Pediatric Hemodialysis Prescription, Complications, and Future Directions

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Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
ACE	Angiotensin converting enzyme
ARB	Angiotensin II receptor antagonists
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
BVM	The Blood Volume Monitor ™
cIMT	Carotid intima-media thickness
CKD	Chronic kidney disease
CRP	C-reactive protein
DDS	Dialysis disequilibrium syndrome
DOPPS	Dialysis Outcomes and Practice Patterns Study
ECV	Extracellular volume
eKt/V	Equilibrated Kt/V
ESA	Erythropoiesis stimulating agent
ESRD	End-stage renal disease
G	Urea generation rate
HD	Hemodialysis
HDF	Hemodiafiltration
IVC	Intracellular volume
IVC	Inferior vena cava
K	Urea clearance
KDOQI	National Kidney Foundation Dialysis Outcomes Quality Initiative
KoA	Mass transfer coefficient of urea
K_{uf}	Ultrafiltration coefficient
LAVI	Left atrial volume indexed to height
L-carnitine	Levocarnitine
LMHW	Low molecular weight heparin
LV	Left ventricular
LVH	Left ventricular hypertrophy
LVH	Left ventricular hypertrophy
NCDS	National Cooperative Dialysis Study
NIVM	Non-invasive blood volume monitoring
nPCR	Normalized protein catabolic rate
PTH	Parathyroid hormone
RBV	Relative blood volume
spKt/v	Single pool method
TAC-urea	Timed-average-concentration of urea
TBV	Total blood volume
TBW	Total body water
UF	Ultrafilter/ultrafiltration
UFH	Unfractionated heparin
URR	Urea reduction rate
USRDS	United States Renal Data System
V	Volume of distribution unless otherwise specified

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Introduction

Hemodialysis (HD) was introduced as a practical treatment for uremia at the end of the Second World War [1]. A decade later, Mateer et al. reported the first experience using HD to treat five uremic children, aged 15–17 years, using 15 m Cellophane tubing and a 32 l dialysis bath. Each dialysis procedure was 13 h, and although the metabolic and fluid status of their patients improved, there were challenges related to anticoagulation of the circuit and achieving normal plasma calcium and potassium levels [2]. Maintenance HD was not practical because vascular access required cannulae placed in the radial artery and saphenous vein prior to each session. This problem was overcome by the development of silastic arteriovenous cannula by Scribner et al. [3] which were inserted in the forearm vessels and could be used for repeated blood access. What followed was the report by Fine et al. [4] describing the use of HD for maintenance treatment of end-stage renal disease (ESRD) in five adolescents who were dialyzed three times weekly for 7–8 h per session using a concentrated dialysis solution mixed with tap water. A urea clearance of 45 ml/min resulted in a urea reduction rate (URR) of 48 % during each 7–8 h treatment. While maintenance HD was now a realistic option for children with ESRD, technical difficulties persisted in small children and the need for 20 h of treatment per week required long periods of time in the hospital.

In 1971, Kjellstrand et al. reported their experience treating ten children <15 kg [5]. Applying data from adults receiving dialysis, the authors recommended a urea clearance in children based on body weight, with a goal of urea clearance 2–3 ml/kg/min during each dialysis session. This clearance, multiplied by the number of hours of dialysis, allowed accurate prediction of the expected fall in urea during a single session (Fig. 66.1). This reduced the risk of disequilibrium syndrome from excessive drops in urea and established a standard formula for dialysis urea clearance in children still used today in many dialysis units.

Despite the initial success of the Scribner shunt, clotting and infection of the vascular access remained common. Arteriovenous fistulae reduced this problem and remain the gold standard for dialysis access. However, creation of fistulae in small children requires great surgical skill and a critical mass of patients to maintain expertise, which are not available in many centers [6]. These technical challenges, combined with the desire to avoid repeated needle punctures in small children, led

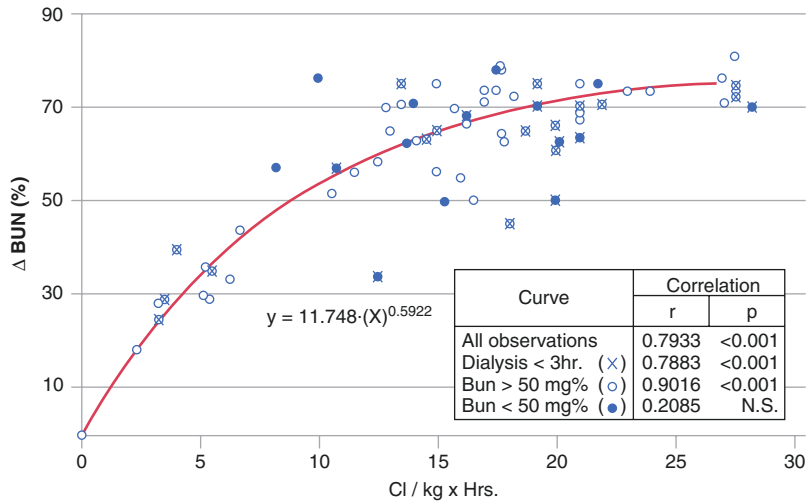

Fig. 66.1 Prediction of the expected fall in urea during a single hemodialysis session (From Kjellstrand et al. [5]. With permission from Dr. Kjellstrand)

Mahan et al. to use a Hickman central venous catheter for prolonged HD vascular access in children [7]. Central venous catheters have since become the most widely used HD access [8]. While allowing children to obtain puncture-free HD, catheters have a high rate of clotting and infection, and therefore should only be used for long term access, when creation of a suitable fistula is not possible.

Technological improvements over the last 50–60 years have made HD widely available for children with ESRD. While overall and cause-specific mortality have decreased for children initiating maintenance dialysis over the last two decades, children with ESRD continue to experience unacceptably high rates of morbidity and mortality compared to the healthy pediatric population [9]. Improvements in dialysis equipment, medications, and consensus treatment guidelines are likely responsible for better patient outcomes (Fig. 66.2) [9]. Today, children often receive less than half the weekly HD treatment time compared to when the therapy first became widely available [4]. To dramatically improve outcomes further may require a fundamental change to the "standard" thrice weekly HD prescription. Initial experiences using short daily or nocturnal dialysis, which improves wellbeing and mortality in adults [10, 11], involving small numbers of children are very positive [12, 13], although widespread application remains futuristic due to logistic and funding barriers.

Prescribing Hemodialysis

Most of the HD literature reports on adults, with less data available in pediatric patients. In theory, the principles learned from adults are universal and applicable to children, but adjustments are required to accommodate the spectrum of age, weight, and physiological development that are specific to children. Ideally, children should receive ESRD treatment at specialized pediatric centers with the necessary technical expertise, staffing, and multidisciplinary resources (physicians, nurses, dieticians, social workers, teachers, and child-life specialists) to provide optimal care [14]. The two primary objectives of HD are to clear metabolic waste products and to ultrafilter (UF) excess fluid. To achieve these goals, the prescriber must calculate adequate clearance and estimate the patient's dry weight. To complete the HD prescription, one must then choose the blood flow rate, dialyzer, extracorporeal tubing, dialysate composition, and anticoagulation.

Adequacy

The publication of the National Cooperative Dialysis Study (NCDS) in 1981 [15, 16] addressed how dialysis might best reduce patient morbidity and mortality by comparing four

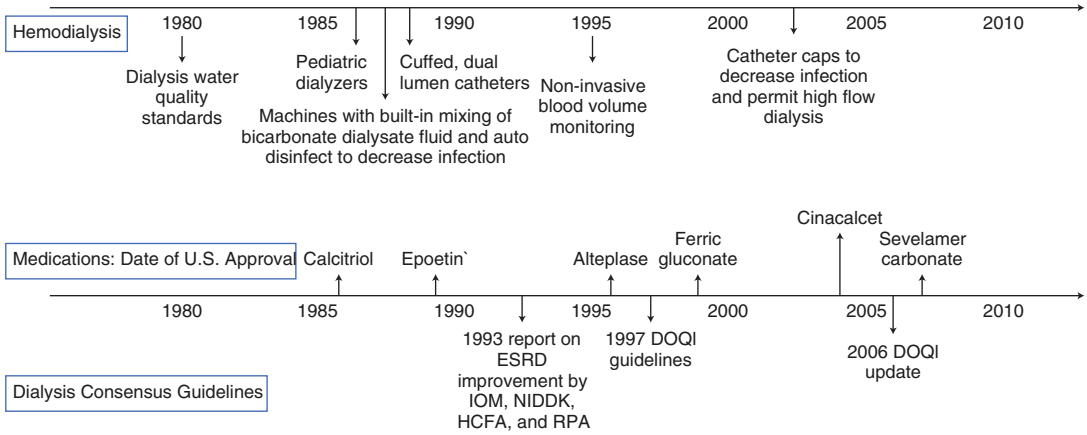

Fig. 66.2 Improvements in hemodialysis from 1980 to 2010 (Used with permission of American Medical Association from Mitsnefes et al. [9])

groups of patients with high or low timed-average-concentration of urea (TAC-urea) and with either long (4.5–5 h) or short (2.5–3.5 h) dialysis sessions. The results showed that the TAC-urea was the most important determinant of patient morbidity and hospitalization. In a subsequent analysis of the NCDS using a single-pool urea kinetic model, Gotch and Sargent argued for the use of Kt/Vurea to measure the adequacy of dialysis [17]. This unitless measure is an estimate of the clearance of urea from the blood during a dialysis session, standardized by total body water (which reflects the urea distribution volume). Kt/V urea has become the standard measure of the delivered dialysis dose and the adequacy of dialysis.

Various methods for calculating Kt/V have been proposed. The single pool (spKt/V) method assumes urea is removed from a single pool and so a delayed post-dialysis sample is not required. However, this method overestimates urea clearance because it ignores urea rebound post-dialysis from access recirculation, cardiopulmonary recirculation, and tissue redistribution. Access recirculation becomes insignificant within 15–20 s of the blood flow being reduced to <50–80 ml/min. Cardiopulmonary recirculation only occurs with arteriovenous access and not with central lines. It is a result of blood returning to the dialyzer after circuiting the heart and lungs without passing through the other tissues and ceases 1–2 min after slowing blood flow. Conversely, urea tissue rebound continues over a longer time because there is diminished blood flow to muscle, which has high urea content, during dialysis [18]. Urea rebound is minimized by using either of the following two methods proposed by National Kidney Foundation Dialysis Outcomes Quality Initiative (KDOQI) guidelines [19]. With the slow blood flow method, the dialysate is turned off and the UF is minimized at the end of dialysis. The blood flow is then decreased to <100 ml/min for 15 s and then the urea sample is obtained. Using the stop dialysate method, the same protocol is used, except the blood flow is maintained at a normal rate for 3 min prior to drawing the post-dialysis urea sample. Standardization is important, especially because different results for Kt/V have been shown in children, depending on which day of the week laboratory studies are performed [20].

The double pool Kt/V recognizes that post-dialysis rebound of plasma urea may be substantial. Therefore, a urea sample drawn 60 min post-dialysis is required to avoid the overestimatation of urea removal. This method is probably the most accurate estimate of Kt/V, but the difficulty of obtaining a delayed post-dialysis blood sample and lack of validation studies have limited its use.

Calculating Kt/V with urea kinetic modeling requires sophisticated computer algorithms which may not be available in many pediatric dialysis units. However, websites including Hypertension Dialysis and Clinical Nephrology (www.hdcn.com) and www.Kt-v.net provide programs for calculation of single and double pool Kt/V measurements, some of which have been used in pediatric studies [21]. The major advantage of kinetically modeled methods to estimate Kt/V is that they also provide an estimate of the urea generation rate from which the normalized protein catabolic rate (nPCR), an estimate of dietary protein intake, can be calculated. Nevertheless, several potential inaccuracies are intrinsic to the measurement of kinetically derived Kt/V. Urea clearance (K) for individual dialyzers is derived from the manufacturer's specifications which do not account for recirculation or reductions in dialyzer efficacy due to clotting of dialysis fibers or interruptions in treatment from kinked lines. Also, determining the urea distribution volume (V) may be imprecise, particularly in children [22].

To overcome these limitations, more simplified equations for calculating Kt/Vurea have been proposed [23]. One such formula [Kt/V= −LognR−0.008t+4−3.5RUF/BW] estimates the spKt/V where R is the ratio of the pre-dialysis to post-dialysis urea, t is the time of dialysis in hours, UF is the ultrafiltration volume in liters, and BW is body weight in kg. This formula varies by only 6 % from formal urea kinetic modeling in children [21]. To correct for post-dialysis urea rebound, additional equations have been developed to calculate the equilibrated (eKt/V) in patients with arteriovenous [eKt/V= spKt/V–0.6×spKt/V/T+0.03] or venovenous

[eKt/V=spKt/V−0.47×spKt/V/T+0.02] access. Standardized (stdKt/V) formulas are available to estimate the Kt/V over a week, which are useful in patients receiving more frequent or intensified dialysis regimens [22, 24].

Finally, the URR measures the percentage decrease in blood urea during a dialysis session. The URR as a marker of dialysis adequacy was evaluated retrospectively in 13,473 patients, and the mortality rate increased by 28 % when URR values of <60 % were obtained [25]. Despite its validation as a measure of morbidity, URR is not recommended as the primary measure of dialysis adequacy because significant variations of Kt/Vurea may be obtained with each URR value, particularly when URR is greater than 65 %. Also, with increasing UF, URR underestimates urea removal. Nonetheless, targeting a URR of <50 % for the first several treatments in a patient initiating chronic dialysis is a useful means of preventing dialysis disequilibrium. As no upper limit of Kt/Vurea has been established, care must be taken with aggressive treatment even in patients who have been on dialysis for a long time as excessive urea removal can lead to symptoms of dialysis disequilibrium.

