-dilution) or after the filter (post-dilution). These solutions are infused directly into blood in order to replace the large volume of filtered fluids (convection volume). The replacement solutions, which also referred to as substitution fluid, are mixed with the blood and should, therefore, be sterile non-

pyrogenic and endotoxin free buffered solutions with a composition similar to plasma water. Combination of the two physiologic principles of diffusion (hemodialysis) and convection (hemofiltration) in the management of patients with ESRD is known as "hemodiafiltration" [6]; a technique that has been described and implemented in 1974 [123] and a treatment modality that simulate to a large extent the natural function of a normal kidney.

11. Online hemodiafiltration

The implementation of hemofiltration (HF) or hemodialfiltration (HDF) as a renal replacement therapy in patients with ESRD requires the supply of large quantities of replacement solutions. These solutions are usually industrially prepared in autoclaved expensive plastic bags, which have been used in earlier studies, in order to fulfill the requirement of sterile non-pyrogenic and endotoxin free buffered solutions [125]. However, the need of large quantities of these bags makes the implementation of this technique rather costly and impractical. The recent advancement and improvement in the performance of water treatment plants that are capable of producing ultrapure water (almost nil bacterial growth and endotoxin free) have greatly contributed to the success of this technique [15, 126]. Such quality of water, which is available continuously and in unlimited amounts at the dialysis machine during each treatment, has been used directly from the water treatment plant to form the dialysate and the replacing solutions for the HDF [125], and hence this technique is known as "online hemodiafiltration" [127].

Online HDF offers the most physiologic clearance profile for a broad range of small, medium-sized and large toxic molecules (table 1). Like conventional HD, online HDF session is usually performed three times per week as an outpatient treatment that usually lasts for four hours. Prescription of effective online HDF should ensure higher blood and dialysate flow rates, ultrafiltration not less than 20% depending on the mode of HDF (it differs between post and pre-dilution HDF), and substitution/replacement fluids 5-25 liters/session. Earlier studies defined replacement fluids of 5–14.9 liters/session as low-efficiency HDF, and replacement fluids of 15–24.9 or more liters/session as high-efficiency HDF [15, 112]. However, the data from recent randomized controlled studies: CONTRAST [128, 129] and Turkish [130] studies suggested a convection volume higher than 15 liters in the post-dilution mode should be targeted in order to achieve successful HDF.

The implementation of both physiologic principles of diffusion and convection has enabled HDF, and in particular online HDF, over that of HD (low- and high-flux) in achieving better adequacy of dialysis and better clearance of small and middle-size uremic toxins [131]. In clinical practice, HDF (low- and high-efficiency) has been shown to be more effective than HD (low-flux and high-flux) in achieving significantly higher values of Kt/V (averages of 1.37 and 1.44 versus 1.35 and 1.33, respectively) [15].

Hyperphosphatemia, which has been associated with vascular calcification and considered as an independent predictor of mortality in dialysis patients [132], has been well controlled with efficient removal of phosphorus by online HDF [113, 129, 133] with marked reduction

in phosphate binders [113]. Furthermore, the reduction ratio of β_2-M per session has been shown to be 20–30% higher with online HDF than with high-flux HD (72.7 versus 49.7%) [134]. Likewise, online high-efficiency HDF achieves higher serum free light chain removal than high-flux HD in multiple myeloma patients [135]. In addition, HDF is highly efficient in clearing other larger solutes such as myoglobin (16000 Dalton), retinol-binding protein (25000 Dalton) and the protein-bound p-cresol than high-flux HD [131, 136]. It has also been shown that online HDF efficiently reduces the circulating levels of advanced glycation-end products [74, 137]. The efficient removal of different types and sizes of uremic toxins by online HDF [138] has been associated with reduction of skin pigmentation [139], promotion of catch-up growth in children on chronic dialysis [140] and nutritional status improvement [141]. More recently, Maduell et al [113] have demonstrated a remarkable improvement in nutritional status with adequate social and occupational rehabilitation.

