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Fluid Convection, Generation and Reinfusion in Haemodiafiltration

Emily J. See, Carmel M. Hawley, John WM. Agar and David W. Johnson

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<http://dx.doi.org/10.5772/62886>

Abstract

Despite widespread use in clinical practice for over 30 years, many questions remain unanswered regarding fluid convection and reinfusion strategies in haemodiafiltration (HDF). Randomised controlled trials have failed to consistently demonstrate improved survival with convective therapies, but a dose-dependent improvement in outcome has been suggested. The 'minimum' and 'ideal' volumes of convection are undefined. Online generation of ultrapure dialysis fluid has allowed unprecedented convection volumes; however, delivery of fluid directly into the blood circuit requires strict monitoring. The replacement fluid may be reinfused at multiple points in the circuit. Post-dilution HDF is highly efficient in terms of solute clearance but is limited by haemoconcentration. Pre-dilution HDF prolongs filter life but requires significant convection volumes to achieve adequate solute clearance. Mid-dilution HDF utilises a specific dialyser, which is associated with additional cost and escalating transmembrane pressure. Mixed-dilution HDF appears to offer an attractive balance between solute clearance efficiency and haemoconcentration, however these findings need to be confirmed in large studies. The majority of trials comparing fluid reinfusion strategies have enrolled small numbers of patients over brief study periods. It is unclear whether high-quality evidence examining fluid convection and reinfusion will become available and practice may need to rely on observational data.

Keywords: convection, online fluid generation, reinfusion, haemodiafiltration, end-stage renal disease, outcomes, adverse effects, haemodiafiltration methods, haemodialysis solutions

1. Introduction

With its innovative integration of convective and diffusive techniques, haemodiafiltration (HDF) enhances solute removal across a broad molecular-weight spectrum, which theoretically may improve patient outcomes. Solute clearance by convection requires substantial volumes of ultrafiltration, which in turn necessitates the administration of exogenous fluid replacement. Whilst this fluid may originate from multiple sources, current practice centres around the online generation of sterile, ultrapure dialysate which may be reinfused directly into the circulation. This process requires strict water quality and safety monitoring but enables reinfusion of unlimited volumes of substitution fluid, traditionally either before (pre-dilution HDF) or after (post-dilution HDF) the dialyser. In recent years, two novel HDF techniques (mixed- and mid-dilution HDF) have been developed which permit simultaneous pre- and post-dilution. Both the optimal 'dose' of convection and the ideal site of fluid reinfusion are yet to be determined. This chapter will discuss the evidence surrounding these topics in contemporary HDF practice.

2. Fluid convection

Convective solute transport occurs due to the sieving of solutes across an open membrane in the context of large volumes of ultrafiltration. To achieve maximal convective flux, the volume of ultrafiltration must be optimised. The total volume of ultrafiltration is determined by the ultrafiltration rate and treatment time and is referred to as the convection volume. This value is related to, but distinct from, the substitution volume, which is the quantity of replacement fluid reinfused into the circuit. The difference between the two represents the net fluid removal during the treatment.

Significant changes in the magnitude of the convection volume have taken place since the inception of HDF in the 1970s. Classic HDF used an average substitution volume of 9 L per session, which was primarily limited by cost and logistical issues associated with commercially produced replacement fluid. This is comparable to the estimated amount of convection that occurs during high-flux haemodialysis (HD) today. Most recently, innovations in fluid generation have allowed online production of substitution fluid, which has facilitated convection volumes of 25–40 L per session (and up to 60 L, depending on the mode). This advance has revolutionised the practice of HDF and has piqued interest in the modality worldwide. Importantly, parallel advances in fluid balancing systems have permitted the safe and accurate regulation of ultrafiltration, even at these exceptionally high volumes.