KDOQI guidelines published in 2000 recommended that the delivered dose of HD in both adults and children should be measured using formal urea kinetic modeling with a spKt/V urea of at least 1.2. In 2002, the HEMO Study randomized 1,846 patients on conventional thrice weekly HD to either a standard or high-dose of dialysis as well as to a low-flux or high-flux dialyzer. In high-dose patients, the URR was 75 % and spKt/V 1.71, compared with standard-dose patients whose Kt/V was 1.32 with a URR of 66 %. Neither dialysis dose nor dialyser flux affected the relative risk of death. The authors concluded that there was no major benefit from a higher dialysis dose than recommended by KDOQI or from the use of high-flux dialysis membranes [26].

However, dialysis dose may be associated with mortality in relation to body mass index (BMI). In patients with lower BMI, a URR of >75 % was associated with a lower risk of death compared to patients with a URR of 70–75 % [27]. Daugirdas et al. found that by normalizing Kt/V to body surface area, most children less than 10 years of age would receive less dialysis compared to older patients, despite acceptable eKt/V and stdKt/V values [22]. Theoretically, it is tempting to postulate that there may be a survival advantage in increasing the HD dose in women and patients with a low BMI, such as children.

In the adult dialysis population as a whole, the Dialysis Outcomes and Practice Patterns Study (DOPPS) review of 22,000 adult HD patients from seven countries found that a higher dialysis dose, as reflected by a higher Kt/V, was important and an independent predictor of lower mortality. Survival was greatest when combining a higher Kt/V with a longer treatment time. For every 30 min longer on HD, the relative risk of mortality was reduced by 7 % [28]. Reports from the Australian and New Zealand Dialysis and Transplant Registry and the United States support that longer treatment times, notably those >4–4.5 h, are associated with a lower risk of death, independent of adequate clearance [29, 30]. Such research sets the scene for intensified dialysis programs (see below), namely a move away from conventional 3–4 h, three-times-per-week dialysis to more frequent and/or more prolonged dialysis sessions.

The KDOQI guidelines for HD adequacy were revised in 2005 to recommend a minimum spKt/V urea of 1.2 per session, with a target spKt/V of 1.4 and URR of 70 %. These recommendations were consistent with the minimal Kt/V reported in the HEMO Study and also the European Guidelines for Hemodialysis, which endorsed a spKt/V of 1.4–1.5 [31]. However, no large scale studies have assessed HD adequacy in children. Buur and colleagues compared two urea kinetic models with direct quantification of urea removal and found that although each method produced different results, correlation between the methods was very high [32]. The authors commented that for practical purposes, and to limit blood sampling, one of the direct single-pool methods of urea kinetic modeling should be used. More recently, a study of eight children <18 years of age compared an online urea monitor (UM 1000™, Baxter Healthcare) with single

Table 66.1 Published guidelines for hemodialysis adequacy

Source	Urea clearance	Other
KDOQI, adults	Minimum spKt/V ≈ 1.2	URR ≈ 65 %
	Target spKt/V ≈ 1.4	URR ≈ 70 %
European, adults	eKt/V >1.2	Double-pool urea kinetics preferred
	spKt/V ≈ 1.4	
KDOQI, children	spKt/V >1.4	Assess nutrition (nPCR)
		Optimize ultrafiltration
European, children	eKt/V ≥1.2–1.4	Assess nutrition (nPCR)
		Monitor growth and cardiac function

and double-pool formulas and separately with single-needle dialysis [33]. They found considerable differences in Kt/V urea between single and double pool formulae and concluded that online urea monitoring was inaccurate during single-needle dialysis.

Despite the limited data in children, expert working groups have developed guidelines for HD in children both in Europe and North America [14] together with European adult guidelines [31]. These are summarized in Table 66.1. We recommend maintaining a spKt/Vurea between 1.4 and 1.8 in children dialysed for 3–4 h per session. It is imperative that the prescribed dialysis dose for an individual child should be based on more than just an estimate of urea removal. Achieving optimal dialysis must also include a careful clinical assessment including growth, nutrition, cardiovascular health (especially blood pressure (BP)), anemia treatment, and the bone and mineral health of a developing child [34].

Estimation of Dry Weight

Ultrafiltration is targeted to an estimated 'dry weight.' Dry weight is most commonly defined as the post-HD weight at which the patient is as close to euvolemia without experiencing symptoms. Overestimation of the dry weight places patients at risk of developing volume-dependent hypertension, left ventricular hypertrophy (LVH), and congestive heart failure. An underestimation of the dry weight increases the risk of symptoms from intradialytic volume depletion. In children, growth and changes in lean body mass and body habitus necessitate regular and frequent re-evaluation of the dry weight to detect subtle differences in the ratio of total body water to body mass. Therefore tests for evaluating dry weight have to be easily accessible, reproducible, and ideally non-invasive.

The clinical examination is the most widely used test; however, at best, it only provides a crude assessment of volume status. In children with ESRD, even the most sensitive signs are rendered imprecise. For example, a number of factors can result in hypotension during fluid removal (cardiac dysfunction, low vascular tone, hypoalbuminemia) and thus changes in orthostatic vital signs are not diagnostic of true hypovolemia. Jugular venous distension, though infrequently assessed in children, is a useful sign in the assessment of central venous pressure, provided heart failure is absent [35].

Biochemical markers including plasma atrial natriuretic peptide and brain natriuretic peptide correlate with increased plasma volume in ESRD [36], but levels can also remain elevated in volume contracted individuals and hence they lack the ability to detect volume depletion. Brain natriuretic peptide appears superior to atrial natriuretic peptide in predicting left ventricular hypertrophy and dysfunction. However, in the context of defining dry weight, results have been variable [37].

Ultrasound guided supine inferior vena cava (IVC) diameter measurement and its decrease on deep inspiration, better known as the collapse index (CI = end expiratory IVC diameter minus end inspiratory IVC diameter)/end expiratory IVC diameter), have been shown to correlate with right atrial pressure and circulating blood volume [38]. Results are influenced by wide interpatient variability, lack of validated normal values for children, the timing of the measurement in relation to dialysis, and the presence of heart failure or tricuspid regurgitation. Although it is a non-invasive test which could conceivably

become available at most centers, it cannot reliably predict dry weight in children.

Bioelectrical impedance technology can directly assess extracellular volume (ECV), intracellular volume (ICV) and total body water (TBW) by detecting differences in the degree of resistance (impedance) as electric currents pass through each fluid compartment. At low frequencies, current cannot cross cell membranes and only flows through ECV; at higher frequencies it flows through both the ICV and ECV. Three methods for assessing dry weight using bioimpedance are available: (1) The normovolemia/hypervolemia slope method uses whole body multi-frequency bioimpedance spectroscopy to measure the ECV (Fig. 66.3) [39]; (2) The resistance-reactance graph method uses whole body single-frequency bioimpedance analysis to estimate TBW, but is unable to separate ECV from ICV, and therefore only useful when trying to differentiate between excessive body water and true weight gain; [40] (3) The continuous intradialytic calf bioimpedance method records changes in extracellular resistance in real-time, generating a curve whose slope flattens as excess ECV is removed and thus dry weight has been achieved (Fig. 66.4) [41]. Premature flattening of the curve may occur in the presence of venous thrombosis or lymphatic edema. The value of bioimpedance techniques to estimate dry weight in pediatrics is unknown and limited by incomplete data in children and from patients with ESRD, and the inherent underestimation of TBW with multifrequency bioimpedance methods. Importantly, changes in electrolyte, red cell counts, protein concentrations, and patient temperature are all known to influence bioimpedance. Bioimpedance may be used more frequently as increasing evidence from clinical studies validate its assessment of fluid status [42, 43].

Finally, on-line non-invasive blood volume monitoring (NIVM) is commonly used in clinical practice. NIVM provides information on intradialytic blood volume changes and vascular refilling rates. The magnitude of blood volume changes differs between patients and dialysis sessions but if combined with post-dialytic vascular compartment refilling rates, dry weight can be assessed. Vascular refilling typically occurs in the first 10 min after stopping UF and is characterized by an increase in the relative blood volume (RBV) which can continue for up to 60 min. Steuer et al. achieved a twofold reduction in intradialytic symptoms using NIVM in six hypotension prone adults, without reducing the UF volume or treatment times [44]. Others have shown an increase in the UF potential, lowering

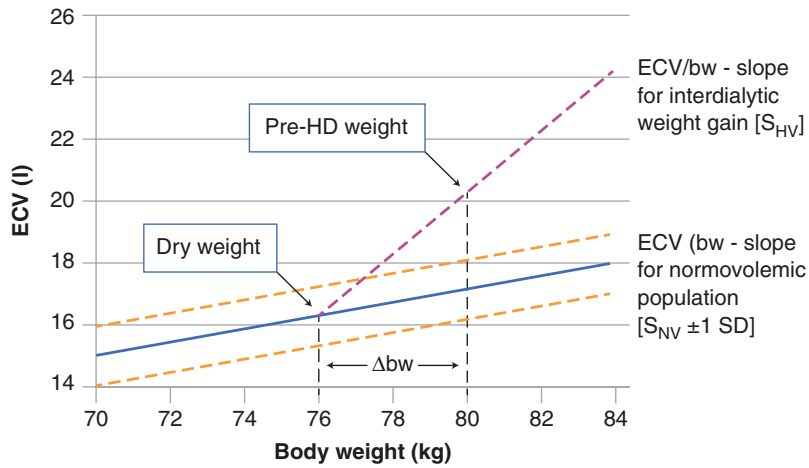

Fig. 66.3 Bioelectrical impedance to estimate dry weight using the normovolemia/hypervolemia slope method with whole body multi-frequency bioimpedance spectroscopy [39] (Used with permission of Wolters Kluwer Health from Kuhlmann et al. [225])

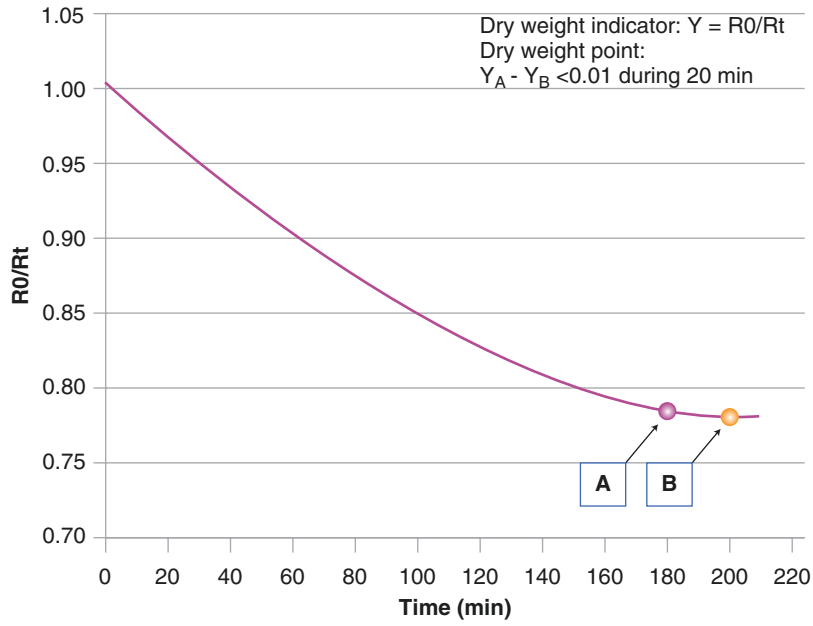

Fig. 66.4 The continuous intradialytic calf bioimpedance method generates a curve whose slope flattens as excess volume is removed and thus dry weight has been achieved [41] (Used with permission of Wolters Kluwer Health from Kuhlmann et al. [225]

of the dry weight, improved patient well-being and reduced hospitalization due to fluid overload.

NIVM is based on the principle of mass conservation: the concentration of measured blood constituents (hemoglobin/haematocrit/plasma protein) confined to the vascular space is proportional to changes in the vascular volume. Individual NIVM devices differ by their intrinsic sensing technique. Optical devices measure the absorbance of monochromatic light via an optoprobe in the arterial line to estimate the hematocrit because the optical density of whole blood is a measure of red blood cell concentration. The Crit-line™ (Fresenius, Bad Homburg vor der Höhe, Germany) is a stand alone device, while the Hemoscan™ (Hospal-Dasco, Medolla, Italy) is a component of the dialysis machine. Blood density monitors are dependent on the total protein concentration (plasma protein concentration + mean cellular hemoglobin concentration). The Blood Volume Monitor™ (BVM, Fresenius AG, Bad Homburg, Germany) measures the velocity of sound through blood, as a reflection of blood density, by means of a cell inserted in the pre-pump segment of the arterial line. Schneditz et al. demonstrated a 2% difference in RBV changes between the Crit-line and BVM which developed 1 h into dialysis and persisted thereafter [45].

NIVM is used to divide patients into four groups. Group 1: Absence of post-dialysis refilling with no symptoms suggestive of intra-dialytic hypovolemia or post-dialytic fatigue: the patient is likely to be at their dry weight. Group 2: Post-dialysis refill, lack of a substantial change in blood volume during HD, and no intra-dialytic or post dialytic symptoms: indicative of extracellular fluid expansion and the need to lower the patient's dry weight. Group 3: Absence of post-dialysis refill, intra-dialytic and/or post dialytic symptoms: indicative of hypovolemia and the need to increase the dry weight. Group 4: Post-dialysis refill but intradialytic symptoms of hypovolaemia: indicative of slow vascular refilling rates, but ECV expansion at the end of dialysis. This suggests that the dry weight needs to be reduced incrementally and slowly following changes to the dialysis prescription to increase the UF potential. Extended duration of dialysis sessions may be necessary.

