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Haemodiafiltration: Principles, Technique, and Advantages over Conventional Haemodialysis

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Introduction and Defining a Need for Convective Clearance on Dialysis

In-center HD, performed three times is the conventionally used standard renal replacement therapy (RRT) for patients with end-stage kidney disease (ESKD). Standard HD clears uraemic toxins primarily through diffusion driven by the thermal energy of the uremic toxin molecules. Clearance is inversely proportional to the molecular size (expressed in daltons) of the toxin and also depends on its protein binding and tissue distribution. As a result, conventional HD does not clear large or protein-bound toxins effectively and fails to adequately correct the uraemic milieu [1–3]. Attempts to improve clearances on HD include initiation of dialysis at higher glomerular filtration rates, aiming for a single-pool Kt/V urea greater than 1.20 per session, increase in dialysis frequency and/or duration, use of high-flux membranes, or alternative haemofiltration. However, greater clearance of low-molecular-weight toxins or the use of high-flux membranes had no impact on patient mortality [4]. Moreover, patients on dialysis have a significantly higher cardiovascular mortality, and even amongst paediatric dialysis recipients, cardiovascular disease is the most common cause of death [5].

Children on dialysis have a very high burden of cardiovascular risk factors, including chronic fluid overload with hypertension and mineral dysregulation with hyperphosphatemia and hyperparathyroidism [6, 7]. Preclinical cardiovascular disease (CVD), measured through surrogate markers such as carotid intima-media thickness (cIMT), pulse wave velocity, and left ventricular hypertrophy, is prevalent in CKD [8, 9], with accelerated progression on dialysis [6–10]. Vascular calcification [7, 9–13], cIMT [13], and hypertension and cardiovascular function [14] worsen with increasing time on dialysis, implying that the dialysis milieu, including biochemical derangements and haemodynamic stresses, lead to a rapidly worsening cardiovascular risk profile; 18–40% of deaths in children [5, 15] and young adults [16] on dialysis are due to cardiovascular events. Even within a short period of 3 months on conventional haemodialysis (HD), biomarkers of inflammation, oxidative stress, and endothelial dysfunction were shown to increase [17]. Interventions that can improve outcomes in children on maintenance HD are

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urgently needed. Haemodiafiltration (HDF), which combines diffusive and convective clearance, was developed in the 1970s [2, 3, 18, 19] and may be a promising option.

Principles of Solute Clearance by HD and HDF

All forms of dialysis are characterised by three main principles that determine solute clearance: diffusion, convection, and ultrafiltration. These are discussed in detail in Chap. 2, and the relative contribution of these processes to HDF therapy is described below.

Haemodialysis (HD)

Solute clearance on HD is predominantly driven by diffusion. Diffusive small-solute transport involves the movement of molecules from an area of high concentration to an area of low concentration across a semipermeable membrane. The dialysis fluid flow and the dialyser surface area (which determines the mass transfer area coefficient (K_oA) and consequently, the solute permeability of the membrane) determine the quality of HD provided.

Haemodiafiltration (HDF)

Solute clearance on HDF involves a combination of diffusion and convection. HDF optimises the removal of middle (up to 300–500 dalton (Da) molecular weight) and larger molecules (greater than 15–50 kilo Da). If the clearance of low-molecular-weight solutes such as urea has reached maximal clearance by HD, then the addition of HDF will not improve the clearances further. With HDF there is no osmotic disequilibrium while arriving at a maximum urea clearance as the continuous iso-osmotic substitution fluid inflow maintains an osmotic stability throughout the whole dialysis session. The effectiveness of a membrane to ultrafiltrate fluid is described by the UF coefficient (K_{UF}), which is $Q_{UF}/\Delta P$ (volume of UF per unit time, divided by the pressure gradient across the membrane, also called the transmembrane pressure gradient [TMP]).

Haemofiltration (HF)

HF is mainly used in the acute setting in intensive care units for rapid fluid removal and allows convective transport of small- and medium-sized molecules, although solute clearance is not the primary goal of HF. HF should not be used as a modality of chronic dialysis and is not discussed further in this chapter.

Definition and Types of HDF Therapy

The European Dialysis Working Group (EUDIAL) has defined HDF as a blood purification therapy that combines diffusive and convective solute removal by ultrafiltration of 20% or more of the blood volume processed through a high-flux dialyser and maintenance of fluid balance by sterile replacement fluid infused directly into the patient's blood [20, 21]. In online HDF, large volumes of sterile replacement fluid are obtained by online filtration of standard dialysate though a series of bacteria- and endotoxin-retaining filters [21]. A high-flux membrane is defined as one that has an ultrafiltration coefficient greater than 20 mL/h/mmHg transmembrane pressure/m^2 and a sieving coefficient for β_2-microglobulin of greater than 0.6. HDF provides greater removal of middle-molecular-weight and protein-bound uraemic retention solutes than does conventional low- or high-flux HD [21].

A high convective volume is a fundamental requirement for HDF. The convective volume is the sum of the net ultrafiltration volume (i.e., the amount of fluid removed during a dialysis session based on the inter-dialytic weight gain) and the amount of substitution fluid (i.e., the sterile replacement fluid given as replenishment for the removal of extra fluid during HDF). Randomised controlled trials in adults [22–25] and a pooled individual participant data analysis [25] suggest that any improved survival associated with HDF occurs when the convective volume exceeds 20

liters/session. Therefore, the EUDIAL group felt that it was necessary to add a lower limit to ultrafiltration, below which the treatment would not qualify as HDF. An ultrafiltration volume equivalent to 20% of the total blood volume processed for the treatment was chosen as the lower limit because it is achievable with post-dilution HDF without excessive haemoconcentration, although with modern dialysis machines an ultrafiltration volume of 30–35% of the total blood volume can be achieved and should be aimed for in order to obtain optimal clearance. In theory, it would be more correct to prescribe convective volume as a proportion of plasma water volume processed rather than blood volume processed. However, as the blood volume processed, and not the plasma water volume processed, is displayed on the machine control panel, this term has been used to avoid confusion.

Modes of HDF

Depending on where in the dialysis circuit the replacement volume is infused, there are different modalities of HDF (Fig. 21.1).

Post-dilution HDF

In post-dilution HDF, the replacement fluid is infused downstream of the dialyser, usually into the venous bubble trap. For solutes which can pass the membrane unimpeded (sieving coefficient = 1), the concentration in the ultrafiltrate is the same as in the plasma water. A potential disadvantage is that haemoconcentration at high ultrafiltration rates can result in the deposition of plasma proteins on the membrane surface, clogging the membrane pores and occluding the blood channels of the dialyser. These effects can raise transmembrane pressure (TMP), causing alarms, reducing clearance, and possibly resulting in clotting of the extracorporeal circuit [21].