Online HDF is empowered with biocompatible high-cut-off membranes, ultrapure water and efficiency of removal of pro-inflammatory stimuli including oxidative stress molecules, advanced glycation end-products, homocysteine [142], p-cresol and pro-inflammatory cytokines, all of which would ensure abolishing virtually the possibility of stimulation of an inflammatory process in dialysis patients [124]. This effect of online HDF, at least in part, has been shown to improve the patients' responsiveness to erythropoetin and reduce the requirement of erythropoietin stimulating agents [143].

Hemodiafiltration, and in particular online HDF, had attracted much attention in recent years as a promising optimum modality of HD [144]. In addition to its efficient improvement in dialysis adequacy and clearing small and large-size uremic toxins [145], HDF significantly reduced inter-dialysis symptoms including less fatigue and cramps together with effective correction of intradialytic haemodynamic instability and blood pressure control [146, 147], especially for elderly, heart-compromised or patients prone to hypotension. A recent study by Maduell et al [113], where high volume (high efficiency) online HDF combined with more frequent (every-other-day nocturnal 7-8 hours) dialysis sessions, showed marked improvement in hypertension control with a substantial reduction in drug requirements and regression of left ventricular hypertrophy; an independent cardiovascular risk factor which has been associated with mortality in dialysis patients [148, 149].

Finally, observational studies have shown the benefit of online HDF in decreasing the mortality rate in patients on dialysis [150, 151]. Canaud et al [15] reported a significant 35% lower mortality risk with high-efficiency HDF compared to low-flux HD. Jirka et al [151] also observed a 35.3% reduction rate in mortality risk in online HDF-treated patients after adjustment for age, co-morbidities, and time on dialysis. More recently, in a randomized clinical trial the subgroup of HDF patients treated with a substitution volume over 17.4 liter per session (n=195), cardiovascular and overall survival were better than both the HDF subgroup with substitution volume ≤17.4 liter per session (n=196) (p=0.03) and the HD group (p=0.002). Primary outcome was similar in these 3 groups (85.2%, 83.8% and 81.2%, respectively, p=0.26). In adjusted Cox-regression analysis, HDF with substitution volume over 17.4 L was associated with a 46% risk reduction for overall mortality [RR=0.54 (95% CI 0.31-0.93),

p=0.02] and a 71% risk reduction for cardiovascular mortality [RR=0.29 (95% CI 0.12-0.65), p=0.003] compared to HD [130].