Table 66.2 Summary of methods for assessing dry weight

Modality	Pros	Cons
Biochemical markers	Ease of use	Wide variability
	Noninvasive	Poor correlation with volume depletion
		Not available at most laboratories
		Inaccurate in patients with congestive heart failure
Inferior vena cava diameter	Correlated with right heart pressure and intravascular volume	No normative values for children
	Noninvasive	Technician dependent
		Cost
		Limited availability
		Unclear which time after HD to measure
Bioimpedance	Measures ECFV and ICFV, estimating fluid shifts from various compartments	Limited normative values for children
	Strong correlation with ultrafiltration volume	Unclear which time after HD to measure
		Cost
		Underestimates volume shifts from trunk
Non-invasive blood volume monitoring	Ease of use	No standardization across devices
	Ease of interpretation	Requires active intervention by providers
	Decreases risk of intradialytic hypotension	Only measures fluid shifts from intravascular space and refilling rates
	Validated use in children	Cost

Adapted with permission of John Wiley and Sons from Ishibe and Peixoto [35]
ECFV extracellular fluid volume, *ICFV* intracellular fluid volume

Information on blood volume status can be particularly helpful in the pediatric HD setting as the prevalence of intra- and inter-dialytic morbidity may be underestimated because children often do not verbalize early warning symptoms. Jain et al. show reduced dialysis associated morbidity with NIVM, with the greatest impact on children weighing less than 35 kg [46]. Michael observed improved targeting of the dry weight in children, which reduced the requirement for antihypertensive medication [47]. Using a constant dialysate sodium concentration of 140 mmol/L, Jain also defined a safe UF rate as an RBV change of <8 % per hour in the first 90 min and then <4 % thereafter, with no more than a 12 % net RBV change per dialysis session [46]. More recently, Hothi et al. reported in 11 pediatric hemodialysis patients that the gradient of the RBV curve in the first hour, as well as changes in heart rate, were the strongest predictors of treatment-related complications [48].

In summary, evaluating a patient's dry weight can be a challenge. The limitations and benefits of the available tests to estimate dry weight are summarized in Table 66.2. As of yet no gold standard has been defined and for the majority, applicability in pediatrics has not been validated. We recommend the use of NIVM combined with clinical assessment.

Blood Flow Rate

The blood flow rate is a major determinant of solute clearance on dialysis. With increased blood flow, more solute is delivered to the dialyzer, resulting in higher dialyser "flow limited clearance." However, clearance is also determined by the membrane's permeability to the solute, which is known as "membrane limited clearance." With poorly permeable solutes, increasing the blood flow will only produce a mild increase in clearance (Fig. 66.5). The dialyser flow clearance is

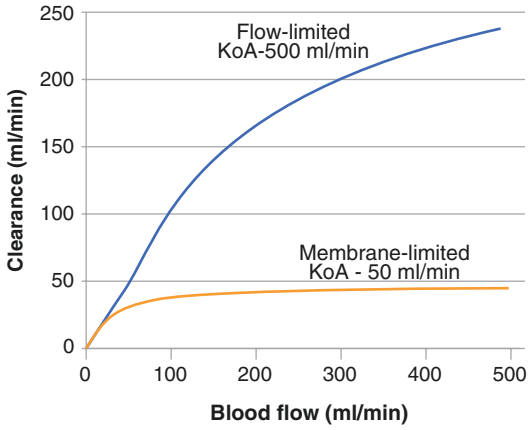

Fig. 66.5 Blood flow-limited and membrane-limited clearance (Used with permission of John Wiley and Sons from Depner [227])

limited and starts leveling off at blood flows of 250–300 ml/min, and therefore some adult dialysis units have set this as their maximum blood flow rate.

The effective blood flow rate is largely determined by the vascular access, especially in pediatrics. For chronic HD we would recommend a blood flow rate that is equivalent to 4–6 ml/kg/min urea clearance obtained from dialyser urea clearance estimates provided by the manufacturer. In infants, a minimum blood flow of 20 ml/min avoids the risk of clotting the circuit. Effective blood flows are often lower than those prescribed due to partially occlusive pumps, malposition of the vascular access needle, access failure, tubing diameter changes, and shear effects. The efficacy of dialysis is also reduced by recirculation effects which are more pronounced with higher dialyzer blood flows, vascular access inflows lower than dialyzer blood flow, stenosis at the access outflow, single lumen access particularly with small stroke volumes, increased length of blood lines, and small needle and tubing diameter [49]. This places infants with blood flows determined by small, high resistance double-lumen central venous catheters or single lumen catheters with high recirculation rates at the highest risk of inadequate dialysis with conventional dialysis regimens. This can be improved by increasing the dialysis time, which in our experience is best tolerated by increasing the frequency and not the duration of treatment.

Choice of Dialyser

When selecting a dialyser for chronic HD, several membrane characteristics need to be taken into consideration [14]. To improve efficacy, dialysers are designed to maximize the surface area available for diffusion. Two designs have predominated, namely hollow fibre and parallel plate dialysers. In the latter, parallel layers of membranes are separated by flat supporting structures. Their greatest disadvantage is their high compliance and thus large filling and priming volumes. Therefore, in children, they have largely been replaced by hollow fibre dialysers which consist of a bundle of capillaries potted at both ends into a plastic tubular housing unit with sealing material. Hollow fibre dialysers have virtually no compliance and lower priming volumes, but the sealing materials are at risk of releasing solvents or ethylene oxide after gas sterilization, and thus producing anaphylactic reactions. As a general rule, the dialyser membrane surface area should be approximately equal to the patient's body surface area.

Because the dialysis membrane is in direct contact with the patient's blood, it can initiate leucocyte and complement activation. The extent of the inflammatory response reflects the biocompatibility of the material that makes the dialyser. Three types of membranes are presently available, those made from unmodified cellulose, modified/regenerated cellulose, and synthetic membranes. Unmodified cellulose membranes, such as cuprophan, are relatively inexpensive but also the most bioincompatible. The modified cellulose membranes such as the cellulose acetate or hemophan® have some or all of the hydroxyl groups esterified to make them more biocompatible. However, such modifications may result in increased activation of the coagulation cascade and thus increase the anticoagulation requirement of the HD circuit. Synthetic membranes are made from polysulfone, polycarbonate, polyamide or polyacryl-polyamide acrylate. These

Table 66.3 Dialyser classification

Class	Surface area	K_{UF} (ml/h/mmHg)	Urea clearance	β2 microglobulin clearance
Conventional	<1.5 m^2	<12	Moderate	Negligible
High Efficiency	>1.5 m^2	>12	High (KoA >600 ml/min)	Negligible
Mid-flux	Variable	12–30	Variable	Moderate
High-flux	Variable	>30	Variable	High (>20 ml/min)

Adapted with permission of Oxford University Press from Clark and Ronco [226]

membranes are relatively biocompatible, except for the negatively charged AN69 polyacrylonitrile membranes which are known to cause hypotension, inflammatory hyperemia, oedema and pain secondary to a bradykinin mediated reactions. Dialysis patients most at risk are infants requiring a blood to prime their HD circuit [50] and children that are concurrently taking angiotensin converting enzyme (ACE) inhibitors [51] or angiotensin II receptor antagonists (ARB) [52]. Synthetic membranes are generally more hydrophobic than cellulose membranes and therefore have higher adsorption properties [53]. Their increased ability to bind proteins may be partly responsible for their improved biocompatibility and also makes them the membrane of choice for therapies such as albumin dialysis or in the treatment of acute toxicities where the undesired toxin is highly protein bound.

Membrane solute permeability refers to the clearance of middle molecular weight molecules, and is assessed by measuring the rate of β2-microglobulin clearance. Solute permeability is determined by the number of pores, the size of the pores, and the membrane wall thickness. A highly permeable membrane is one that is thin, with a high pore density and large diameter pores. Efficiency, represented as the KoA or mass transfer coefficient of urea, is a measure of urea clearance, a surrogate marker of small molecule clearance. Traditionally, membranes have been characterized as low-flux or high-flux according to their solute permeability. High-flux membranes are highly permeable membranes that can permit convective solute clearance of molecules weighing between 5,000 and 25,000 Da but urea clearance rates vary. Highly efficient membranes have high urea clearance rates but differ in their hydraulic permeability, and thus may be limited in their ability to clear middle molecules (Table 66.3).

A useful measure of the hydraulic permeability of a membrane is the K_{UF}, the UF coefficient, defined as the volume of UF produced per hour per mmHg transmembranous pressure, which is determined at a blood flow of 200 ml/min. K_{UF} is most directly influenced by the membrane's mean pore size. In turn, the mean pore size influences the solute sieving coefficient and molecular weight cut-off for a membrane. High-flux dialysers with larger mean pore sizes have a higher molecular weight cut-off and are most efficient in clearing larger uremic compounds. The ultrafiltration rate and the dialyzer membrane's sieving coefficient are the most important determinants of convective solute removal [54]. Therefore, in consideration of predominantly convective therapies such as hemofiltration or hemodiafiltration, high-flux dialysers are required.

Analyzing the United States Renal Data System (USRDS) database, Bloembergen et al. demonstrated a 20 % decrease in the relative risk of death for modified cellulose and synthetic membranes compared with cellulose membranes [55]. In a retrospective analysis of 715 patients, Woods et al. [56] compared mortality in a group treated exclusively with low-flux polysulfone dialysers with another treated for at least 3 months with high-flux polysulfone dialysers. The high-flux group had a significant 65 % reduction in the risk of death compared with the low-flux group. A Kaplan-Meier analysis suggested a higher 5-year survival in the high-flux group, but a statistically significant difference was only seen after 4 years of dialysis.

In conclusion epidemiological studies suggest improved morbidity and mortality in dialysis

patients treated with modified cellulose or synthetic membranes but few have been able to demonstrate whether the effects were due to differences in flux, biocompatibility or middle molecule clearance. Few, if any, paediatric centers practice dialyzer reuse. Reuse is associated with a reduction in the incidence of "first use" reactions, but may be associated with allergic reactions to residual sterilizing agents, such as formaldehyde. Inadequate sterilization of dialyzers may cause pyrogen reactions or frank infection, which present as fever, chills, and rigors [57].

Extracoporeal Circuit

Multiple dialysis machines are on the market, each with different sizes, weights, capabilities for home therapy, and interfaces with providers (reviewed in [58]). Regarding the extracorporeal circuit, during pediatric dialysis, if the total blood volume of the circuit is greater than 10 % of the estimated total blood volume (TBV), a circuit prime with 5 % albumin or blood is recommended. Even though traditionally blood has been preferred, these recommendations come from an era when severe anaemia was the rule for children with ESRD. However, minimizing exposure to blood products may decrease the risk of human leukocyte antigen sensitization in young children awaiting transplantation. The TBV is approximately equal to 100 ml/kg body weight in neonates and 80 ml/kg for infants and children. As a general rule we use blood primes if the patient is anaemic. To avoid the risk of clotting the circuit, we suggest priming with packed red blood cells diluted with normal saline or 5 % albumin to achieve a final haematocrit of 30–35 %. The potassium load to the patient can be minimized by using fresh blood, and once priming is completed, recirculating the blood through the dialyser for 10 min, without connecting to the patient. At the end of dialysis we do not recommend retransfusing the blood back into the infant, and if a blood transfusion is required, to give this during the dialysis session infused through a peripheral line or via a Y-connection at the venous return site to reduce the possibility of clotting the circuit.

Dialysate Composition

The dialysate content may be adjusted to address specific therapeutic needs but always starts with an assessment of the quality of the dialysate water. National quality standards for the water that is used to prepare dialysate have been set, but the criteria are different around the world. Dialysate contaminants can be both chemical and biological in nature and can cause significant morbidity (Table 66.4). It is therefore imperative that each dialysis unit ensures that disinfection practices are in place to achieve these standards combined with regular surveillance to ensure that they are sustained.

In recent years the emphasis has been drifting towards the use of ultrapure dialysate. Dialysate quality is known to be an important component of the biocompatibility of the HD procedure and therefore also contributes to the chronic inflammation of dialysis [59]. In vitro studies have shown that bacterial products can cross both high-flux and low-flux dialysis membranes and stimulate synthesis of inflammatory mediators such as cytokines within the blood compartment [60, 61]. The degree of cytokine stimulation is related to the concentration of endotoxin and other 'cytokine-induced substances' in the dialysate compartment [62, 63] and the permeability of the dialysis membranes to these substances. In general, polysulfone and polyamide based membranes are effective barriers to endotoxins because of their high adsorptive properties [62] whereas high-flux and low-flux cellulose based membranes are less protective [64, 65]. There is evidence supporting a link between dialysate bacterial and endotoxin contamination and chronic inflammation but the impact is dependent on the permeability of the dialysis membrane. In our opinion the question of whether ultrapure dialysate provides a survival and morbidity advantage, especially in children, has not been answered. Therefore at present we cannot justify the additional cost that

Table 66.4 Water purity standards, contaminants, and associated complications

	Water		*Dialysate*	
	Bacteria (CFU/ml)	Endotoxin (EU/ml)	Bacteria (CFU/ml)	Endotoxin (EU/ml)
AAMI, RD5: 1981	200	Not specified	2000	Not specified
AAMI, RD62: 2001	200	2	Not specified	Not specified
AAMI, proposed	Not specified	Not specified	200	2
ERA-EDTA best practice guidelines	100	0.25	100	0.25
European pharmacopoeia	100	0.25	Not specified	Not specified
Swedish pharmacopoeia	100		100	0.25
Ultrapure	0.1	0.03	0.1	0.03
	Contaminants		*Complications*	
	Pesticides, herbicides		Unknown	
	Chloramines, chlorine		Severe hemolytic anemia	
	Bacteria, pyrogens		Bacteremia, fever, chills, hypotension, vomiting, inflammation	

Adapted with permission of Springer Science + Business Media from Fischbach et al. [14]; Used with permission of John Wiley and Sons from Ward [59]
AAMI Association for Advancement of Medical Instrumentation, *CFU* Colony forming unit, *EU* Endotoxin unit

will be incurred with implementation of ultrapure dialysate for routine pediatric HD. However, use of ultrapure dialysate is mandatory for hemodialfiltration practices and should be considered during treatments associated with a significant risk of backfiltration and those using cuprophan membranes.