The degree of haemoconcentration is dependent on the filtration fraction (a practical clinical concept defined as the ratio of ultrafiltration rate to plasma water flow rate and described further in the next section), which in turn depends on haematocrit, protein concentration, and blood flow rate. Haemoconcentration generally limits the filtration fraction to 20–25% of the blood flow rate in post-dilution HDF. The ultrafiltration rate is controlled in proportion to the actual blood flow

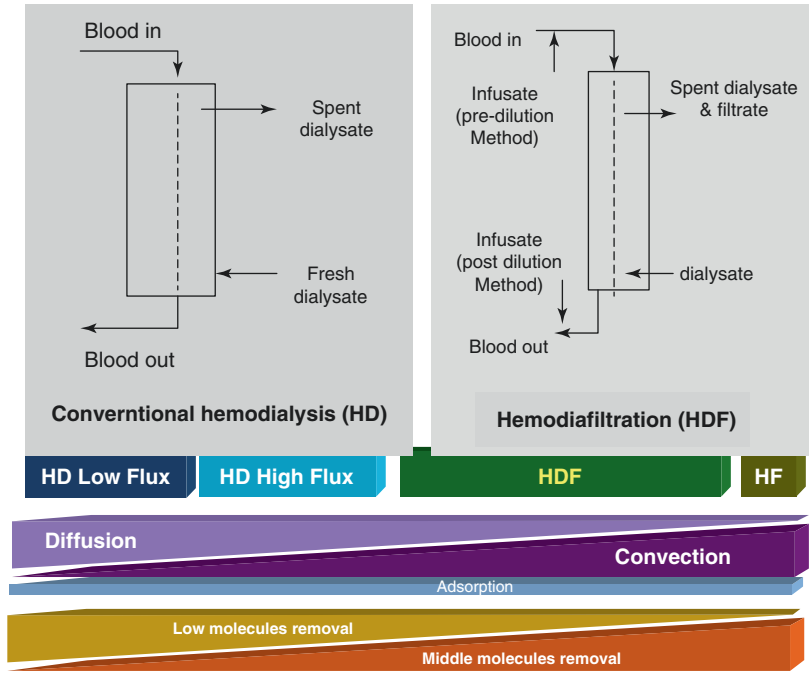

Fig. 21.1 Schematic presentation of HD and HDF therapies

rate or guided by TMP. A filtration fraction up to 35% of the blood flow rate is possible using systems designed to optimise filtration rate, based on automatic adjustment of TMP according to ultrafiltration flow rate measurements [26, 27].

Pre-dilution HDF

The haemoconcentration associated with post-dilution HDF can be avoided by infusing the replacement fluid upstream of the dialyser. With pre-dilution HDF, higher filtration rates are possible than with post-dilution HDF. Ultrafiltration rates up to 100% of the blood flow rate are used. However, pre-dilution reduces the efficiency of both the diffusive and convective components of solute removal by reducing solute concentrations in the blood compartment, and small solute clearance by pre-dilution HDF may be lower than conventional high-flux HD. For equivalent clearance, the convective volume needs to be two to three times greater for pre-dilution HDF than the post-dilution [28].

Mid-dilution HDF

The replacement fluid is infused part-way down the blood pathway using specially designed dialysers or systems. Thus, the first part of the blood circuit is operated in post-dilution mode and the second part in pre-dilution mode [29]. Very large filter sizes, up to 1.9 m^2, are required, and hence, this technique is not suitable for children.

Mixed Dilution HDF

In mixed dilution HDF, the replacement fluid is infused both upstream and downstream of the dialyser. The ratio of upstream and downstream infusion rates can be varied to achieve the optimal compromise between maximising clearance and avoiding the consequences of a high TMP and haemoconcentration [30]. As with mid-dilution HDF, large filter sizes are required, so this technique is not feasible for children.

Choosing the Optimal HDF Modality

In theory, post-dilution is the most efficient mode of HDF for clearing middle- and large-molecular weight substances and is the routinely used HDF technique in adults and children. However, successful post-dilution HDF requires a high extracorporeal blood flow rate, a reliable vascular access, an ability to achieve adequate anticoagulation throughout the procedure, and the absence of any condition that increase blood viscosity (such as a high haematocrit). In children, the 3H study has shown that adequate blood flow rates can be achieved through both central venous catheters and arteriovenous fistulas in order to achieve a high convective volume and optimal HDF [31].

However, in patients with low blood flow rates (typically less than 200 mL/min in adults and comparative rates in children), pre-dilution HDF allows for adequately high volumes of substitution fluids. Compared with post-dilution HDF, pre-dilution HDF removes more low-molecular-weight proteins and protein-bound toxins and is associated with less bio-incompatibility (shear stress or membrane-cell or cell-cell activation) [32]. The Japanese Renal Data Registry compared the one-year prognosis of patients receiving pre-dilution HDF and standard HD using a propensity score-matched method. Pre-dilution HDF with a higher convective volume (more than 40 L/session) decreased all-cause mortality and cardiovascular mortality compared with standard HD or pre-dilution HDF with small convective volumes [33, 34]. Japanese experience shows an increase of adult patients' survival in pre-dilution HDF with an optimal substitution volume estimated to be 33 L/m^2/session in patients dialysed 3 times a week [35]. Pre-dilution HDF has been used effectively in children and is associated with excellent growth outcomes, especially when used in a frequent dialysis regimen (5 days per week) [36]; the authors have shown that for pre-dilution blood HDF, blood flow rates of 5–8 ml/min/kg body weight or 150–240 ml/m^2 body surface area were acceptable, with substitution volume of 75–100% of blood volume [37].

Requirements for HDF and Technical Aspects

Essential requirements for performing HDF include:

- 'Ultrapure' water for replacement of convective volume
- High-flux dialyser membranes
- Dialysis machines that allow careful regulation of UF

Important technical terms unique to HDF practice and equations for the calculation of solute clearances on HDF are also described here.

'Ultrapure' Water for HDF

The sterile, non-pyrogenic fluid used to maintain fluid balance, referred to as replacement fluid or substitution fluid, can be provided either as a terminally sterilised, packaged solution or as an online prepared solution. It is not practical to provide the volumes of replacement fluid used for the most effective forms of convective therapy using prepackaged solutions. Instead, replacement fluid is generated online by filtering dialysis fluid through bacteria- and endotoxin-retentive filters to prepare a sterile and pyrogen-free solution that is immediately infused into the patient. Therapies performed in this manner are referred to as online convective therapies. As large volumes of fluid are removed from, and added to, blood during online therapies, patients are exposed to risks beyond those associated with routine HD. Strict safety standards and regulatory oversight are required. Some recommendations related to HDF are also included in the European Best Practice Guidelines [38].