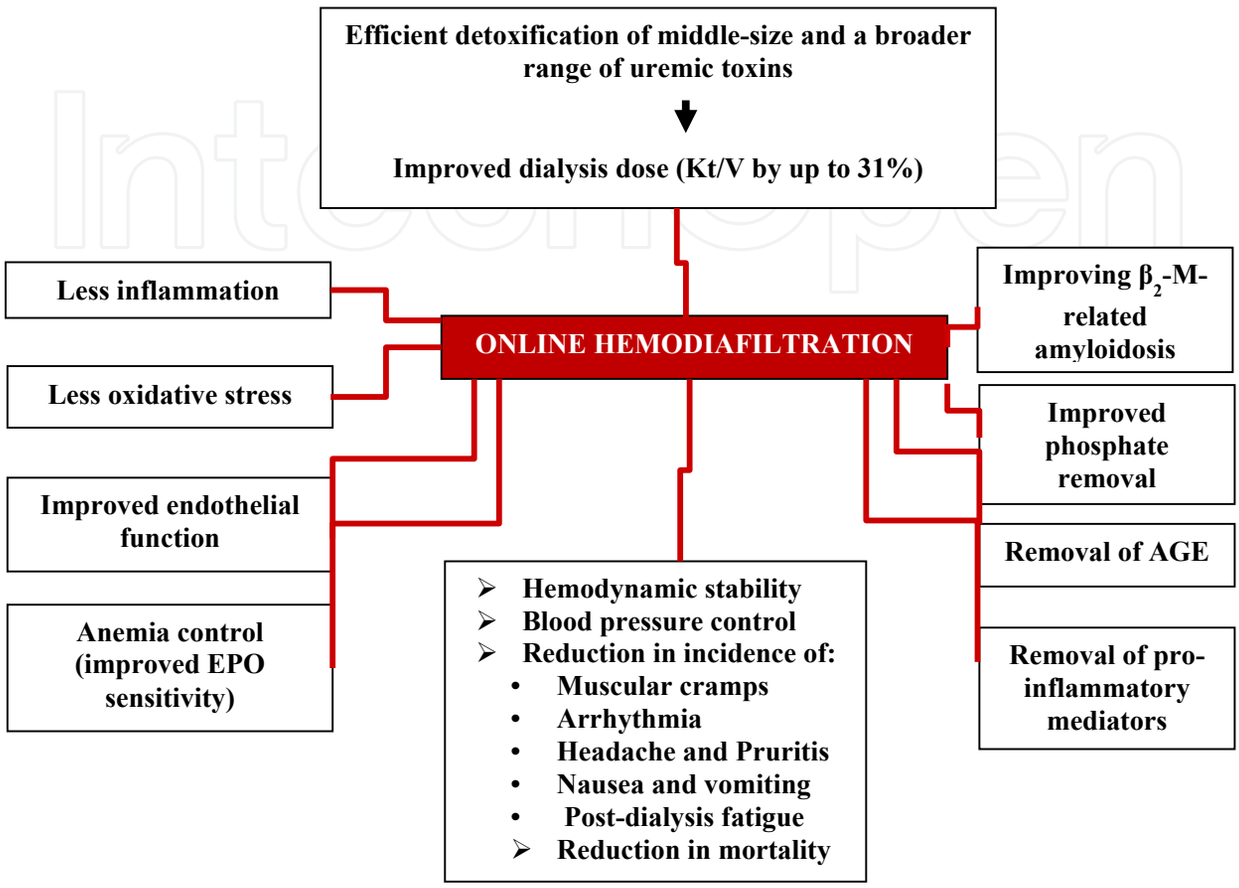

Figure 2. Benefits of online hemodiafiltration EPO: Erythropoetin, β_2-M: Beta 2-microglobulin, AGE: Advanced glycation end-product

The performance, success and benefits of online HDF (figure 2), however, depends on availability of special requirements. These include (1) experienced nephrologists and nursing staff, (2) high quality water treatment plant that can provide ultrapure water (bacterial growth < 0.1 colony factor unit/ml and endotoxin level < 0.03 endotoxin unit/ml) with frequent assessment of water quality [152-154], (3) dialysis machine specially designed and approved for online fluid preparation, (4) high-flux dialyzers and (5) good functioning vascular access with adequate blood flow. These essential requirements for ensuring successful online HDF therapy may incur extra costs and may limit its widespread implementation. However, training of medical and nursing staff is achievable, high flux dialyzers have already be recommended and in use in conventional HD with lower cost, different quality online HD machines are becoming cheaper and more affordable, and investing in quality ultrapure water treatment plant should not be a major barrier toward implementation of this premium modality of HD. In fact, investing in these requirements would not only improve the quality of life of dialysis patients but reduce the rates of morbidity and mortality. Fur-

thermore, additional savings can be achieved by (1) reduction in the costs associated with hospitalization due to high morbidity rate of conventional HD [12, 155], (2) less requirements of phosphate binders due to better clearance of phosphorus [114], (3) better control of hypertension with less use of antihypertensive drugs [114], (4) less doses required of erythropoietin stimulating agents (ESA) and iron supplements, due to improved sensitivity to ESA as a result of abolishing or reducing the inflammatory response [125], and (5) improved hemodynamic stability, with no or less frequent hypotension episodes [114, 147], and consequently less consumption of normal saline and human serum albumin.