Sodium

Following a sodium load, even in the presence of renal failure, the mechanisms responsible for preserving plasma tonicity will maintain plasma sodium within narrow limits by changing the plasma volume. During HD, dialysate sodium generates a crystalloid osmotic pressure and thus influences fluid shift between the different body compartments, but it also permeates the dialysis membrane and thus has the potential for becoming a sodium load.

Diffusive sodium transport is proportional to the difference in sodium activity between blood and dialysate compartments. Dialysate sodium activity is approximately 97% of the measured sodium concentration, but varies with changes in dialysate temperature, pH, and the presence of additional ions. The proportion of plasma water free sodium ions that are unbound to protein and other anions can be measured by direct ionemetry. Plasma sodium activity is influenced by the Donnan effect: negatively charged proteins (mainly albumin) produce a small electrical potential difference across the membrane (negative on the plasma side) that prevents movement of the positively charged sodium ions. In the absence of UF, the concentration of dialysate sodium needed to achieve isotonic dialysis can be approximated by correcting the blood sodium measured by direct ionometry for a Donnan factor of 0.967.

Hyponatremic dialysis causes osmotic fluid shift from the extracellular to intracellular compartment, contributing to dialysis disequilibrium and intra-dialytic hypotension. Hypernatremic dialysis transfers sodium to the patient, causing interstitial edema, interdialytic thirst, increased inter-dialytic weight gain and worsening hypertension. A therapeutic advantage can be gained by manipulating the dialysate sodium concentration throughout dialysis, known as sodium profiling, and typically utilizes a sodium concentration that falls in a step, linear, or exponential fashion (Fig. 66.6). The higher dialysate sodium at the start allows a diffusive sodium influx to counterbalance the rapid decline in

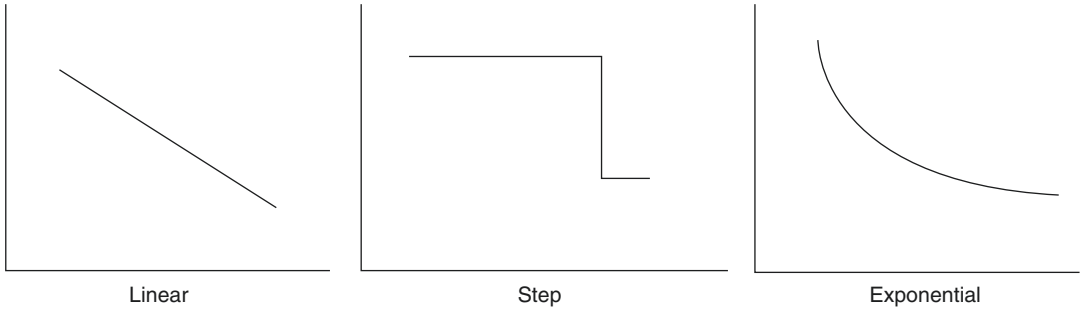

Fig. 66.6 Sodium profiling options

plasma osmolarity due to clearance of urea and other small molecular weight solutes. Low dialysate sodium at the end aids diffusive clearance of the sodium load and minimizes hypertonicity. Compared with a constant dialysate sodium bath, profiling has been shown to increase stability of intradialytic blood volume and reduce both intradialytic cramps and interdialytic fatigue in children and adults [66, 67]. Compared with exponential profiles, step profiles are most effective at attenuating post-dialytic hypotension and early intra-dialytic hypotension, while linear profiles best reduce cramps and late intra-dialytic hypotension. Sodium profiling is also indicated in the prevention of dialysis dysequilibrium.

The difficulty with sodium profiling is finding the concentration gradient that offers the benefits of cardiovascular stability without exposing the patient to a small but repeated sodium load. A net sodium gain of 1 mmol/L will result in a 1.3 % expansion of the extracellular space. Based on concerns of inducing hypervolemia, neutral sodium balance profiles may be preferred. Protocols of isonatremic dialysate are similar with time averaged dialysate sodium 2–3 mmol/L lower (Donnan effect) than the predialysis sodium [68]. Results indicate benefits similar to those described with sodium profiling but with a significant decrease in the inter-dialytic weight gain and thirst score [69, 70]. The difference is likely to be due to an improvement in sodium balance, but as neutral balance is unlikely even with the "isonatraemic" protocols we recommend monitoring for changes in inter-dialytic weight gain and BP.

Potassium

Patients are typically dialysed against a potassium bath of 1–2 mmol/L. In severe hyperkalemia, a lower dialysate potassium concentration of 0–1 mmol/L is necessary and if pre-dialysis serum potassium levels are normal a potassium bath of 3–4 mmol/L may be required. Potassium homeostasis is influenced by a number of factors including acid-base status, diet, hypoaldosteronism from medications, tonicity, glucose, insulin concentration, and catecholamine activity [71] and as a consequence, there is a wide variability in the total amount removed. The rate of potassium removal is high at the start of dialysis and then declines as the plasma potassium falls. The risk of arrhythmia, QT dispersion [72] and ventricular ectopic beats is increased with hypokalemia and also if the rate of decline is rapid early in dialysis even if the actual plasma potassium levels are normal. This is one of the postulated mechanisms for the phenomenon of sudden cardiac death in HD patients. Conversely failure to normalize serum potassium levels is also arrhythmogenic [73].

Bicarbonate

Acetate was originally used as the buffer in dialysate as it was cheap, offered equimolar conversion to bicarbonate, and was bacteriostatic. However, 10 % of patients, especially women, are poor metabolizers of acetate. The high plasma acetate levels led to impaired lipid and ketone acid metabolism, vasodilatation, depressed left

ventricular function, intra-dialytic hypotension, and hypoxaemia, particularly in the first hour [74]. Consequently, most centers switched to sodium bicarbonate.

The preparation of bicarbonate based dialysate requires a second proportioning pump that mixes solution or dry powder bicarbonate to water, and an 'acid' compartment containing a small amount of acetate or lactate, sodium, potassium, calcium, magnesium, chloride and glucose. During the mixing procedure the acid in the acid concentrate reacts with an equimolar amount of bicarbonate to generate carbonic acid and carbon dioxide. The generation of carbon dioxide causes the final solution pH to fall to approx 7–7.4. It is this lower pH, combined with the lower concentrations of calcium and magnesium that prevents precipitation from occurring in the final solution. Often cartridge systems containing pure, dry sodium bicarbonate powder are preferred as they are less conducive to bacterial growth and liquid bicarbonate has to be used within 8 h of opening the container to avoid significant bicarbonate loss.

Dialysis aims to correct the metabolic acidosis of ESRD by the removal of organic anions and restoration of the bicarbonate deficit. Plasma bicarbonate levels rise by 4–5 mmol/L and then fall to pre-dialysis levels by 48 h. The adjusted survival of HD patients decreases with pre-dialysis serum bicarbonate levels <18 and >24 mmol/L [15], suggesting a "U" shaped correlation with mortality. The severity of metabolic acidosis also correlates with bone disease [75], muscle wasting [76], and ß2microglobulin levels [77]. With standard dialysate bicarbonate concentrations of 35 mmol/L, the HEMO study showed that 25 % of patients had predialysis levels below 19 mmol/L [78]. Increasing the dialysate bicarbonate concentration to 39–40 mmol/L will improve the pre-dialysis bicarbonate levels but in some will result in a transient alkalosis. This has a hypothetical risk of facilitating calcific uremic arteriolopathy, reducing phosphate removal because of shift of phosphate into cells, and intra-dialytic vascular instability by causing a sudden drop in the plasma potassium and calcium levels.

Alkalosis has been shown to rapidly reduce dangerously high serum potassium levels, albeit with a potentially increased post-dialysis rebound effect [79]. Finally on a more experimental level, the use of citric acid in place of acetic acid in the dialysate acid concentrate was shown to improve both acidosis and delivered dose of dialysis [80]. The role for citrate is expanding in the dialysis community; however, caution is advised as it increases aluminum absorption and therefore plasma aluminum levels must be monitored.

Calcium

Owing to fear of inducing extra-skeletal calcium deposition, KDOQI guidelines suggest maintaining plasma calcium levels in the low normal range. Using a dialysate calcium concentration of 1.25 mmol/L permits higher doses of vitamin D and calcium based phosphate binders in the management of hyperparathyroidism. In a proportion of patients this can lead to hypocalcaemia and worsening hyperparathyroidism [81]. Hypocalcaemia also depresses myocardial contractility and reduced vascular reactivity [82] and thus increases the risk of intra-dialytic hypotension. These are both indications for the short-term use of a higher calcium bath. In our experience, the only situation requiring routine use of 1.5 mmol/L calcium baths are in patients receiving nocturnal HD who have a reduced need for calcium containing phosphate binders and increased calcium clearance [83].

Phosphate

Phosphate is the major anion in the intracellular compartment and the steep gradient between the intracellular and extracellular compartments is maintained by active carrier systems. The factors that limit the removal of excessive phosphate are dialysis clearance and the kinetics of phosphate distribution within the body. During dialysis plasma phosphate levels initially fall but thereafter plateau or increase, with a post-dialysis rebound effect persisting for up to 4 h [84]. The implication is slow

mobilization of phosphate from the intracellular stores and bone and phosphate generation from reserves triggered by falling extracellular [85] or intracellular levels [86]. The point at which phosphate generation is initiated appears to correlate with pre-dialysis phosphate levels. There is also evidence for a "switching on" effect to protect against critically low intracellular phosphate levels.

Phosphate supplementation to dialysate may occasionally be required in severely hypophosphatemic patients with tubulopathies, severely malnourished children who develop hypophosphataemia secondary to re-feeding syndrome, and those receiving more frequent, daily, or nocturnal HD.

Magnesium

Typically the concentration of magnesium in dialysate is 0.5–1 mmol/L. If magnesium containing phosphate binders are used a lower concentration may be required to avoid hypermagnesemia. Conversely low magnesium levels can result in cramping and arrhythmias and therefore higher magnesium baths may help to improve cardiovascular stability and intra-dialytic symptoms.

Glucose

Glucose concentration of dialysate usually approximates 100–200 mg/dL (6–11 mmol/L). This level of glucose should ensure patients remain normoglycemic unless hyperglycemic or hypoglycemic at the start. If hyperglycemic, a dialysate glucose in the recommended range will remove glucose, and if hypoglycemic the dialysate will provide supplemental glucose. There is a theoretical risk of inducing hypertriglyceridemia by addition of glucose to dialysate but this should not be significant with dialysate values of 100–200 mg/dL. If the patient is hyperkalemic, less potassium might be removed when dialysate glucose is elevated, causing hyperinsulinemia which pushes potassium into cells. However, this should not be a problem with the dialysate glucose levels recommended above.

Dialysis Flow Rate

Typically, dialysate flow rates of 300–500 ml/min are employed. During infant dialysis the practice within our unit is to start with a dialysate flow rate of 300 ml/min. If clearance is inadequate increasing the dialysate flow rate can produce improvements, but eventually plateaus. The HEMO Study provided in-vivo confirmation of increased hemodialyzer mass transfer-area coefficients for urea at high dialysate flow rates [87]. A subsequent study showed that the relative gains in spKt/V for increasing the dialysate flow rate from 300 to 500 ml/min and 500–800 ml/min were shown to be 11.7 % ± 8.7 % and 9.9 % ± 5.1 %, respectively [88].

Dialysate Temperature

By modifying skin blood flow we can control heat exchange between the body and the environment. This is mediated by two sympathetic nervous system effects, an adrenergic vasoconstrictor and a lesser understood sympathetic vasodilator. During times of increased body core temperature, tonic sympathetic vasoconstriction is relaxed and active vasodilatation is initiated [89] and the skin blood flow rate can increase from a baseline of 5–10 % of the total body cardiac output to approximately 60 % [90, 91].

Traditionally dialysate temperatures have been set at ≥37 °C based to match physiological normal values and to compensate for losses of heat in the extracorporeal circuit. Both of these assumptions have in fact been found to be untrue. In a study of adult HD patients 62.5 % of 128 patients had pre-dialysis body temp below 36.5, with marked inter- and intra-individual differences [92]. There is growing evidence in both adults and children of a net gain rather than loss of heat during dialysis. This is the result of higher resting energy expenditure in HD patients compared to the normal population, especially in those with residual renal function [93]. Secondly, UF activates sympathetic vasoconstriction, reducing skin blood flow and therefore heat exchange, with a direct correlation between UF

volume and net heat gain [94]. If the accumulation of heat causes an increase in the body core temperature, UF induced vasoconstriction is overridden by active vasodilatation. Blood is redistributed to the skin [95], the peripheral vascular resistance falls, resulting in decreased cardiac refilling and hypotension [55]. Fine and Penner [92] showed that dialysis patients with subnormal body temperature (below 36 °C) dialyzed against a 37 °C dialysate had a 15.9 % incidence of symptomatic hypotensive episodes, which fell to 3.4 % with 35 °C dialysate.

The hemodynamic advantage of "cool" HD has been documented but may be uncomfortable for patients and reduce urea clearance as a result of compartmental dysequilibrium. Application of thermoneutral (no gain or removal of thermal energy from the extracorporeal circuit) and isothermic (patient temperature is kept constant) dialysis is technically possible, but the dialysis circuit has to be adapted to accommodate a feedback control circuit. A more practical option is to individualize the dialysate temperature based on the patient's pre-dialysis temperature. Even then, efforts may be hampered by the current standards of the Association for the Advancement of Medical Instrumentation (AAMI) that requires the dialysate temperature at the dialyser to be maintained within ±1.5 °C of its set point.

Infants have an increased susceptibility to hypothermia. As a result infants have traditionally been dialysed against higher dialysate temperatures of 37.5–38 °C. Alternatively one may consider more physiological dialysate temperatures with the use of external warming methods to maintain normothermia. The impact of either strategy on thermal balance and cardiovascular stability has not been studied.