Water Purification Systems A standard water treatment device consists of a water softener, an activated carbon filter, a sediment filter, and a reverse osmosis system [39]. Water softeners contain a resin that exchanges sodium cations for calcium, magnesium, and other polyvalent cations. The effectiveness of softening is monitored by measuring the hardness of the effluent water. Water softening not only prevents hard water but also protects the reverse osmosis membrane which is used in the final step of water treatment from the build-up of scale and subsequent failure. The resin is regenerated periodically with concentrated sodium chloride solution, which also reduces bacterial growth in the resin bed. Activated carbon filters remove chloramines and organic solvents but tend to release carbon particles and therefore require a sediment filter placed downstream. The final purification step is performed by reverse osmosis where the water is forced through a semipermeable polyamide or polysulfone membrane at 14–28 bar. This step removes 90–99% of inorganic and organic substances, pyrogens, bacteria, and particulate matter. The purified water is pumped from the reverse osmosis module to the individual treatment stations in a recirculating ring loop which delivers the water produced in excess back to the reverse osmosis module, avoiding wastage of high-quality water. The ring loops themselves require regular disinfection, and this is performed either by heat or chemical disinfection.

Testing Water Quality The International Organization for Standardization (ISO) has published a series of standards addressing fluids for extracorporeal therapies. Specifically, ISO 11663:2009, *Quality of dialysis fluid for haemodialysis and related therapies*, requires that the replacement fluid used for HDF be sterile and pyrogen-free [40]. Typical testing for water quality follows the French regulations: 500 mL of replacement fluid is collected via the membrane filtration method and is cultured to determine endotoxin levels at least once every three months [41]. The currently accepted norms for ultrapure dialysate are defined as containing <0.1 colony-forming unit/ml and <0.03 endotoxin unit/ml. In addition, the chemical composition of water must be tested at least once per year.

Bacteria- and endotoxin-retentive filters installed on the inlet dialysis fluid circuit are the key components of the online HDF safety system. Those filters are disinfected after each dialysis treatment according to manufacturer's recommendations, and the repetitive disinfection

cycles can alter the membrane characteristics. Therefore, the filters should be replaced periodically to ensure proper operation of the cold sterilization process. The type of filter used and the frequency of replacement should comply with the HDF machine manufacturer's instructions. The integrity of the filters may also be assessed online by regular pressure testing or the use of other validated tests according to the manufacturer's instructions.

The dialysate can also be contaminated with other bioactive microbial contaminants, such as peptidoglycans [42] and fragments of bacterial DNA [43]. The extent to which the latter contaminants are removed by the techniques currently used for online preparation of replacement fluid is unclear, as are the consequences of inadequate removal.

High-Flux Membranes

Only highly permeable membranes are suitable for HDF in adults or children. Highly permeable membranes are defined as membranes characterised by a UF coefficient (K_{UF}) greater than 20 mL/hr/mmHg transmembrane pressure/m^2 and a sieving coefficient (S) for β2-m of greater than 0.6 [4, 21, 44]. The UF coefficient (K_{UF}) defines the hydraulic permeability of a membrane and is expressed in mL/min/mmHg transmembrane pressure. Whereas a low-flux membrane will allow only a small and undetermined convective flow and can be used for HD only, a high-flux membrane allows a larger and predefined convective flow as required for HDF. In practice, the KUF should be high enough to allow 50 mL/m/m^2 body surface area (equivalent to 2 mL/min/kg body weight) convective flow in post-dilution HDF. The albumin loss through a high-flux membrane should be <0.5 g in a 4-hour HD session [44, 45].

As with conventional HD, the dialyser surface area must be equal to (or slightly higher than) the body surface area for maintenance dialysis, so that the internal volume of the dialyser and blood lines is less than the safe extracorporeal blood volume permissible (i.e., less than 10 ml/kg body weight). Manufacturers provide an optimal range of blood flow for a given dialyser as a higher membrane surface is associated with the need for a higher blood flow in order to decrease the risk of coagulation and hollow-fibre obstruction [46, 47]. Theoretically, fiber length and diameter, as well as membrane material, membrane thickness, surface area, pore size, and pore density all may influence solute sieving and convective transport [44]. For HDF a biocompatible dialyser must be selected; biocompatibility is assessed by complement activation, thrombogenicity, contact activation, and cytokine generation [48]. European recommendations state that ultrapure dialysate must be used with synthetic high-flux membranes [21].

Dialysis Machines with Accurate Ultrafiltration Control

Today almost all new dialysis machines allow for both HD and HDF. In Europe, HDF machines suitable for children are manufactured by Gambro, Fresenius Medical Care, and Nikkiso. These machines are suitable for children from 10 to 17 kg body weight and require a paediatric circuit with low extracorporeal volumes.

Gambro AK 200™ ULTRA S and Artis® Dialysis System. These systems bear resemblances and dissimilarities. Both can be used in a pressure-control mode (fixed TMP and variable substitution flow rate) and a volume-control mode. In the latter, the target substitution volume must be set in the AK 200™ ULTRA S system, while the substitution flow rate must be set in the Artis® machine. In the AK 200™ ULTRA S, the actual convective volume and convective flow rate are also shown. Both machines display the FF value online (as 'QF/QB'), based on the real blood flow rate. The maximal value recommended by the manufacturer, however, is different for both systems. Of note, the older Gambro dialysis machine AK 200™ as well as their latest machine AK98™ do not perform HDF, and the AK 200™ is no longer manufactured. The Artis dialysis machine is only suitable for children above 20 kg.

Fresenius 5008 with ON-LINEplus™. This machine (*Fresenius Medical Care, Bad Homburg, Germany*) has an automatic substitution mode (AutoSub Plus™), in which the substitution rate is automatically regulated in response to variations in diverse patient- and treatment-related parameters throughout the session. The estimated final substitution volume is displayed on the monitor. When this mode is disabled, it is possible to set the substitution rate or target substitution volume manually. In this system, FF is automatically regulated but not displayed on the screen. A newer model of the Fresenius dialyser called the 6008 series is due to be launched very soon and will come with smaller paediatric lines that will allow HDF even in children from 10 kg in size.

Nikkiso DDB07 and DBB-EXA haemodialysis system. These machines enable HDF in children: the DDB07 system has low volume blood lines and requires a manual setting of FF, whereas the DBB-EXA can be used in children weighing more than 20 kg with an automatic substitution mode (i.e., the substitution rate is automatically regulated in response to TMP throughout the session).

Commonly used dialysis machines and blood line volumes are shown in Table 21.1.