12. Continuous hemodialysis

Continuous renal replacement therapy (CRRT) is defined as "any extracorporeal blood purification therapy intended to substitute for impaired renal function over an extended period of time and applied for or aimed at being applied for 24hrs/day" [156]. CRRT modalities include slow continuous ultrafiltration (SCUF), continuous HD, continuous hemofiltration (HF), and continuous hemodiafiltration (HDF) [157]. SCUF technique is based on passing the blood through the dialyzer without dialysate or replacement fluids, and is basically used to remove excess body fluids as in patients with congestive heart failure and pulmonary edema [158]. The technique of continuous HD is similar in principle to that of intermittent/conventional HD except that it is continuously applied for a longer period of time and at slower blood (100-200 ml/minute) and dialysate (40-70 ml/minute) flow rates. The techniques of hemofiltration (HF), which is based on the physiological principle of convection (dialysate is not used but replacement fluids) and hemodiafiltration (HDF), which based on the physiological principles of diffusion and convection (both dialysate and replacement fluids are used), are the same as those described earlier in this chapter, but are applied in continuous format and over a long period of time [159]. These techniques/modalities of CRRT are usually applied and used for critically ill patients with septic acute kidney injury and/or multi-organ failure in intensive care units. Other indications include cardiopulmonary bypass, fulminant hepatic failure, rhabdomyolysis, respiratory distress syndrome, severe burns, cerebral oedema, and tumor lysis syndrome [160]. The dialysis dose effect in these treatment modalities is assessed by adequacy and efficiency of fluid balance (and replacement/effluent fluids volume in HF/HDF), electrolyte balance, acid-base balance, and removal of small and middle-size uremic toxins [161]. Although expensive, these modalities provide smooth dialysis without fluctuation, hemodynamic/cardiovascular stability, improved fluid balance, removal of inflammatory mediators, allow supportive measures (nutrition), steady biochemical correction, and possibly improve survival rate [162, 163]. The disadvantages of these techniques include necessity for continuous anticoagulation, hypothermia, severe depletion of electrolytes (particularly potassium and phosphorus), where care is not taken, immobilization of the patient, possible side effects from lactate-containing replacement fluid or dialysate, 24 hour staffing (well trained and dedicated staff) and increased cost [160].

13. Slow low-efficiency hemodialysis

This slow low-efficiency dialysis (SLED) technique combines both intermittent and continuous modalities of HD [164]. It is based on providing intermittent/conventional HD but with low blood and dialysate flow rates (100-200 ml/minute) and for longer period of time usually 8-12 hours per session usually for 5 or 6 days per week [165]. SLED technique provides a gentle reduction of small solutes clearances over prolonged periods with an efficacy comparable to that of conventional intermittent HD and continuous hemofiltration [166, 167]. It has been considered an ideal technique of HD for critically ill patients with multi-organ failure and acute kidney injury in intensive care unit (ICU). SLED technique has several advantages which include easy-to-perform treatment, flexible timing of treatment (nocturnal SLED has the benefits of unrestricted physician access to the patient during the day and minimizing the interference of renal replacement therapy with other ICU activities), reduced costs [164], and hemodynamic/cardiovascular stability [168].

In conclusion, conventional or standard HD remains a valuable and basic life-supporting treatment for ESRD patients. This modality had over many years improved the survival rate of patients with end-stage renal disease. However, standard or conventional HD prescription is far from being optimal in replacing the function of normal kidneys. Its unphysiologic clearance pattern and inability to remove all types and sizes of uremic toxins results in inter and intra-dialysis complications and an unacceptable high rate of cardiovascular morbidity and mortality. The efficiency of HD can be improved by increasing blood and dialysate flow rates, the dialyzer size and surface area, and by increasing the duration and frequency of dialysis sessions. Home HD, where short daily or long slow nocturnal HD sessions can conveniently be performed, provides an excellent choice for quality of life improvement and reduction in morbidity and mortality. SLED technique is an ideal modality for critically ill patients in ICU with multiple organ failure and acute kidney injury. The recent innovations in the specifications of HD machines, HD medical devices and the improvement in dialysis membranes characteristics including the high-flux dialyzers, and water treatment technology paved the way for achieving quality HD. These advancements have resulted in efficient implementation of adsorption, diffusion and/or convection principles using adsorption HD, hemofiltration, hemodiafiltration and online hemodiafiltration modalities aiming at achieving optimum HD. High-flux dialyzer provides significantly less cardiac and cerebrovascular mortality rates, and has been associated with higher survival rate in dialysis patients with low serum albumin and diabetic patients. Therefore, since there have been no better results with low-flux dialyzers, high-flux dialysis should not be limited to high risk dialysis patients. Online HDF is an ideal HD technique with much less morbidity and mortality rates. In fact, online HDF is considered currently as the premium modality of HD that ensures optimum dialysis. Therefore, these HD modalities, and particularly online HDF, should be considered more seriously, if financial and human resources are available and/or affordable, to replace conventional HD should we aim at improving the quality of life and reducing the morbidity and mortality rates among HD patients, which are still unacceptably high, and reducing the costs associated with conventional HD.

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