Anticoagulation

Anticoagulation of the extracorporeal circuit is usual but not mandatory and should be determined by estimating the risk of bleeding against that of clotting the circuit which results in blood loss and reduced dialysis efficacy. In children, unfractionated heparin (UFH) remains the agent of choice for systemic anticoagulation but low molecular weight heparin (LMWH) and citrate have been used.

UFH is a mixture of polyanionic branched glycosaminoglycans that bind with high affinity to antithrombin causing a structural change, converting it from a slow to a very rapidly (1,000 times) acting inhibitor of thrombin. It interacts with other components of the coagulation cascade, producing a combined effect of inhibiting fibrin formation and thrombin-induced platelet activation and increasing vessel wall permeability. The polyanionic nature of heparin allows non-selective binding to other proteins and cell membranes. This mediates the adverse effects associated with UFH use such as activation of lipoprotein lipase causing increased generation of free fatty acids which can induce platelet aggregation, and loss of bone mass resulting in osteoporosis [96, 97].

UFH has to be administered intravenously as intestinal absorption from oral therapy is poor. Following a bolus injection, the non-specific interactions reduce bioavailability to approximately 30 %. Consequently, an initial bolus is usually recommended to saturate these non-specific binding sites as the dose-response relationship becomes almost linear thereafter. UFH is metabolized by the liver and the kidney clears desulfated fragments. Owing to a marked inter-individual sensitivity to heparin and the possibility of heparin inactivation in the extracorporeal circuits, it is essential to individualize heparin requirements during dialysis and review dosing needs with time (Fig. 66.7).

The consensus on the desired degree of anticoagulation varies amongst different dialysis units ranging between 25 % and 300 % above baseline. In our experience, for the majority of patients, adequate anticoagulation is achieved with activated clotting time 50 % above the baseline. Standard regimens consist of a bolus dose of 15–20 units/kg of heparin at the start of dialysis followed by a continuous infusion of 15–20 units/kg/h, stopping the heparin infusion over the last 30 min of dialysis. In children weighing less than 10 kg, the likelihood of clotting is increased. Nonetheless, safe, effective anticoagulation with

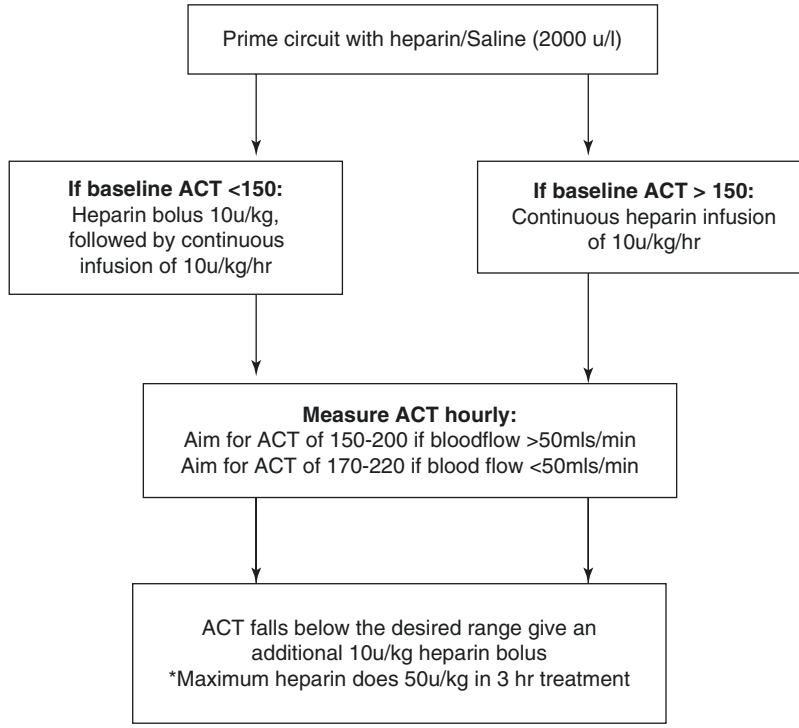

Fig. 66.7 Tight heparin regimen

lower activated clotting time target ranges is possible with tight heparin regimens [98].

In high-risk groups, there is a 10–30 % risk of bleeding with unfractionated heparin. Alternative options include regional anticoagulation with citrate, use of prostacyclin infusion, high flow rate HD, calcium free dialysate with calcium infusion back to the patient in a closely monitored setting, or modification of the standard heparin regimen. Low dose heparin or heparin free dialysis combined with regular intermittent saline flushes is possible without compromising dialysis dose or causing unwanted bleeding complications in children at increased risk of bleeding [98].

LMWHs are smaller molecule prepared from UFH through enzymatic or chemical depolymerization. They act predominantly by inhibiting factor Xa but also cause a variable degree of thrombin inactivation. Following a single subcutaneous injection, bioavailability reaches 100 %, but with differences in inter-individual sensitivity, fixed dosing is inappropriate. LMWHs are principally cleared by the kidney and therefore in ESRD, the drug's pharmacokinetics are unpredictable.

Due to the prolonged half-life in kidney failure and lack of a commercially available antidote, there has been a reluctance to use LMWHs. However, several adult trials show that sustained intra-dialytic anticoagulation can be achieved following a single bolus dose at the start of dialysis, making it a very convenient option. The negative charge of the LMWH complexes makes them impermeable across dialysis membranes and therefore, in spite of their low molecular weight, there is no relevant elimination either through HD or hemofiltration [99, 100]. One meta-analysis comparing the safety and efficacy of LMWH compared with UFH showed no difference in preventing extracorporeal thrombosis and demonstrated comparable bleeding risks [101].

Table 66.5 Dosing recommendations for low molecular weight heparin for a 4 h hemodialysis session

Drug	Molecular weight (kDa)	Average half-life (hours), may vary based on residual renal function	Adult single bolus dose for a 50–100 kg patient)	Pediatric dose for a >50 kg patient, unless specified
Tinzaparin	5.0	4.5	1,500–3,500 IU	50 IU/kg
Dalteparin	6.0	5.0	5,000 IU	40 IU/kg
				<15 kg, 1,500 IU
				15–30 kg, 2,500 IU
				30–50 kg, 5,000 IU
Reviparin	4.0	5.0	85 IU/kg	85 IU/kg
Nadroparin	4.5	5.0	3,800–5,700 IU	114 IU/kg
			70 IU/kg	<50 kg, 3,000 IU
Enoxaparin	4.2	27.7	0.5–0.7 mg/kg	24–36 mg/m^2
				0.5–1.0 mg/kg

Adapted with permission of Springer Science + Business Media from Davenport [103]
IU international units

The use of LMWH was first described in children on HD by Bianchetti et al. who successfully hemodialyzed seven children for an average time of 4 h, using enoxaparin 24–36 mg/m^2 [102]. More recently, Davenport has reviewed the issue of anticoagulation for children on HD and has proposed doses for LMWH in children receiving HD (Table 66.5) [103].

It has become our routine practice to use LMWH in our home HD population in London. All patients are commenced on 50 units/kg of dalteparin as a single intravenous dose at the start of dialysis. The dose is then adjusted in 20 % aliquots according to percentage of visible clot formation in the dialyser at the end of dialysis, pre-dialysis anti-Xa levels, and in those with fistulae the presence of prolonged bleeding times after removing fistulae needles. All the patients with fistulae are also placed on low dose aspirin. No patient has lost a circuit from excessive clotting. The final dose of dalteparin ranges from 21 to 58 units/kg with a trend for infants and young children to be on higher doses of dalteparin (52–58 units/kg) compared with teenagers (21–41 units/kg). Those switching from an evening dialysis schedule to nocturnal schedule require on average a 50 % increase in their dalteparin dose. The anti-Xa level 1 h after dosing ranged from 0.13 to 0.6 and pre-dialysis anti-Xa suggest no suggestion of bioaccumulation of dalteparin.

Citrate is a small molecule and is dialyzable with an extraction coefficient similar to that of urea and any citrate that escapes into the systemic circulation is rapidly cleared by the tricarboxylic acid pathway primarily in the liver and skeletal muscle. Citrate exerts its anticoagulant effect by chelating ionized calcium ions, preventing activation of calcium-dependent procoagulants. Regional anticoagulation of the extra-corporeal circuit without systemic effects is achieved by infusing citrate solution through the arterial limb of the circuit, removal of citrate through dialysis, and then neutralizing its anticoagulant effect by infusion of ionized calcium into the venous limb of the circuit. This makes it a very attractive option for patients with a bleeding risk despite a lack of supportive data in children on maintenance dialysis.

Each method of anticoagulation is associated with specific side-effects. Heparin induced thrombocytopena is mediated by heparin-dependent IgG antibodies that bind to platelets causing platelet activation and subsequent risk of thromboembolic events, characterized by markedly increased thrombin levels. Several alternatives to heparin are commercially available but only danaparoid sodium use has been documented in pediatric HD, reporting stabilization of both thrombocytopenia

and thromboembolic risk [104]. However, it has 30 % cross-reactivity with platelet-heparin antibodies [105]. The direct thrombin inhibitor, hirudin, is efficacious but its half-life is prolonged in renal failure and it is associated with anaphylactic reactions [106, 107]. Argatroban, a synthetic direct thrombin inhibitor shows the greatest promise owing to its rapid onset of action, a half-life ranging from 39 to 51 min, hepatic metabolism, and the fact that it can be used in dialysis patients with no dose adjustment as only a 20 % systemic clearance is seen even with high-flux dialyzers. Complications reported with citrate dialysis include hypocalcemia resulting in arrhythmias and paresthesias, hypernatremia, volume expansion, and metabolic alkalosis (one molecule of trisodium citrate is metabolized to three molecules of bicarbonate). Citrate toxicity with metabolic acidosis can occur from citrate accumulation due to ineffective dialysis clearance or poor metabolism secondary to impaired synthetic liver function. It is diagnosed biochemically by an increased anion gap acidosis and high total plasma calcium combined with low plasma ionized calcium (so-called citrate lock).

Additionally, recent evidence suggests a role of citrate in attenuating the chronic inflammatory response to HD which is linked to atherosclerosis, arteriosclerosis and malnutrition [108]. The use of citrate in pediatrics is growing through its application in plasmapharesis and continuous renal replacement therapy and because its actions are easily neutralized with calcium. These factors make it an attractive option but until protocols are simplified and validated in children, it cannot presently be recommended as an alternative to heparin for routine dialysis therapy.

Commonly Encountered Hemodialysis Complications

Dialysis Disequilibrium Syndrome (DDS)

Dialysis disequilibrium occurs as a result of changes in osmolarity inducing water shifts from the extracellular to the intracellular compartment across the highly permeable blood brain membrane. It manifests during or immediately after HD as a self-limiting entity, but recovery can take several days. Symptoms typically include nausea, vomiting, headache, blurred vision, muscular twitching, disorientation, hypertension, tremors, seizures and coma but others such as muscular cramps, anorexia, restlessness, and dizziness have been reported. The diagnosis is often one of exclusion.

The exact pathophysiology of disequilibrium remains unknown, although two mechanisms have been proposed. Both mechanisms support that rapid changes in brain volume disrupt the blood brain barrier and cerebral autoregulation. The reverse urea effect postulates that urea is cleared from plasma more rapidly than from brain tissue, resulting in a transient osmotic gradient and cerebral oedema. The second theory is based on the observation of a paradoxical acidaemia of the cerebral spinal fluid and cerebral cortical grey matter in patients and animals treated with rapid HD. This is accompanied by increased brain osmole activity due to displacement of sodium and potassium ions and enhanced organic acid production. The increased intracellular osmolarity induces fluid shifts with subsequent cytotoxic oedema.

The dialysis prescription can be adjusted to reduce the rate of plasma urea clearance by using a smaller dialyser, decreasing the blood or dialysate flow rate, or switching to more frequent, shorter, treatments. Intradialytic osmotic shifts can be minimized with the use of sodium profiles or higher dialysate sodium concentrations, the substitution of bicarbonate for acetate in the dialysate, or if the patient is grossly fluid overloaded, sequential HD in which an initial period of UF alone is followed by conventional dialysis. Mannitol is an osmotically active solute that artificially increases plasma osmolarity at the time of rapid urea clearance. It rapidly lowers intracranial hypertension within minutes of administration and has a peak effect at 20–40 min. A maximal intradialytic dose of 1 g/kg is recommended once a week in high risk patients. If more frequent dosing is required, a smaller dose of 0.5 g/kg is advised as mannitol accumulates in

renal failure (half-life: 36 h) and can cause a rebound rise in the intracranial pressure, especially in the face of acidosis. Other adverse effects include nausea, vomiting, lower limb oedema, thrombophlebitis, headaches and chest pain. An alternative to mannitol is infusion of 3–5 % sodium chloride or the use of higher dialysate sodium baths. Concurrent antiepileptic therapy is required with both therapies if the patient is seizing.

Intra-dialytic Hypotension

The major barrier to achieving optimal UF is the development of hemodynamic instability, manifesting as intra-dialytic hypotension. Hypotension occurs in about 20–30 % of treatments, can result in underdialysis because of treatment interruptions, and may leave the patient volume overloaded. Frequent hypotensive episodes may accelerate a decline in residual renal function and potentially lead to serious vascular complications such as cerebral, cardiac, and mesenteric ischaemia. In children, the UF goal is often higher because of nutritional supplements or poor adherence to fluid restrictions.

As fluid is removed, plasma refilling, passive venoconstriction, active increases in heart rate, heart contractility and in the arterial tone are working simultaneously to preserve the effective plasma volume. As a result, even with a UF volume equal to the entire plasma volume, the measured blood volume only changes by 10–20 %. Impaired compensatory responses cause hypotension in the face of total body water expansion. Most of the plasma volume resides in the veins, with a marked difference in the venous capacitance between organs. During fluid removal, the ability to mobilize blood from the splanchnic venous pool is vital for preserving the central blood volume. Venous tone is affected by vasoactive hormones, the sympathetic nervous system, and upstream filling pressures. The De-Jager Krogh phenomenon refers to the transmission of upstream arterial pressure through the capillaries to the veins causing venous distension and altered venous capacitance. During arteriolar constriction the distending pressure to the vein is reduced and blood is extruded centrally towards the heart to maintain cardiac refilling. Conversely, factors that cause arterial dilatation, such as antihypertensive medications, increase venous capacitance, reduce cardiac filling pressures and through transmission of increased hydrostatic pressure to the capillary bed, inhibit vascular refilling. Adenosine is thought to augment splanchnic blood pooling through an inhibitory effect on norepinephrine release and by causing regional vasodilatation. It is hypothesized that during a sudden, but not gradual intra-dialytic hypotensive episode, ischaemia leads to increased consumption of adenosine triphosphate and generation of adenosine [109].