Recently, EUDIAL has set a minimum convection volume for a treatment to be classified as HDF. This threshold is equivalent to 20% of the total processed blood volume [1]. For example, a 4-h treatment with a blood flow rate of 350 ml/min (~84 L/treatment) must have a minimum convection volume of 17 L. Below this, the treatment would be classified as high-flux HD. In general, the convection volume in the post-dilution HDF should be between 17 and 27 L per session [2].

Due to the obvious impact on solute clearance efficiency, the convection volume must be standardised according to the site of fluid reinfusion. This corrected value is termed the *effective convection volume*. In post-dilution HDF, the effective convection volume is the same as the ultrafiltration volume. In mid-dilution HDF, conversion reference tables are provided by the manufacturer. In pre- and mixed-dilution HDF, the ultrafiltration volume must be standardised using a dilution factor (DF) [1]. This is calculated using the plasma water flow rate (Q_{pw}), upstream reinfusion flow rate (Q_{inf}), blood flow rate (Q_b), haematocrit (Hct) and protocrit (Pct) according to the equation:

$$DF = \frac{Q_{pw}}{Q_{pw} + Q_{inf}}$$

$$Q_{pw} = Q_b \times (1 - Hct) \times (1 - 0.016 - Pct)$$

N.B. (1 - 0.016 - Pct) is approximated to 0.93.

2.1. Determinants of convection volume

The maximal achieved convection volume is dependent on several patient- and treatment-related factors, the most important of which are treatment time and blood flow rate (**Table 1**). Other determinants include the transmembrane pressure gradient (TMP), specific characteristics of the dialyser (e.g. membrane surface area, UF coefficient, capillary dimensions, biocompatibility), haematocrit and serum albumin [3, 4]. The term *filtration fraction* is used to describe the ratio between the ultrafiltration rate and the blood flow rate. In post-dilution HDF, it is limited to <0.3 to avoid complications relating to haemoconcentration, namely membrane clotting and high TMP.

<i>Increase convection volume</i>	High blood flow rate
	Long treatment time
	High filtration fraction
	Large membrane surface area
	Biocompatible dialyser
	High UF co-efficient
<i>Decrease convection volume</i>	Hypoalbuminaemia
	Poor vascular access
	High haematocrit
	Small calibre membrane fibres

Table 1. Determinants of convection volume.

2.2. Effect of convection volume on patient outcome

Whilst an overall survival benefit favouring convective therapies has not been established, several studies have supported a ‘dose–response’ relationship between convection volume and survival (**Table 2**). The Dialysis Outcomes and Practice Patterns Study (DOPPS) first suggested this effect when it showed a 35% relative risk (RR) reduction in mortality between HDF with substitution volumes of 15–25 L and low-flux HD [5]. Since then, there have been three large randomised controlled trials published with similar findings—the CONvective TRANsport STudy (CONTRAST) [6], the Turkish HDF study [4] and the Estudio de Supervivencia de Hemodiafiltración On-Line (ESHOL) study [7]. In the post hoc analyses of the CONTRAST and the Turkish HDF study, patients with the highest convection volumes were shown to have a survival benefit [4, 8]. In CONTRAST, this difference was seen in the tertile of patients treated with convection volumes >21.95 L (hazard ratio (HR) 0.61) and in the Turkish HDF study, it was seen in patients with a substitution volume >17.4 L (HR 0.54). The ESHOL study demonstrated a similar dose–response effect in its primary analysis: patients treated with convection volumes above 23.1 L had improved all-cause and cardiovascular mortality (HR 0.60) with a further improvement seen at convection volumes >25.4 L (HR 0.55) [7]. Further supporting a dose-dependent effect, a pooled analysis of CONTRAST, the Turkish HDF study, the ESHOL study and a French HDF study demonstrated a statistically significant reduction in all-cause mortality in patients receiving the highest convection volumes (24.4–27.4 L) compared with standard HD [8].

The effect of cumulative convection dose on survival has recently been investigated by a retrospective observational study of incident HDF patients. They showed an association between weekly convection volume and survival which began to be apparent at 55 L/week (30 L/week/m²) and plateaued at 70–75 L/week (40–45 L/week/m²) [9]. This is the first paper to recognise the importance of cumulative treatment dose, taking into account session frequency, which may be particularly relevant to mortality outcomes.