Table 21.1 Blood line volumes for machines that perform HDF

Dialysis machine	Double needle	Single needle	Blood line volume (ml)	olHDF	BVM
Baxter Artis	Yes		132	Yes	Yes
		Yes	227		Yes
Braun Dialog iQ	Yes		122	Yes	Yes
		Yes	186		Yes
Fresenius 5008	Yes		108	Yes	Yes
	Yes		136	Yes	Yes
		Yes	142		Yes
		Yes	169		Yes
Fresenius 6008	Yes		83	Yes	Yes
	Yes		122	Yes	Yes
		Yes	137–187		Yes
Nikkiso DBB-07	Yes		56	Yes	No
	Yes		86	Yes	Yes
	Yes		113	Yes	Yes
		Yes	93		No
		Yes	123		Yes
		Yes	150		Yes
Nikkiso DBB-EXA	Yes		143	Yes	Yes
		Yes	202		Yes

olHDF online haemodiafiltration, *BVM* blood volume monitoring

Filtration fraction (FF) is a parameter unique to HDF as it quantifies the relation between convective flow rate and blood flow rate. It is also an important determinant for the amount of convective volume achieved [21]. FF is defined as the ratio of the ultrafiltration (UF) rate to the plasma water flow rate [21], where UF represents the total amount of plasma water removed from the patient. In clinical practice, however, blood flow rate (Q_b) is used as a surrogate for plasma water flow rate, as Q_b is indicated on all dialysis machines. The formula for calculating FF is:

$$\mathrm{FF} = \left[\left(Q_{\mathrm{subs}} + Q_{\mathrm{UF}} \right) / Q_b \right] \times 100$$

where $Q_{\mathrm{conv}} = Q_{\mathrm{subs}} + Q_{\mathrm{UF}}$

FF is in %, Q_{conv}, Q_{subs}, and Q_{UF} are the convective flow rate, substitution flow rate, and ultrafiltration flow rate, in mL/min (or L/h), respectively.

In clinical practice, net UF is the sum of the desired intradialytic weight loss in kilograms and the amount of fluids administered during treatment. The higher the FF, the greater the convective volume extracted from the blood. In post-dilution HDF because the substitution fluid is administered after the dialyser, haemoconcentration within the filter increases proportionately to the FF. As a result, filter clotting and loss of membrane integrity with altered dialyser performance may occur [30]. A filtration fraction up to 30–35% of the blood flow rate is possible using systems designed to optimise filtration rate, based on automatic adjustment of TMP.

It is important to keep in mind that the FF can vary based on several caveats:

(i) The true blood flow rate may vary from the set rate. This is particularly true at higher values of Q_b. If FF calculation is based on the set value, the real FF may be underestimated.
(ii) FF actually depends on the plasma water flow rate, but for practical purposes Q_b is used as surrogate. Unlike plasma water, Q_b depends on haematocrit (Ht) and total protein concentration.
(iii) Blood viscosity and clogging of membrane pores increase during the HDF session, so a high FF may be obtained at the start, but not at the end of a session. Thus, a higher TMP is needed to obtain the same substitution rate towards the end of the session.

Calculation of Solute Clearances in HDF

(i) The *diffusive component* (K_D) of clearance in HDF can be estimated using Michael's equations [49] from the blood flow rate (Q_b), the dialysis fluid flow rate (Q_d), and the solute-specific dialyser mass transfer – area coefficient (K_oA).

$$K_D = \frac{1 - e^{K_oA \times \left(\frac{Q_b - Q_d}{Q_b \times Q_d}\right)}}{\frac{1}{Q_b} - \frac{1}{Q_d} \times e^{K_oA \times \left(\frac{Q_b - Q_d}{Q_b \times Q_d}\right)}}$$

For pre-dilution, the actual blood and dialysis fluid flow rates at the inlet ports of the dialysers should be used by correcting for pre-dilution infusion, which will add to the blood flow rate and subtract from the dialysis fluid flow rate. For clearance of urea, Q_b is considered to be the blood water flow rate, while for other solutes, Q_b is considered to be the plasma water flow rate since only urea diffuses rapidly enough across erythrocyte membranes to allow erythrocyte water to be cleared [50, 51].

(ii) The *convective component* (K_C) is calculated using Ficheux's equation [52, 53] taking the sieving coefficient, S, into account.

$$K_C = \frac{Q_b - K_D}{Q_b} \times Q_f \times S$$

where Q_f is the ultrafiltration rate.

(iii) The *total clearance,* K_T, is calculated by adding the diffusive and convective components and taking the dilution factor (DF) into account.

$$K_T = \left(K_D + K_C\right) \times \mathrm{DF}$$

The Concept of 'Backfiltration'

The concept of 'backfiltration' needs to be considered here. The hydrostatic pressure of both blood and dialysis fluid decrease as they pass through the dialysis filter. Since blood and dialysis fluid pass through the filter in counter-current directions, the resulting TMP may become negative at the venous side especially when the venous blood pressure is low. This phenomenon leads to influx of dialysis fluid into the blood compartment of the dialyser; this is called backfiltration. This phenomenon is a routine occurrence during high-flux HD [54], but not in low-flux HD. Therefore, a high internal ultrafiltration rate may increase the convective transport of middle molecules [46, 55]. In adults it has been shown that the convective volume achieved by backfiltration is no more than 1–10 L per session depending on the dialyser type and can vary throughout the dialysis session depending on TMP. Since the convective volume achieved by backfiltration is low and unreliable, it should not be considered a form of HDF and in fact is termed the 'poor man's HDF'!

Importantly, given the phenomenon of backfiltration, it has been suggested that dialysis fluid used for high-flux HD should also be sterile and pyrogen-free. Clinical experience suggests that the barrier provided by the dialysis membrane is

safe for backfiltration volumes of up to 8 L per treatment [38].

Writing a HDF Prescription

In addition to the routine management of any child on dialysis, the following points should be considered when writing an HDF prescription:

1. A *high-flux membrane* with surface area equal to the child's body surface area is used.
2. The total *extracorporeal circuit* should be less than 10 ml/kg body weight. Single- or double-needle circuits are available, although HDF is rarely ever performed with single-needle circuits. Paediatric blood lines (36–105 ml volume) with or without the possibility to do online HDF and to monitor blood volume variation are available (Table 21.1).
3. *Replacement fluid* that is generated online from the dialysate must be 'ultrapure' (<0.1 CFU/ml and <0.03 endotoxin unit/ml) as discussed earlier. The microbiologic purity (bacterial count and endotoxin level) should be determined regularly at intervals of 1–3 months.
   (European guideline Dialysate purity 2002, European Pharmacopoeia 2009).
4. *Blood flow*: HDF requires an optimal arterial blood flow of 5–8 mL/min/kg body weight or 150–250 mL/m^2 body surface area per minute. Both the diffusive clearance of molecules with a high K_0A and the substitution volume in post-dilution HDF depend on the blood flow rate. An optimal blood flow can be achieved through either a fistula or a central venous line, although in most cases a fistula allows a higher blood flow rate in order to (i) maintain arterial blood aspiration pressure of more than −150 to − 200 mmHg and venous restitution pressure of less than 200 mmHg and limit endothelial trauma, and (ii) vascular access recirculation of less than 10%. Vascular access recirculation can be measured by thermodilution (by dialysis machine), saline dilution, or ionic dialysance [56]. It is suggested that the blood flow rate is progressively increased from 90–100 mL/m^2/min in the first HDF sessions to 200–250 mL/m^2/min, increasing by 10 mL/min per week.
5. *Dialysate flow* of twice the blood flow is sufficient to optimise the diffusive blood purification process using highly permeable membranes for HDF. As with conventional HD, the dialysate runs counter-current to the blood flow. Modern dialysis machines control thermal exchanges during the dialysis session and perform isothermic dialysis, without changing the patient's body temperature.
6. *Convective flow* is equal to total UF flow, i.e., the sum of the desired ultrafiltration volume and the replacement fluid.
   - *Post-dilution HDF*: The convective flow needs to be maximal but is limited by the risk of the filter clotting. It typically decreases over the dialysis session. In order to maintain TMP within safe limits (usually TMP < 300 mmHg is suggested by manufacturers, but varies across dialyser), modern dialysis machines automatically adjust the convective volume throughout the session in order to optimise this convective flow without increasing the coagulation risk.
   - *Pre-dilution HDF*: The convective flow is set at 100% of the blood flow. This can be done despite the dilution of the blood potentially impacting negatively on urea clearance.

     β2-m and phosphate dialytic removal is optimised as is the clearance of uraemic protein-bound toxins.

     The actual substitution volume obtained per session has to be monitored regularly in order to ensure that the goal of 23 L/1.73m^2 per session in post-dilution and 75–100% of blood volume treated in pre-dilution is achieved.
7. The *dialysate* and substitution fluid are produced 'online' by the dialysis machine by dilution of acid concentrate and bicarbonate powder with dialysis water produced by the water treatment system. Dialysate composition is similar to that used in HD, but careful attention to dialysate sodium concentration is

important in order to maintain sodium balance and haemodynamic tolerance of the session [57]. To avoid the risk of positive sodium balance, the dialysate sodium concentration required is lower than in conventional HD, particularly when high convective volumes are infused, as with pre-dilution HDF. Sodium is predominantly drained in ultrafiltered water by convection. A low dialysate sodium enables additional sodium removal by diffusion, but it may be associated with a risk of intradialytic hypotension and disequilibrium syndrome. On the other hand, a high dialysate sodium increases haemodynamic tolerance but causes sodium and water overload that leads to hypertension and increased thirst post-session.

As with conventional HD, sodium profiling (high dialysate sodium at dialysis start with decrease during the session) with or without ultrafiltration profiling (high ultrafiltration rate at dialysis start and low at dialysis end) can help to correct fluid and sodium overload and maintain intradialytic haemodynamic stability and dialysis tolerance. This strategy needs to check that sodium delivered to the patient at session start is indeed drained at session end. Some new dialysis machines automatically modify the dialysate sodium concentration throughout the dialysis session in order to keep it equal to plasma sodium, delivering isonatraemic dialysis [57].

8. *Anticoagulation* is necessary to prevent filter clotting, particularly in post-dilution HDF. A single dose of low-molecular-weight heparin is effective for a 4-hour session. A starting dose of 50–100 U/kg of enoxaparin is suggested with a half dose added after 2 hours if the session lasts more than 4 hours. Alternatively, a continuous heparin infusion may be used.

Practical Guide for the Optimization of the Convective Volume

Just performing HDF does not automatically result in high convective volumes. For the optimization of convective volume, an understanding of its determining factors is essential. A post-hoc analysis of the CONTRAST study showed that treatment-related parameters, such as blood flow rate and treatment time, play a greater role in determining convective volume, rather than patient characteristics such as serum albumin, haematocrit, or body size [58–60].

To attain a high convective volume, one needs a high blood flow rate (because filtration fraction depends on blood flow and cannot be higher than 35%), optimization of substitution volume by automated programs in new dialysis machines and careful monitoring of the dialysis prescription and blood results to ensure that all dialysis-related parameters are achieved [61–63]. Practical problems and tips to optimise convective volume are discussed below.

(i) *Optimal vascular access* Both central venous catheters and fistulas can be used for HDF provided a good extracorporeal blood flow rate is achieved. The 3H study in children showed no difference in the blood flow achieved through either type of access [31, 64], although several studies in children report that a higher blood flow is usually achieved through a fistula [65, 66].

(ii) *Needle size* The choice of a fistula needle is based on the type, vintage and expansion of the access, bleeding susceptibility, and preference of patients. A common concern is that larger needles are associated with a poor shunt outcome. Although no specific recommendations can be made for needle size, with the exception of initial cannulation, the largest needle size suitable for the access type must be used.

(iii) *Avoid single-needle HDF* Given the high convective volume goals, single-needle HDF should not be performed. In single-needle systems, clamps on the arterial and venous lines are opened and closed alternately in order to pump blood from and to the patient through the same lumen. As a result, mean blood flow is lower than that with a double-needle procedure. Moreover, as a result of the variable blood flow, both transmembrane pressure and FF fluctuate

may lead to an inadequate and unpredictable convective volume [60].

(iv) *Access recirculation* When blood flow rate increases, recirculation may occur [63]. This phenomenon is especially prominent in case of an insufficient arterial inflow or obstruction in the venous outflow tract [62]. As an increase in the size of the convective volume by recirculation is inefficient and undesirable, regular monitoring is advisable.

(v) *Effective* versus *set blood flow rates* The true blood flow rate may often be somewhat lower than the set value, and the higher blood pump speed, the wider the difference [63, 67, 68]. This phenomenon is explained by partial collapse of the tubes at a more negative pre-pump pressure. In addition, the type of access may also influence this discrepancy: it has been shown that a set blood flow of 350 mL/min resulted in a markedly lower real blood flow in a CVC than in an AVF (316 ± 4 versus 342 ± 4 mL/min) [59].

(vi) *Anticoagulation* Because a high FF may induce considerable haemoconcentration and clotting within the dialyser, adequate anticoagulation with either unfractionated heparin or low-molecular-weight heparin (LMWH) is required. The optimal dose of these agents is unknown. Unfractionated heparins have a molecular weight in the range of 2–20 kDa, so large convective volumes are likely to alter their pharmacokinetics [69]. Higher doses than customary with both low-flux and high-flux HD may be required [70, 71].