The sympathetic nervous system is the principle control mechanism of arteriolar tone and therefore of central BP. Patients with ESRD show increased basal level of peripheral sympathetic activity [110]. In HD patients prone to hypotension, a paradoxical decrease in sympathetic activity is seen at the time of a hypotensive episode [110] which results in a rapid decline in the peripheral vascular resistance and increased vascular bed capacitance. Problems with sympathetic end-organ responsiveness and the efferent parasympathetic baroreceptor pathway have also been reported but the underlying mechanism remains unexplained. Some believe this may be a heightened manifestation of the Bezold-Jarisch reflex, a cardiodepressor reflex resulting in a sudden loss of sympathetic tone causing abrupt severe hypotension accompanied by bradycardia. It is postulated that conditions associated with reduced cardiac refilling pressures such as left ventricular hypertrophy, diastolic dysfunction, or structural heart defects stimulate cardiac stretch receptors and thus is a maladaptive variant of the Bezold-Jarisch reflex resulting in hypotension.

The final and interconnecting component relating to intradialytic hypotension is plasma refilling, the movement of fluid from the extravascular to the vascular compartment under the influences of hydraulic, osmotic, and oncotic pressure gradients at the capillary wall. If UF rates exceed refilling rates the intravascular volume will fall. Arterial vasoconstriction decreases hydrostatic

pressures in the capillary bed, facilitating vascular refilling. The oncotic pressure which is effectively the plasma protein concentration promotes refilling. Plasma sodium and glucose mobilizes fluid from the intracellular space as a result of increased plasma tonicity [111]. Finally, refilling is facilitated by greater tissue hydration and occurs at a faster rate when the interstitial space is overloaded. Hypovolaemia within the uremic milieu can augment ineffective venoconstriction, inadequate cardiac refilling, reduced plasma refilling and activation of the Bezold-Jarish reflex leading to sudden hypotension.

Haemodynamic stability during dialysis is improved by withholding antihypertensive medications on dialysis days, avoiding food during dialysis, cooling dialysate, using bicarbonate buffers, high sodium dialysate, and treating intradialytic hypocalcaemia. In some patients, the intradialytic BP can be artificially maintained by pharmacological measures. One study demonstrated that prophylactic caffeine administration, an adenosine antagonist, reduced the occurrence of sudden intradialytic hypotensive episodes [112]. A more widely used alternative is midodrine, a prodrug of a specific α-1 adrenergic receptor agonist, desglymidodrine. It maintains intradialytic BP by mediating constriction of both arterial and venous capacitance vessels and preventing venous pooling while increasing the central BP. Administered orally, it achieves peak levels at 1 h, and has a half-life of 3 h. We have used it in children successfully, starting with doses of 2.5 mg incrementally increased to 10 mg. A systematic review of nine trials, using midodrine doses of 2.5–10 mg given 15–30 min before dialysis reported a benefit in six trials with attenuation of the drop in BP during dialysis, and a decrease in number of hypovolaemia related symptoms. No serious adverse events were described, but minor reactions such as scalp paraesthesia, heartburn, flushing, headache, weakness and neck soreness were reported [113].

Modifying the UF rate throughout dialysis to allow adequate vascular refilling may optimize fluid removal. This is the rationale behind UF profiles. The plasma refilling capacity increases proportionately with interstitial volume expansion. Decreasing stepwise or linear profiles start with high UF rates at the time of maximal tissue hydration, progressively reducing the rate in line with decreasing interstitial hydration in the hope of maintaining the crucial balance between fluid removal and vascular refilling. Intermittent profiles aim to provide periods of active mobilization of interstitial fluid into the vascular space when UF rates are low, making it amenable to removal during periods of high UF rates (Fig. 66.8).

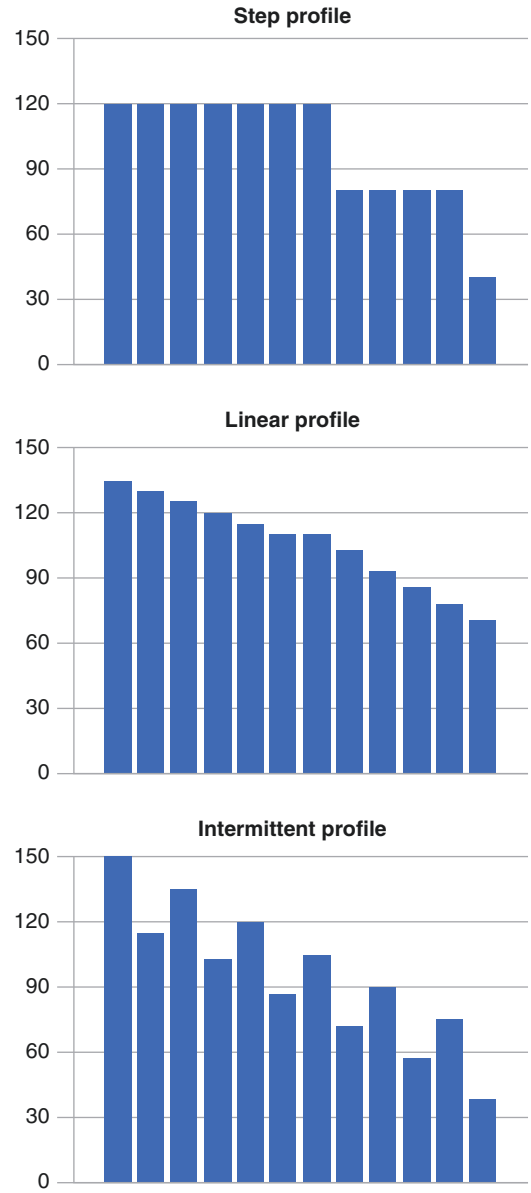

Fig. 66.8 Ultrafiltration profiles

Donauer et al. reported less symptomatic hypotension with the decreasing profiles, but the intermittent profile was associated with an increased incidence of symptomatic hypotension and post-dialysis fatigue [114]. The incidence of intradialytic hypotension was highest with UF rates greater than 1.5 times the average. Ronco et al. observed hypotension at a rate of 6.7/100 treatments when the UF rate was 0.3 ml/min/kg increasing to 15.8 at an UF rate of 0.4 ml/min/kg, 25.6 at a rate of 0.5 ml/min/kg, and 67.4 at a rate of 0.6 ml/min/kg [115]. In children application of these figures would suggest that hypotension may occur in 255 of patients if a UF rate of 30 ml/kg/h (300 ml/h in a 10 kg child) is exceeded. These data have not been validated in children, but in our experience increasing the UF rate increases the likelihood of intradialytic morbidity. UF profiles will inevitably result in higher UF rates for part of the treatment and the maximal UF rate has to be factored in when considering the most appropriate profile for a patient.

Combining UF profiles with sodium profiles can induce plasma hypertonicity through utilization of a high UF rate during a high-sodium period, and thus provide a greater driving force for plasma refilling. It has been shown to be superior to either sodium or UF profiles alone in attenuating intradialytic symptoms and cardiovascular instability. Finally, the supportive measures for managing hemodynamic instability in high risk patients have a ceiling effect and in resistant cases patients may need to be switched to alternative dialysis programs. HDF, short daily HD, and home nocturnal HD can all potentially be of benefit in these situations.

Myocardial Stunning

Acutely, intradialytic hypotension requires immediate action to stop or reduce the severity of symptoms that may precede or follow the drop in BP. These include a temporary suspension of UF, a 5 ml/kg fluid bolus, and in resistant cases, premature discontinuation of the dialysis treatment. Such measures, although necessary, have an adverse impact on dialysis outcomes by reducing UF goals and adequacy of solute removal. Of greater concern, however, is the evidence linking repeated episodes of intradialytic hypotension with a more severe effect on morbidity and mortality. Several observational studies in adult patients with essential hypertension have described a "J" shaped curve between BP and mortality [116]. The same trend has been described in adult dialysis patients, with a suggestion that hypertension is associated with morbidity, but mortality is more closely associated with hypotension [117]. Zager et al. reported a fourfold increase in the relative risk of cardiac-related death in adults patients with pre-dialysis systolic BP less than 110 mmHg compared with a systolic BP between 140 and 149 mmHg, and a 2.8-fold increase in relative risk for a cardiac-related death with post dialysis systolic BP less than 110 mmHg compared with systolic BP 140–149 mmHg [118].

Frequent intradialytic hypotensive episodes have been implicated in accelerating the decline in residual renal function and precipitating serious vascular complications. There is growing evidence from isotopic, electrocardiographic, biochemical and echocardiographic studies implicating HD as a source of recurrent ischemic injury. Silent intradialytic ST depression [119, 120] associated with acute changes in serum cardiac troponin levels both in adults [121, 122] and children [123] have been demonstrated. Using single photon emission computed tomography McIntyre et al. demonstrated an acute reduction in global and segmental myocardial blood flow in adults during dialysis with matched reductions in segmental contractile function, even in patients without angiographically proven epicardial coronary artery disease [124]. A direct correlation was seen between the degree of myocardial dysfunction and intradialytic BP changes and UF volume [125]. Such transient myocardial ischemia with resultant reversible regional left ventricular dysfunction is known as myocardial stunning [126]. In the model of coronary heart disease repeated stunning is progressive and leads to myocardial hibernation, defined as ischaemic, non-infarcted myocardium that exists in a state of contractile dysfunction [127]. In dialysis patients myocardial stunning also appears to be progressive. In a 12 month follow up of adult HD

patients the presence of acute HD induced regional myocardial dysfunction negatively influenced survival, increased the likelihood of cardiac arrhythmias [128], and resulted in regional fixed systolic dysfunction and a reduction in global systolic function [125, 129] with resultant congestive heart failure. Records from the USRDS have shown that HD associated de novo and recurrent congestive heart failure is highly relevant as it is associated with a 2-year mortality as high as 51 % [130]. The left atrial volume is commonly driven by intravascular volume overload and progressive diastolic dysfunction. In a single observational study the strongest predictor of left atrial volume indexed to height (LAVI) was the presence of stunning. LAVI was a better predictor of mortality than left ventricular (LV) mass index, but both were displaced as independent determinants of mortality with the addition of myocardial stunning [131].

Of greater concern, perhaps, has been the demonstration of dialysis induced acute regional myocardial dysfunction in 15 children aged 2–17 years. This was associated with varying degrees of compensatory hyperkinesis in unaffected segments and thus the global LV function was maintained throughout HD. In children, intradialytic systolic BP reduction was significantly associated with mean segmental shortening fraction but no correlation was seen with actual intradialytic systolic BP or dialysis vintage [132, 133]. Interestingly, patients on peritoneal dialysis do not appear to have an increased risk of myocardial stunning, despite changes in systemic hemodynamics [134].

We know HD poses a significant hemodynamic challenge. It is conceivable that other vulnerable vascular beds with defective vasoregulation may also be susceptible to significant episodic dialysis-related ischemia. The gut for example is also a high-flow vascular bed. Translocation of endotoxin across the gut wall causes endotoxinaemia and becomes a profoundly pro-inflammatory stimulus. In both children and adults on HD, circulating endotoxin levels were 1,000 times greater than in patients without chronic kidney disease (CKD) and almost quadrupled from pre-dialysis levels after initiating HD [135]. Serum endotoxin levels correlated with intradialytic instability, systemic inflammation and dialysis-induced myocardial stunning [135]. One group have even postulated that post dialysis fatigue is a clinical manifestation of cardiac ischemia and cardiac fatigue [136]. The acute cardiac injury that occurs as a direct effect of the HD procedure may be attenuated by altering the dialysis prescription. Cooling, biofeedback and frequent dialysis have all been demonstrated in adults to lower the risk of myocardial stunning [137–139].

Intradialytic or Paradoxical Hypertension

Hypertension is endemic in HD patients and is most often due to salt and volume overload, which responds to UF. The prevalence of hypertension in children receiving HD is reported at 65–69 % in studies conducted in Europe and the United States [140, 141]. Intradialytic or paradoxical hypertension is less well characterized but nonetheless important. Estimates of its frequency are hampered by the lack of a standardized definition in the literature. Suggested definitions include an increase in mean arterial pressure of more than 15 mmHg during or immediately after dialysis or an increase in BP that is resistant to fluid removal. Estimates of the incidence in adults range from 5 % to 15 %, with no pediatric data available [142].

The pathogenesis of intradialytic hypertension is complex and poorly understood. There may be an iatrogenic aetiology with mobilization of extracellular fluid or in response to osmotic agents such as sodium, mannitol, or concentrated albumin solutions or dialysis induced hypokalemia. Dolson et al. demonstrated significant rebound hypertension at 1 h post dialysis in patients dialyzed against lower potassium baths [143]. In these instances the hypertension is frequently transient and improves with UF.

Sustained hypertension is commonly due to failure to achieve an appropriate dry weight [144]. However, some patients manifest intradialytic hypertension refractory despite appropriate UF. It is speculated that overzealous UF activates

the renin-angiotensin system with resultant vasoconstriction. In support of this theory is the lower incidence of hypertension in anephric HD patients.