	Substitution volume	Convection volume	RR or HR (CI)
DOPPS [5]	>15 L/session	>17.5 L/session	0.65
CONTRAST [6]	>19.45 L/session	>21.95 L/session	0.61 (0.38–0.98)
TURKISH OL-HDF [4]	>17.4 L/session	>19.9 L/session	0.54 (0.31–0.93)
ESHOL [7]	20.6–22.9 L/session	23.1–25.4 L/session	0.60 (0.39–0.90)
	>22.9 L/session	>25.4 L/session	0.55 (0.34–0.84)

Table 2. Volumes required to achieve a reduction in mortality (expressed as RR or HR with confidence interval (CI), and assuming an average net fluid removal of 2.5 L).

2.3. Assessment of adequate solute clearance

Assessment of HDF adequacy must take into account removal of solutes across all molecular weights. Specifically, enhanced middle- and large-molecule clearance should not occur at the expense of inferior small-solute clearance. For practical purposes, small-solute clearance

should be quantified using the same approach as for HD, whether that be calculation of Kt/V_{urea} or percentage reduction in urea. Of note, blood samples must be taken upstream of any fluid reinfusion port to avoid sample dilution. This is especially relevant in the pre-dilution and mixed-dilution HDF modes where substitution fluid is infused before the dialyser. In terms of assessing middle-molecule clearance, convective dialysis 'dose' appears to be a linear function of substitution volume so reporting of this value is routinely used [11, 12].

2.4. Consequences of high convection volume

Due to the indiscriminate nature of solute removal by large-volume ultrafiltration, inadvertent removal of beneficial solutes is unavoidable. The most significant example of this is albumin. The degree of albumin loss in a HDF treatment is dependent on the membrane type, ultrafiltration volume and TMP. The site of fluid reinfusion is also relevant as a key determinant of ultrafiltration volume and TMP; the use of post- and mid-dilution HDF may increase the loss of albumin up to fivefold [12]. Albumin removal can be minimised by profiled filtration modes, which limit initial filtration, or by regulated TMP control. Fortunately, as described in the randomised trials and observational studies, albumin loss did not appear to affect nutritional parameters or serum albumin concentration [4, 6, 9, 10, 13]. It should therefore not limit the utilisation of HDF or the prescribed convection volume in current practice, but will require ongoing evaluation in future trials given the lack of robust safety data.

2.5. Individualising convection volume

The requisite 'dose' of convection likely varies between individuals. This in turn has theoretical implications for future trial design and practical implications for HDF prescription. Two important patient characteristics that should be considered are patient size and residual renal function [1]. Having an absolute convection volume target for all patients is not logical since patients vary widely in size, body composition and metabolic rate. Recently, the HDF Pooling Project Investigators looked at the effect of convection volume on mortality when stratified convection volumes were standardised according to patient size. The survival advantage for higher convective dose was maintained after standardising for total body water and body surface areas, which are surrogate markers of lean body mass, but not for body weight or body mass index [8]. Other patient factors may also be important in determining optimal convection volume including age, ethnic background, comorbidity index, diabetic status and dialysis vintage. The importance of these additional factors is yet to be studied.

3. Substitution fluid

The degree of ultrafiltration that occurs in HDF necessitates reinfusion of large volumes of replacement fluid into the extracorporeal circuit. This fluid must be sterile and non-pyrogenic with a biochemical composition similar to plasma water. The replacement fluid may be obtained in two ways: internal substitution (e.g. internal filtration HDF, push-pull HDF,

double high-flux HDF and paired filtration dialysis) or external substitution (e.g. classic HDF and online HDF).