Clinical Studies and Potential Advantages of HDF over Conventional HD

HDF: Potential Advantages over Conventional HD

HDF is thought to be superior to conventional HD in the following key areas:

I. *Improved dialysis efficiency and clearance of toxins across a wide molecular weight range* In HD circulating uraemic toxins, such as β2M, and other molecules, such as retinol-binding protein, adiponectin, leptin, ghrelin, cholecystokinin, and cystatin C, accumulate and are responsible for systemic inflammation, endothelial dysfunction, and oxidative stress [72, 73]. HDF has been shown to clear 70–80% of β2M compared to HD [72] and increase removal of inflammatory cytokines with reduction in inflammation and oxidative stress [17].

II. *Improved haemodynamic stability* HDF increases UF and improves intradialytic haemodynamic stability [74], leading to less intradialytic hypotension [75], reduced incidence of strokes [23], and faster recovery time post-dialysis [31].

III. *Biocompatibility and reduced inflammation* The use of 'ultrapure' dialysate and increased removal of inflammatory cytokines reduce inflammation and oxidative stress [17].

Studies in Adults

In adults on dialysis, the Estudio de Supervivencia de Hemodiafiltración On-line (ESHOL), one of the largest RCTs comparing HDF vs high-flux HD in adults and achieving convective volumes of 23 L/session, has shown a priori that patients on high-volume HDF have a survival benefit compared to those on high-flux HD [23]. Earlier RCTs including the CONvective TRAnsport STudy (CONTRAST) [22], Turkish Online Haemodiafiltration [24] studies, and French Convective versus Hemodialysis in Elderly (FRENCHIE) [75] aimed for lower convective volumes, and only a small proportion of their patients achieved these target volumes. Hence, these studies were not able to demonstrate an a priori benefit of HDF. However, on post-hoc analysis, the Turkish [24] and CONTRAST [22] studies also showed that HDF patients who achieved a higher convective volume (>17.4 L/session in the Turkish study [24] and >20 L/session in the CONTRAST study [22]) had lower all-cause and cardiovascular mortality. Pooled data [25] from the RCTs has indicated a critical dose-response relationship between the magnitude of the convective volume and

survival, with a goal of at least 23 L per session. Similarly, other RCTs, observational studies, and registries provide conflicting results, which to some extent can be explained by differences in the convective volume [63, 74, 76–80], with patients achieving the highest convective volumes benefiting most. A Cochrane review suggests that there is no clear benefit of HDF over HD, but these meta-analyses combine outcomes of both haemofiltration and HDF studies as 'convective therapies', and do not interpret outcomes based on convective volumes [81]. As stressed above, not all convective therapies are equal [82, 83].

HDF has been correlated with improved cardiovascular outcomes in adults [21], partly explained by improved haemodynamic stability, leading to less intradialytic hypotension and faster recovery time after dialysis [23, 24, 75]. ESHOL [23], FRENCHIE [75], and several observational studies have shown that HDF improves intradialytic haemodynamic stability compared to HD. Post-hoc analysis of the CONTRAST study showed that HDF helps improve phosphate control (more than 30%) when compared to HD [84], and fibroblast growth factor 23 has a 30% greater clearance by HDF [85]. In addition, patients on HDF compared to HD may have a lower erythropoietin resistance index, possibly associated with reduced inflammation, better biocompatibility, and reduced removal of erythropoiesis-inhibiting factors [78, 86].

Studies in Children

HDF is increasingly used in children, but until recently there have been few data on outcomes. Fischbach et al. showed improved nutrition and growth [36], reduced inflammation [87], regression of left ventricular hypertrophy [87, 88], improved anaemia control [87] and reduced post-dialysis recovery time [36] in a small number of children undergoing daily HDF. In the study by Fischbach et al. impressive catch-up growth, achieving a normal height, at/or above their target mid-parental height was shown [36]. However, this small single-centre study utilised 6 days per week HDF in the pre-dilution mode. Daily HDF improved appetite and corrected metabolic acidosis, but other hypothetical mechanisms for improved growth may also be involved. It is postulated that HDF may have a possible anabolic effect associated with the greater removal of uraemic toxins such as inflammatory cytokine and hormones that regulate appetite and growth, as well as superior clearance of accumulated endogenous somatomedin and gonadotropin inhibitors, improving target tissue sensitivity to growth hormone [73]. Further single-centre studies have shown improvements in left ventricular function within a short period of HDF therapy [89, 90]. A small single-centre study also suggests that switching children from nocturnal in-centre HD to nocturnal in-centre HDF may significantly improve BP, phosphate, and PTH control [31]. Recent studies from our group have shown that when HD patients are switched to HDF keeping all other dialysis-related parameters constant, a significant improvement in inflammation, antioxidant capacity, and endothelial risk profile is achieved within 3 months [17]. This study suggests that even in children who have a short anticipated time on dialysis, HDF is superior to conventional HD. Table 21.2 summarises paediatric studies on HDF and the key outcomes. A recent report from the Italian Registry suggests that HDF use in Italy has been limited to approximately a quarter of patients on extracorporeal dialysis, particularly those with high dialysis vintage, younger age, or a long expected waiting time to renal transplantation [91].

The International Pediatric Hemodialysis Network (IPHN) has recently performed a multicentre observational study to test the hypothesis that HDF improves the cardiovascular risk profile, growth and nutritional status, and health-related quality of life outcomes in children compared to conventional HD – the HDF, Hearts, and Height (3H Study) [31, 64]. 3H suggests that HDF halts the progression of increasing carotid intima-media thickness (Fig. 21.2), is associated with an increase in height standard deviation score, and improves patient-related outcomes compared to HD (Fig. 21.3) [31].