Sympathetic nervous system over activity is well documented in CKD secondary to a number of mediators including angiotensin II, afferent renal nerve stimulation, impaired brain nitric oxide synthesis and increased production of catecholamines [145–149]. Recent studies have shown enhanced endothelin I production during dialysis in hypertensive patients and in particular those exhibiting paradoxical hypertension [150–152]. This raises the possibility of paradoxical hypertension secondary to an imbalance in nitric oxide and endothelin I production [153]. Pearl et al. suggested a role for a new pressor protein a 30-kD extra-renal enzyme related to the coagulation factor β-FXIIa that exhibits cardiotonic and pressor activity in rats. The serum of three anephric children produced characteristic pressor responses, suggesting in vivo activation of this protein as a contributory factor in their hypertension [154].

Finally, a number of antihypertensive drugs are removed by dialysis and this conceivably may result in paradoxical hypertension. As a general rule the beta blockers (atenolol, nadolol, metoprolol), ACE inhibitors (captopril, enalapril, lisinopril, ramipril) and vasodilators such as minoxidil, nitroprusside and diazoxide are removed, by a variable degree, during dialysis. Calcium channel blockers such as amlodipine and ARBs such as losartan are generally not cleared during HD. No data exist for α-blockers such as doxazocin.

The management of intradialytic hypertension should start with an assessment of the dry weight and salt and fluid intake. Treatment options include further salt and water restrictions, and where feasible, augmentation of urine output with loop diuretics. The dialysate composition should be examined for the sodium, potassium and calcium content to ensure that the dialysis procedure does not result in acute hypokalemia or a net transfer of sodium and calcium load. Consideration should be given to replacing conventional HD prescriptions with intensive HD or hemodiafiltration (HDF). If hypertension persists despite appropriate salt and water control, blockade of the renin-angiotensin system with ACE inhibitors or ARBs have been shown to improve BP control and reduce sympathetic tone in HD patients. If this produces insufficient BP control, the addition of α-blockers, β-blockers or centrally acting antihypertensives such as methyldopa is physiologically logical. Attention should be paid to the timing of BP medications to ensure they do not contribute to intradialytic hypotension. Similarly, if drug removal by HD is contributing to suboptimal BP control, consideration should be given to switching to an agent that is not significantly removed by dialysis such as calcium channel blockers. Finally, the incidence of hypertension in dialysis patients appears to have increased in the post-erythropoiesis stimulating agent (ESA) era. This may relate to increased viscosity, increased peripheral vascular resistance or a direct effect of ESAs on the vascular endothelium. While there are no published studies showing a direct relationship between hemoglobin and hypertension, efforts should be made to avoid excessive hemoglobin values in patients with intradialytic hypertension.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) is common in dialysis patients. At the initiation of dialysis 69–82 % of children show evidence of LVH [155] and during maintenance dialysis, 40–75 % of children have LVH [156]. Several factors increase the risk of developing cardiac hypertrophy including chronic hypervolemia, a hyperdynamic circulation secondary to arteriovenous fistulae or anemia, increasing arterial stiffness and elevated parathyroid hormone (PTH) levels [157]. There is emerging evidence from established animal models of CKD also implicating a klotho-independent, causal role for FGF23 in the pathogenesis of LVH. This raises the possibility of FGF23 being directly involved in the high rates of LVH and mortality in HD patients [158]. Somewhat surprisingly, both adult data and now pediatric data from the ESCAPE trial have failed to demonstrate any relationship between office

BP or ambulatory BP monitoring and left ventricular mass [159].

Cardiac hypertrophy in combination with continued mechanical stress triggers pathways that result in myocardial remodeling characterized by decreased capillary density and reduced coronary flow reserve predisposing the heart and other organs to ischemic injury. Fortunately cardiac hypertrophy in HD patients is amenable to treatment with evidence of resolution in patients on intensified dialysis programmes and HDF.

Endothelial Dysfunction

Endothelial dysfunction is thought to be the initiating step in atherosclerosis and arteriosclerosis. It starts early in renal failure, progressing in dialysis as a number of pathophysiological pathways come into play. HD is pro-inflammatory as a consequence of an immune mediated response to bioincompatible membranes, blood contact with non-sterile dialysate solution and/or "back-leaking" of dialysate across the membrane. UF changes endothelial cell dynamics through its effects on blood viscosity and laminar shear stress [160]. Intradialytic hypotension and resultant ischemia causes apoptosis of the vascular endothelium. Finally, reduced clearance of asymmetric dimethylarginine, decreased bioavailability of endothelial nitric oxide, activation of angiotensin II, hyperhomocystinemia and hyperlipidemia are postulated mechanisms for endothelial dysfunction. Compounding these effects, uremia is also associated with reduced hematopoiesis and capacity for repair. In adults, endothelial progenitor cells are reduced with pronounced functional impairment [161, 162] and HD depletes this source further. In contrast, the pool of smooth muscle cell progenitor cells are preserved and with it the potential for adverse remodeling [163]. Little is known about circulating endothelial progenitor cells in children, but there is clinical evidence of endothelial dysfunction with loss of flow-mediated dilatation and increased aortic pulse wave velocity in children on dialysis [164, 165]. Importantly, the degree of endothelial injury is attenuated by switching adult HD patients to either HDF or home nocturnal HD [166, 167].

Sudden Cardiac Death

Sudden cardiac death is a common phenomenon in dialysis patients that appears to be temporally related to the HD procedure. In adults the risk of sudden death is 1.7 times higher in the 12 h period starting with the dialysis procedure and three times higher in the 12 h before HD at the end of the weekend interval [168]. Cardiac arrests are 50 % higher for HD patients 3 months after dialysis initiation. The risk remains higher in HD compared with peritoneal dialysis for up to 2 years on maintenance dialysis, but then the trend reverses at 3 years of maintenance dialysis. The most vulnerable patients are infants aged 0–4 years, with a five to tenfold increase risk of cardiac arrest compared to other age groups [169].

The precise aetiology of sudden cardiac death remains elusive but a number of dialysis specific and uremic factors have been implicated. Myocardial interstitial fibrosis, LVH, endothelial dysfunction, cardiac and vascular calcification, microvascular disease with decreased perfusion reserve and diminished ischemia tolerance are all prevalent in dialysis patients and increase the vulnerability of the heart. This, in combination with dialysis related acute fluid shifts, acid/base disturbances and rapid electrolyte shifts and autonomic imbalance with abnormal sympathetic activity, suddenly places patients at risk of sudden cardiac death.

Clinically the only modifiable risk factor for fatal cardiac events is manipulation of the dialysate potassium. Patients who suffered a cardiac arrest at the time of dialysis were twice as likely to be dialyzed against a 0 or 1.0 mEq/L potassium dialysate compared to controls, despite no difference in pre-dialysis potassium levels [170]. Kovesdy et al. found that serum potassium between 4.6 and 5.3 mEq/l was associated with the best survival but levels below 4.0 mEq/l or

higher than 5.6 mEq/l were associated with increased mortality [171]. As a result there is a growing consensus of nephrologists advising against zero potassium dialysate baths.

Atherosclerosis, Arteriosclerosis, and Calcification

Calcification of the cardiovascular system is accelerated in dialysis patients. Studies of young adults who developed ESRD during childhood found a high prevalence of abnormal carotid intima-media thickness (cIMT), diminished arterial wall compliance and coronary artery calcification [172, 173]. Such vascular and cardiac aberrations were also demonstrated in children on dialysis [174]. The vascular measures positively correlated with serum phosphorus levels, while cIMT and cardiac calcification scores also correlated with intact PTH levels and dosage of vitamin D. Patients with mean intact PTH levels less than twice the upper limit of normal demonstrated stiffer vessels and increased cIMT and cardiac calcification scores. In contrast, 1,25 dihydroxy vitamin D levels showed a U-shaped distribution with a significantly greater cIMT and calcification scores in patients with low and high 1,25 dihydroxy vitamin D levels compared with patients with normal levels. Calcification was most frequently observed in patients with the lowest 1,25 dihydroxy vitamin D and the highest high-sensitivity C-reactive protein [175]. Litwin et al. reported vascular abnormalities in children with CKD but again found the most marked changes in the dialysis patients. The degree of arteriopathy correlated with conventional cardiovascular disease risk factors such as hypertension and dyslipidemia in pre-dialysis CKD and with hyperphosphatemia, hyperparathyroidism and treatment with calcium-containing phosphate binders in dialysis patients [176]. In contrast, in a study examining the effects of dialysate calcium concentrations on changes in arterial stiffness, increased pulse wave velocity was seen even in the group dialysed using the lowest dialysate calcium [177]. Therefore, it is highly probable that factors other than simple net calcium influx and efflux during dialysis are involved in the pathogenesis of accelerated vascular calcification in HD patients.

Inflammation

Inflammation predicts mortality in dialysis patients and may contribute to cardiovascular risk. C-reactive protein (CRP), an acute phase protein, is a recognized marker of inflammation, but is also reported to be predictive of mortality, structural heart changes such as LVH, and higher coronary calcification scores. Recent data have also implicated CRP in the pathogenesis of vascular inflammation and atherosclerosis [178]. Plasma CRP levels increase with declining kidney function and then continue to rise after initiation of HD with levels correlating with the length of the dialysis session [179]. It has been postulated that an interaction of circulating monocytes with bio-incompatible membranes, blood contact with non-sterile dialysate solution and/or "back-leaking" of dialysate across the membrane results in a chronic inflammatory state. However, because there is a high incidence of pre-dialytic inflammation [180], the dialysis procedure is unlikely to be the only factor associated with inflammation [181]. Changes in CRP may also represent an acute inflammatory stimulus [182]. Additionally, vitamin D deficiency has been correlated with inflammatory cytokine levels (IL-10 and SIL-2R) in children receiving HD [183].

The dialysis prescription can be modified to become less inflammatory by using ultrapure dialysate and synthetic biocompatible membranes. Both ACE inhibitors and statins, more commonly recognized for their respective roles in treating hypertension and hypercholesterolemia, have been reported to have anti-inflammatory actions [184, 185]. Finally, lifestyle and dietary changes maybe be associated with decreasing inflammation and uremic toxins (p-cresyl sulfate and indoxyl sulfate), although data are limited in children [186].

Malnutrition

Protein malnutrition and growth delay commonly occurs in underdialyzed patients and may be associated with mortality in children [187, 188]. Measurement of the nPCR has become an indirect measure of daily protein intake in stable dialysis patients. Measurement of nPCR has traditionally relied on the availability of formal urea kinetic modeling and is included with the web-based programs (www.hdcn.com, and www.Kt-v.net) alluded to above. Goldstein, however, has demonstrated strong agreement between nPCR calculated from urea kinetic modeling and the formula $\left[\text{nPCR} = 5.43 \times \text{G} / \text{V} + 0.17\right]$ [187]. This calculation requires a blood urea nitrogen (BUN) level 30 s after a mid-week dialysis session, documentation of the time until the next dialysis session, and a BUN value prior to the second dialysis session. In this formula the urea generation rate (G) is calculated as as G (mg/min) = (predialysis BUN2 × predialysis V) – (postdialysis BUN1 × postdialysis V)/T, where V is total body water estimated from 0.58 × body weight, and T is time in minutes from the end of the mid-week dialysis treatment to the beginning of the next dialysis treatment. Validation of this formula has eliminated the need for complicated computer modeling in order to measure nPCR and estimate daily protein intake. A subsequent report, which compared the values of nPCR calculated as above with a simplified formula using only pre- and post-dialysis BUN specimens from the same mid-week session, found a significant and variable difference between the two methods and invalidates the simplified formula [189].

Although nPCR values are a useful guide to protein intake, because nPCR values may be influenced by factors other than nutrient intake, these values should be interpreted in combination with a review of weight gain and the dietary history. Goldstein et al. [190] demonstrated a substantial increase in nPCR associated with improvement in nutritional status of three adolescents treated with intradialytic total parenteral nutrition. However, in a comparison of protein intake from dietary records kept by children, with an estimate of nPCR calculated using an on-line urea monitor, Van Hoek et al. showed significant variation, and PCR significantly underestimated the prescribed and recorded protein intake [33]. These authors concluded that use of their online urea kinetic monitor is therefore not recommended for estimation of nPCR. Also, as reported by Grupe et al. [191], nPCR may be significantly affected by factors other than nutrient intake in as many as 25 % of patients.

The safety of enteral intake during dialysis should be assessed on a patient-by-patient basis as blood is diverted to the splanchnic circulation, potentially increasing the risk of intra-dialytic hypotension. However, for the majority, eating during dialysis offers an opportunity to consume restricted foods and anecdotally these controlled treats may improve adherence to dietary restrictions. Intra-dialytic parenteral nutrition is an alternative method of providing calories and protein to undernourished patients during HD. While this increases the amount of fluid needed to remove, utilizing a constant UF to parallel the infusion can minimize excessive UF rates. Use of recombinant growth hormone is another important means of maximizing growth in children on HD [192].

Dialysis-Related Carnitine Disorder

Levocarnitine (L-carnitine) facilitates the transport of fatty acids across the inner mitochondrial membrane and is thus a critical cofactor for normal energy production in cardiac and skeletal muscle. There is growing evidence of reduced plasma free carnitine levels in HD patients with an inverse relationship between muscle carnitine and duration on dialysis [193]. Within a single dialysis session, clearance is 30 times greater than would be expected in a healthy individual [194] and HD results in an abnormal acylcarnitine: free carnitine ratio (normal <0.25).

Low carnitine may be associated with anaemia that is hyporesponsive to ESAs, intradialytic hypotension, cardiac dysfunction, fatigue, muscle cramping, and reduced exercise

tolerance [195]. The National Kidney Foundation Interdisciplinary Consensus Panel recommends L-carnitine [196] supplementation for those patients with these clinical findings even in the absence of low plasma carnitine levels. As measuring skeletal muscle L-carnitine concentrations is not feasible, some advocate a trial of therapy with discontinuation at 9–12 months if no benefits are observed [196]. Repeated doses of 20 mg/kg given intravenously at the end of dialysis appear to be the most beneficial, as oral carnitine is not recommended in ESRD due to the toxicity of metabolites which accumulate in renal failure.