Table 21.2 Key studies in children on HDF

Outcomes	No. of participants/ (reference)	Conclusions
Uraemic toxin clearance, endothelial risk profile, inflammation	22 children (Agbas et al. [17])	Significant improvement in inflammation, antioxidant capacity, and endothelial risk profile achieved within 3 months of HDF compared to HD treatment: Reduction in b2M ($p < 0.001$), hCRP, ADMA, SDMA, AGEs, ox-LDL ($p < 0.01$ for all) Increase in total antioxidant capacity ($p < 0.001$) compared to HD
	30 children (Morad et al. [90])	HDF associated with decreased pro-inflammatory cytokine profile (IL-6, TNF-a, hsCRP) compared to conventional HD: hsCRP 3.41 μg/mL vs. 7.98, IL-6 11.44 pg/mL vs. 168.40 pg/mL ($p = 0.002$) TNF-a 11.45 pg/mL vs. 15.70 pg/mL ($p = 0.008$) in the HD vs. after 6 months on HDF
	33 children (Fadel et al. [89])	Significant decrease in hsCRP upon changing from HD to online HDF: hsCRP 7.9 ± 8.9 (range 0.3–35.7) μg/mL after 6 months of conventional HD vs. 3.4 ± 3 (range from 0.2 to 13) μg/mL after 6 months of online HDF ($p = 0.01$)
	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	At 12-month follow-up, hsCRP levels increased in HD but remained static in HDF: Median CRP 3.9 vs. 0.9 mg/L ($p < 0.0001$)
Phosphate and PTH	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	Serum phosphate levels similar between HD and HDF patients but significant difference in PTH: PTH levels declined in HDF cohort over 12 months ($p = 0.03$) but remained static in HD ($p = 0.13$), resulting in lower levels in HDF at 12 months (86 vs. 365 pmol/L, $p = 0.004$). No difference in the type of phosphate binders or cinacalcet use, serum and dialysate calcium, and 25-OH- vitamin D levels
Blood pressure and cardiovascular outcomes	33 children (Fadel et al. [89])	Improved systolic function of the myocardium in the group treated by HDF: mean systolic function in HD vs. HDF was 35 ± 5.6% vs. 39 ± 6% ($p = 0.007$) and mean ejection fraction 68 ± 8.5% vs. 72 ± 8% ($p = 0.05$). Significant reduction in diastolic dysfunction prevalence with HDF compared to conventional HD ($n = 25$ vs. $n = 19$, $p = 0.03$).
	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	Annualised change in cIMT-SDS was a median increase of 0.41 in the HD group and decrease −0.07 in the HDF group ($p = 0.02$), resulting in a significant difference between groups at 12 months ($p = 0.009$). On propensity score analysis, children on HD had a +0.47 greater increase in annualised cIMT-SDS change (95% CI 0.07–0.87; $p = 0.02$) compared to those on HDF. PWV-SDS higher in HD compared to HDF (2.07 vs. 0.68, $p = 0.002$) at baseline and at 12 months (1.43 vs. −0.31, $p = 0.0008$), but no difference in sensitivity analysis 24 h MAP-SDS higher in HD compared to HDF (2.75 vs. 0.98, $p < 0.0001$) at baseline and at 12 months (3.74 vs. 1.38, $p < 0.0001$). MAP-SDS increased from baseline to 12 months in HD ($p < 0.0001$) whereas unchanged in HDF ($p = 0.35$). *LVMI* at baseline comparable in HD and HDF ($p = 0.07$), but higher in HD at 12 months (47.4 vs. 39.3 g/[$m^{2.16 + 0.09}$], $p = 0.017$).

(continued)

Table 21.2 (continued)

Outcomes	No. of participants/ (reference)	Conclusions
Growth and nutrition	15 children switched to daily online HDF (Fischbach et al. [36])	Significant increase in growth velocity upon switching to daily online HDF, increase in height SDS from −1.5 ± 0.3 to +0.2 ± 1.1 SDS, $p < 0.05$ Increased appetite, decreased metabolic acidosis, BMI increase from 16.5 ± 2.0 to 18.0 ± 2.4, $p < 0.05$
	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	Small but statistically significant increase in the annualised change in height SDS in children on HDF ($\Delta = -0.16$; $p = 0.02$), whereas height SDS remained static in HD; HDF patients were taller than HD patients at 12 months ($p = 0.04$). Effect was independent of growth hormone therapy. In children above 13 years of age ($n = 49$ on HD and $n = 32$ on HDF), the median annualised change in height-SDS was significant between groups (HD $\Delta = -0.01$ and HDF $\Delta = +0.15$; $p = 0.005$).
Anaemia	190 children enrolled and 133 (78 on HD and 55 on HDF) completed 1-year follow-up (Shroff et al. [31])	Median Hb levels (g/dL) at baseline: 10.3 vs. 10.9 ($p = 0.41$), after 12 months: 10.4 vs. 12.0 ($p = 0.001$) Haemoglobin levels comparable between groups at baseline, unchanged in HD but increased in HDF during treatment, resulting in significantly higher haemoglobin at 12 months in HDF group, with no difference in EPO dosage:

MBD metabolic bone disease, *RR* relative ratio, *CI* confidence interval, *B* regression coefficient, *RRF* renal residual function, *b2M* beta-2 microglobulin, *mo* month(s), *RCT* randomised-control trial, *hsCRP* high sensitivity C-reactive protein, *IL-6* interleukin 6, *IL-10* interleukin 10, *AGEs* advanced glycation end-products, *ox-LDL* oxidised low-density lipoprotein, *ADMA* asymmetric dimethyl arginine, *SDMA* symmetric dimethyl arginine, *BMI* body mass index, *OL-HDF* online haemodiafiltration, *pwv* pulse wave velocity, *MAP* mean arterial pressure, *SDS* standard deviation score, *LVMI* left ventricular mass index, *PTH* parathyroid hormone

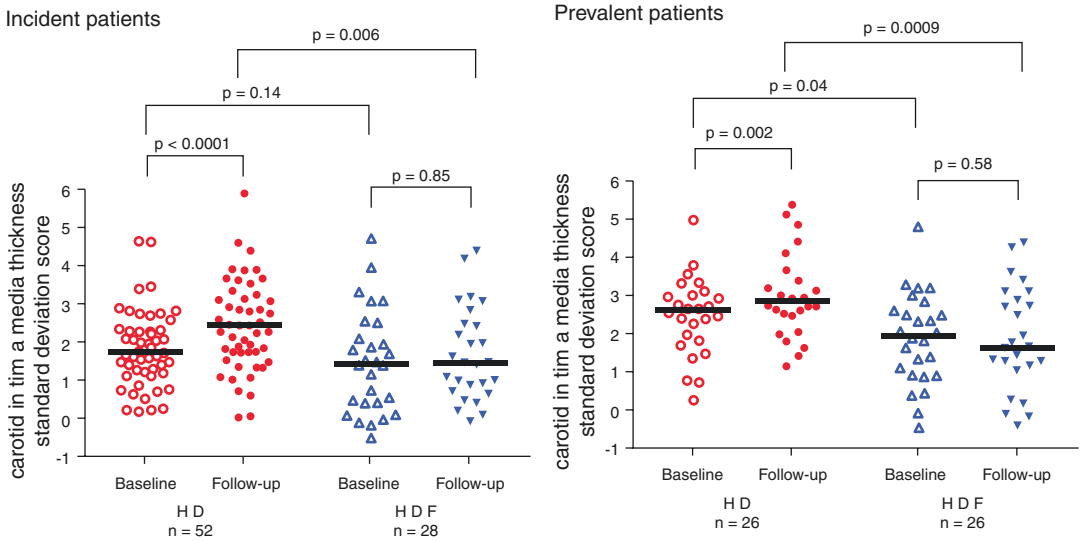

Fig. 21.2 Data from the 3H study showing the carotid intima-media thickness standard deviation score (cIMT-SDS) at baseline and 12 months in incident and prevalent HD and HDF patients. Data are shown as median and interquartile range. Incident patients on HD and HDF did not show any difference in cIMT-SDS at baseline ($p = 0.14$). Prevalent patients on HD had a significantly higher cIMT-SDS at baseline compared to HDF ($p = 0.04$). cIMT-SDS increased significantly from baseline in incident and prevalent HD patients ($\Delta = +0.64$; $p < 0.0001$ and; $\Delta = +0.34$, $p = 0.002$ respectively), but was static in HDF patients ($\Delta = -0.13$, $p = 0.85$ and $\Delta = -0.04$, $p = 0.58$ respectively)

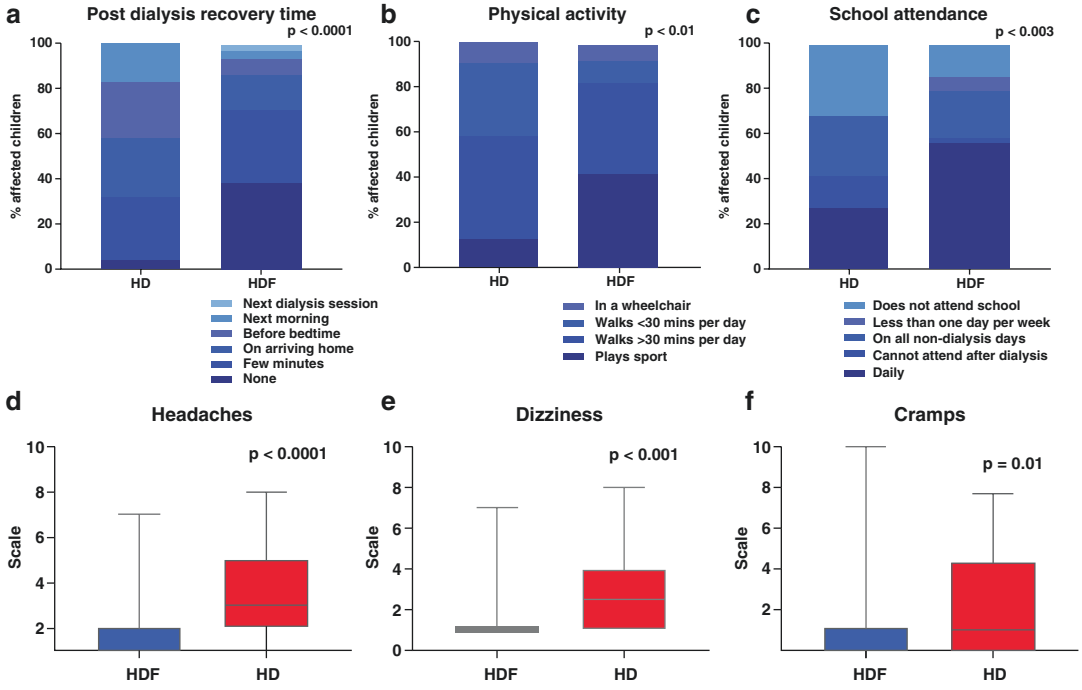

Fig. 21.3 Self-reported patient-related outcome measures. (**a**) Post-dialysis recovery time, (**b**) physical activity index, and (**c**) school attendance – individual scales for each measure shown on the figure. (**d**) Headaches, (**e**) dizziness, (**f**) cramps – graded on a scale of 1–5 (5 = most severe or frequent)

Children on HDF had improved blood pressure and haemodynamic stability, reduced inflammatory markers, and lower β2-microglobulin compared to children on HD [31]. The annualised change in vascular measures correlated with improved BP control and clearances on HDF. The 3H study demonstrated a very high prevalence of sub-clinical cardiovascular disease in children on dialysis and an attenuated progression of vascular changes in children receiving HDF compared to children receiving conventional HD [31]. Within 1 year of conventional HD, the cIMT increased by 0.41 SDS, whereas there was no change observed in HDF patients [31]. Improved fluid removal as well as clearance of middle-molecular-weight uraemic toxins by HDF were strongly correlated with improved vascular outcomes in HDF.

In the 3H trial, growth rate, a sensitive overall health parameter in children, was significantly higher in HDF compared to HD patients, independent of growth hormone treatment [31]. Convection may clear insulin-like growth factor-1-binding proteins and their metabolites that dampen the response to endogenous somatomedin and gonadotropins [73, 92]. Although mechanisms of improved growth in HDF are not clear, the 3H study showed an inverse correlation between height-SDS increase and β2-microglobulin, suggesting that clearance of middle-molecular-weight compounds may partly alleviate growth hormone resistance in dialysis patients.

Importantly, children treated with HDF rather than conventional HD reported a reduction in the frequency and/or severity of headaches, dizziness, and cramps on dialysis (Fig. 21.3), as well as a reduction in the post-dialysis recovery time, leading to an improvement in school attendance and physical activity [31]. Patient-related outcome measures that are primarily associated with fluid status, such as the post-dialysis recovery time, headaches, dizziness, and cramps, were less frequent and less severe in HDF compared to HD patients. Lower inter-dialytic weight gain on

HDF, implying lower ultrafiltration rates per session and greater haemodynamic stability, was strongly associated with fewer symptoms. Similar reports of fewer symptomatic intradialytic hypotensive episodes and muscle cramps were reported in a vulnerable population of elderly dialysis patients in the FRENCHIE study [75], and a lower risk of stroke, attributed to improved intradialytic haemodynamic stability in HDF patients, was reported in ESHOL [23, 93]. The Standardized Outcomes in Nephrology – Hemodialysis (SONG-HD) workgroup has identified fatigue as one of the most highly prioritised outcomes for dialysis patients and clinicians [94], and children value 'life participation' as their most important outcome measure.

In the 3H study, median convection volumes of 13.4 L/m^2 were achieved in children [64], which is comparable to the 23 L per 1.73 m^2 per session that proved beneficial in the pooled adult studies [25]. Importantly, the convection volume was independent of patient-related factors, such as age, gender, access type, or dialyser used, but strongly correlated with the blood flow rate [64], implying that convection volume is a modifiable factor that can be manipulated and optimised by the dialysis team.

Importantly, no reduction in serum albumin levels was observed with HDF, and no difference in the rate of change of residual renal function [31] was observed in children on either dialysis modality, implying that HDF is a safe treatment. Moreover, HDF patients who had a significant loss in residual renal function during the study period were able to maintain constant β2-microglobulin levels, whereas levels increased in HD patients [31]. Although the 3H study included over 40% of children on extracorporeal dialysis in Europe, it is not a randomised trial, so confirmation of the observed results through randomised trials is required.

Conclusions

HDF is a safe and effective dialysis therapy that has been shown to have significant benefits over conventional HD both in children and adults. Careful attention to the HDF technique, particularly focusing on achieving optimal convective volumes, is important in order to gain maximum benefit from this treatment.

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