Hyperhomocysteinaemia

Homocysteine is a non-protein forming amino acid that results from methionine metabolism. Only 1–2 % of total homocysteine circulates freely in the blood in a reduced form, 70–90 % is protein bound, and the rest exists in oxidized forms. Studies have shown that plasma homocysteine concentrations start rising in chronic kidney disease and are inversely related to glomerular filtration rate. ESRD results in hyperhomocysteinaemia from altered metabolism and impaired clearance. There is conflicting evidence on the impact of hyperhomocysteinaemia on outcomes. A meta-analysis reported a positive association between hyperhomocysteinaemia and atherosclerosis, ischemic heart disease, stroke, and thrombosis [197]. Conversely, others have found no significant or even an inverse association between plasma homocysteine levels, cardiovascular events, and mortality in ESRD patients [198].

Treatment options have included folate and vitamin B12 supplementation to achieve supranormal plasma levels and intravenous N-acetylcysteine [199]. An alternative therapeutic strategy involves using high-flux dialysers to achieve greater clearance, but this has not impacted pre-dialysis plasma concentrations [200]. With these therapeutic options, plasma homocysteine levels improve but normalization is uncommon.

Future Directions

Convective Modalities

Traditional methods of iso-osmotic fluid removal during sequential dialysis techniques (pure ultrafiltration followed by dialysis) are used to achieve higher UF rates without inducing hemodynamic instability. Isolated UF can be performed by placing the HD machine in bypass or the UF mode. However, as the patient is no longer being warmed by the dialysate, hypothermia can develop. This concern of temperature regulation combined with reduced clearance efficacy limits the time that can be spent on isolated UF.

Retention of middle and larger uremic toxins has been related to adverse clinical outcome in patients with chronic kidney disease. Traditional HD prescriptions that have a greater reliance on diffusion for purification have a limited capacity to manage the excess of such toxins. Convection is a superior method for middle molecule clearance. HDF is a dialysis modality where diffusion is combined with convective transport, enabling the removal of middle molecular weight substances up to 40 kDa. An HDF circuit comprises of a standard HD circuit combined with a substitution fluid circuit infused directly into the bloodstream of the patient pre-dilution, mid-dilution or post-dilution relative to the hemofilter. This provides a superior convective component to the dialysis treatment by filtering considerably larger volumes of plasma water through the dialyser. A high flux synthetic membrane is a pre-requisite, as the hemofilter has to be able to tolerate high transmembrane pressures while retaining its high permeability to achieve the high UF rates necessary to obtain sufficient clearance. Ultrapure dialysate is recommended to limit the inflammatory response induced by dialysate fluid as it makes direct contact with the patient's blood, and this is most typically prepared online [201]. Predilution mode is often used in children as it helps to overcome the limitations of blood flow and it reduces the risk of the circuit clotting by limiting the rise in blood viscosity with UF. Higher substitution volumes offer higher filtration rates and greater convective middle molecule clearance.

The trade-off is reduced small molecule clearance due to dilution of the blood entering the dialyser and therefore larger volumes of substitution fluid are required to achieve the same degree of small molecule purification as post-dilution modes. Post-dilution modes achieve excellent small and middle molecule clearance, but at the expense of increased albumin losses and the dialysis prescription and efficacy is limited by the degree of hemoconcentration of the blood compartment by filtration. The mid-dilution mode is a relatively newer mode that allows the substitution fluid to infuse with the blood compartment as it passes through an advanced hemodiafilter. High filtration rates are achievable with superior small and middle molecule clearance without significant albumin loss even in patients unable to provide sufficient blood flow [202].

Currently, HDF is mainly used in Europe with a wide variation between countries. HDF is used to a lesser extent in Asia and Canada and is rarely prescribed in the United States [203]. The evidence in adults from observational and smaller randomized controlled trials suggests that HDF, when compared to conventional HD, reduces all-cause mortality. Recently, the results of three large randomized controlled trials: the Convective Transport Study (CONTRAST) [204], the Turkish HDF Study [205], and the Estudio de Supervivencia de Hemodiafiltracion On-Line (ESHOL) [206] were published using post-dilution HDF. Neither CONTRAST nor the Turkish HDF study showed a statistically significant difference in all-cause mortality or cardiovascular events between HDF and HD over a median follow-up period of 2–3 years [204, 205]. The ESHOL trial reported improved all-cause mortality, as well as cardiovascular mortality of HDF over HD [206]. Post-hoc analyses in all three studies suggested a dosage and effect relation such that the patients treated with higher convection volumes had a survival advantage even after adjustment for potential confounders. The average achieved convection volume was 20.7 L per session in CONTRAST, 19.5 L per session in the Turkish HDF study and 23.7 L per session in ESHOL. In the RISCAVID cohort study comparing 424 HD patients against 204 patients treated with HDF performed with bags and 129 treated with online post-dilution HDF, all-cause mortality was significantly lower in both HDF groups compared with HD. The cardiovascular mortality was significantly lower in the online HDF group compared with HD and HDF with bags. The average amount of replacement fluid in the HDF group with bags was 14 ± 3 l per treatment, and the mortality rates of the patients 9 % and 16 % after 1 and 2 years, respectively. The average amount of replacement fluid in the online HDF group was 23 ± 3 l per treatment, and the mortality rates of the patients 6 % and 16 % after 1 and 2 years, respectively [207]. In the DOPPS cohort study, patients were stratified into four groups: low flux HD (n = 1366), high flux HD (n = 546) and two HDF groups classified according to the amount of replacement fluid per treatment: 5–14.9 l was considered low-efficiency HDF (n = 156) and 15–24.9 l high-efficiency HDF (n = 97). The mortality risk in the group of patients treated with low efficiency HDF was not significantly different from the HD group but significantly lower in the high efficiency HDF group [208]. Therefore the current evidence seems to support a dose response relationship between the convection volume achieved and the reduction in mortality risk but the cut point of achieved convection volume above, which the risk potentially reduces, is uncertain.

The published evidence in children is limited to the observations from a single centre experience. Fischbach reports safety and efficacy data with pre-dilutional HDF in children, prescribed six times per week for 3 h; using the Fresenius 4008® and FX 6 polysulfone dialysers; blood flow rate of 180 ± 50 ml/min and fixed dialysate flow rate of 500 ml/min. The substitution fluid rate was 0.65–1.0 times the blood flow rate (limited to a maximum of 200 ml/min) and the UF rate was limited to 1.5 ± 0.5 % body weight. Daily HDF was well tolerated by all children with a reduction in pre-dialytic clinical symptoms, and an elimination of post-dialytic recovery times and dialysis related fatigue. The pre-dialysis plasma haemoglobin levels increased, phosphate levels increased accompanied by a slow reduction of the mean pre-dialysis ß2-microglobulin

levels, withdrawal of antihypertensives in most of the children; and improved LV function [12]. Particularly relevant to children, the group also reported catch-up growth in their cohort. The mean growth velocity increased from 3.8 ± 1.1 cm/year at inclusion to 14.3 ± 3.8 cm/year during the first year of HDF, resulting in a change in height standard deviation score from −1.5 ± 0.3 to +0.2 ± 1.1. The catch-up growth velocity noted in the first year of daily dialysis declined over time, nevertheless the mean height remained in the range of the familial target height. What remains unclear is whether the benefits described are related directly to increased dialysis intensity, converting from HD to on-line HDF, or both.

The literature clearly alludes to a symptom, morbidity and mortality benefit of switching from a purely dialysis modality to HDF; however, the mechanisms behind this remain unclear. We can speculate on superior removal of uremic toxins. During HD the peripheral vascular resistance falls but with HDF it is maintained [209], and therefore for an equivalent blood volume loss there is a significantly smaller decline in systolic BP [210] resulting in better hemodynamic stability, with fewer episodes of hypotension and consequently less adverse cardiac consequences such as cardiac stunning. During HDF there is significant cooling within the extracorporeal circuit, which counteracts the heat generated during dialysis and prevents the increase in core temperature and subsequent peripheral vasodilatation. Finally it has been proposed that the improved hemodynamic stability is secondary to decreased sodium clearance [211]. HDF is a safe and efficacious treatment that may be of benefit to children prone to intradialytic hypotension or worth pursuing in those facing longer periods of dialysis.

Intensified Hemodialysis Options

Our current standard of three times weekly hemodialysis evolved during the 1960s from one 24 h treatment per week, to twice weekly treatments of 16–24 h each, and finally three weekly sessions of 8–10 h performed at home. By the time Medicare adopted its end stage renal disease program in 1973, the three times per weekly schedule offered the optimal balance between patient outcome, quality of life, and cost. Remarkably, the first patient treated with these prolonged sessions lived for more than a decade. More than 50 years later, similar outcomes have become difficult to achieve [212].

To improve the health of patients receiving three times weekly in-center hemodialysis, researchers have trialed alternative, intensified dialysis regimens. These methods include short daily hemodialysis, nocturnal home hemodialysis, and in-center nocturnal hemodialysis. In 2010, the Frequent Hemodialysis Network, sponsored by the National Institutes of Health, published their findings in 245 adults randomized to three times versus six times per week in-center hemodialysis. After 1 year of treatment, those in the more frequent group averaged about five sessions per week and demonstrated improvements in mortality, LVH, reported physical health, hypertension, and hyperphosphatemia. However, they were also more likely to receive vascular access interventions compared to the three times per week treatment group [11]. A treatment benefit was not observed among adults randomized to six times per week home nocturnal hemodialysis as compared with three times per week in center hemodialysis, although a decrease in adherence to the intensive home treatment schedule and the study's small sample size may have precluded detecting a significant difference [213].

Smaller, uncontrolled studies in children have also supported the potential benefits of intensified dialysis regimens. As mentioned above, Fischbach et al. reported their experience treating 12 children (median age 7 years) in France with five to six times per week in center HDF. After a median follow-up of 11 months, dietary restrictions could be lifted and BP and phosphate control improved [214]. Observations by the same group have also noted decreased LVH and post-dialysis fatigue with six times per week treatments [12]. In children, weekly treatment times of 15–18 h have been associated with improved growth, measured as improvements in height velocity [12, 215–217].

The success noted by the investigators in France has prompted others to trial alternative dialysis regimens in children. Four children treated at The Hospital for Sick Children had improved dietary intake, BP control, and school attendance with home nocturnal hemodialysis [13]. Calcium and phosphate metabolism improved, even requiring dialysate phosphate supplementation during therapy [83]. These experiences have been expanded to a larger group of children in Europe, resulting in no post-dialysis recovery time, improved energy, and quality of life. Patient selection criteria for home therapy have included weight >20 kg, adequate family support and supervision, and the necessary technology to operate the dialysis equipment [13, 218]. While the therapy may represent a 30 % cost savings compared with in-center treatment, the requirements for staffing and family resources are high [13]. Future technology may allow home HD to be performed in infants.

In the United States, a published report of four children treated for an average of 2.5 h, six times per week, in-center or home hemodialysis used the NxStage™, which provides sterile dialysis fluid without the requirement for home modifications for a reverse osmosis water treatment system [219, 220]. After a 16 week pilot study, though Kt/v urea values were only slightly greater than what is achieved with traditional thrice weekly HD, these children no longer needed antihypertensive therapy and had improved BP control as measured by 24 h ambulatory monitoring, without reporting treatment-related complications [220]. In London we have dialysed 15 children aged from 3 to 17 years on the NxStage™ system. We are currently using three circuits: the standard CAR172 circuit, CAR124 for those developing intradialytic thrombocytopenia and CAR125 for children weighing less than 18 kg. Routinely, children start on 5 h of dialysis four evenings per week, except in infants. From 2 months onwards we discuss the possibility of switching to nocturnal HD where appropriate. All children report reduced or no post dialysis recovery times, greater energy and quality of life scores and vastly improved school attendance, social and family lives. All the children on 20 h or more of dialysis/week are free of diet and fluid restrictions, appetites have improved with better growth. Cardiac echocardiograms were normal at baseline in 6/11, in the 5 remaining signs of LVH and/or fluid overload had regressed within 6 months. PTH levels were successfully maintained within twice upper limit of normal in all except two teenagers who became calcium deficient on 1.5 mmol/L calcium dialysate baths.

Combining the benefits of more frequent treatments, the quality of life offered by nocturnal therapy, and the safety and convenience of monitoring available in the clinic, investigators in Germany have reported their experience in 16 children and adolescents treated with in-center, nocturnal hemodialysis. Children were prospectively enrolled over an almost 5 year period and there were over 2,000 treatments provided. Participants were treated 8 h per session for 3 days per week and each treatment was monitored by a pediatric nephrologist and two dialysis nurses. During the study, quality of life was reported to improve and children missed fewer days of school. Nutrition indices improved, phosphate levels decreased, and the number of antihypertensive decreased compared to matched control patients [221].

While pediatric studies have been mostly uncontrolled and have included a small number of subjects, most demonstrate that intensified hemodialysis is associated with improved quality of life, biochemical markers (especially phosphate clearance), growth, nutrition, and BP control [222]. Nevertheless, significant barriers exist, precluding the more wide-spread adoption of these potentially beneficial options for children with end stage kidney disease. These include financial hurdles related to treatment costs, transportation, missed work time for parents, and equipment and supplies for those choosing home therapy [223]. Missed time from school and other social activities is a concern for children treated with non-nocturnal, more frequent in-center hemodialysis. We must also be mindful of patient, caregiver, and provider burnout in a patient population already struggling with the management of a very significant chronic disease [13, 219, 222, 223].

It is clear that change is needed to improve the health and survival of children with end stage kidney disease. Health-related quality of life remains poor in children with chronic kidney disease, especially in those receiving HD, in whom daily life activities are greatly limited [224]. While the data suggest that the current treatment is not optimal and more intensified treatment may offer benefit, we must also not minimize the subjective input of our patients. To this end, a 16 year old female, after being switched to three times per week long nocturnal hemodialysis, noted, "regular dialysis was hell and I never want to go back to it again" [222].

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