3.1. Internal substitution

3.1.1. Internal filtration HDF

Internal filtration HDF uses pressure profiling to take advantage of the substantial volumes of plasma water that can be filtered across high-flux dialysers. Difference in pressure between the blood and dialysate compartments results in proximal ultrafiltration followed by distal backfiltration (**Figure 1**). Backfiltration of dialysate is analogous to reinfusion of substitution fluid. Sudden shifts in plasma water may lead to increased rates of haemolysis. Backfiltration poses an additional risk of biological and endotoxin contamination; however, the use of dialysis membranes with a high endotoxin retention capacity minimises this risk.

3.1.2. Push-pull HDF

Push-pull HDF involves rapid alternations in ultrafiltration and backfiltration across a single high-flux dialyser using a double-pump system installed on the effluent line (**Figure 1**). These alternations are controlled by fluctuations in pressure that occur due to varying the volume of the dialysate compartment. Fluid is reinfused along the course of the dialyser, favouring the blood outlet port where the pressure in the blood compartment is lowest. The convection volume may be as high as 120 L throughout a standard 4 h treatment [14]. Albumin loss is significantly lower than in post-dilution HDF due to lower TMP [15]. Intermittent backfiltra-

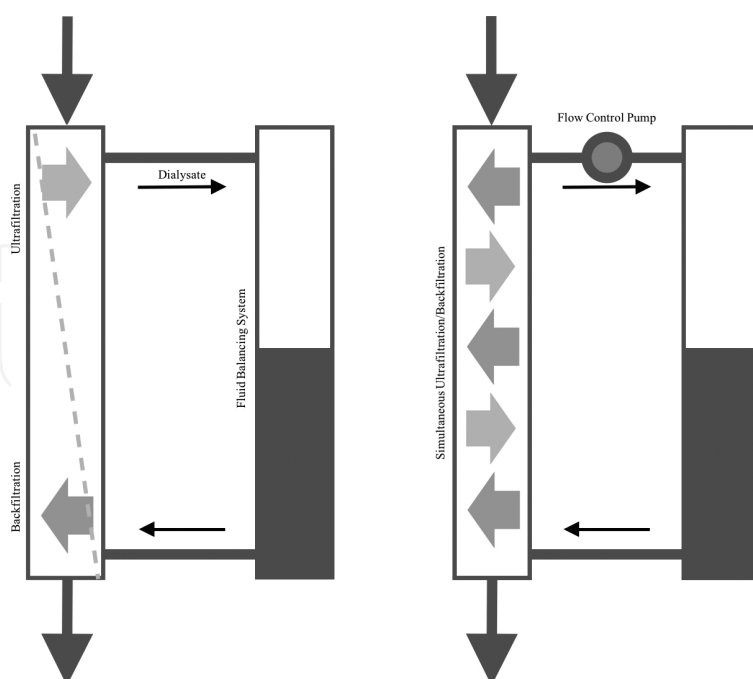


Figure 1. Internal filtration HDF and push-pull HDF.

tion removes protein deposition on the blood side of the membrane making this technique also suitable for extended-hour renal replacement therapy (e.g. nocturnal or continuous HDF).

3.1.3. Double high-flux HDF

Double high-flux HDF consists of two high-flux membranes connected in series and subjected to high blood and dialysate flow rates (**Figure 2**). Simultaneous diffusion and convection occur across the first membrane, whilst backfiltration of sterile dialysate occurs across the second. Variation in pressure and flow across the two dialysers is controlled by a resistance valve. Using this system, von Albertini was able to achieve 13 L convection per 2 h treatment and significant clearances of both small and larger solutes [16].

3.1.4. Paired filtration dialysis

Paired filtration dialysis uses two high-flux membranes connected in series. The first is a haemofilter with a small surface area, which performs ultrafiltration, and the second is a haemodialyser which performs diffusion. The substitution fluid is infused between the two. The main variation of this technique is paired filtration dialysis with endogenous reinfusion. This is also referred to as haemodiafiltration with endogenous reinfusion (HFR): In HFR, ultrafiltrate passes through a purifying charcoal/resin filter before being reinfused as substitution fluid (**Figure 2**).

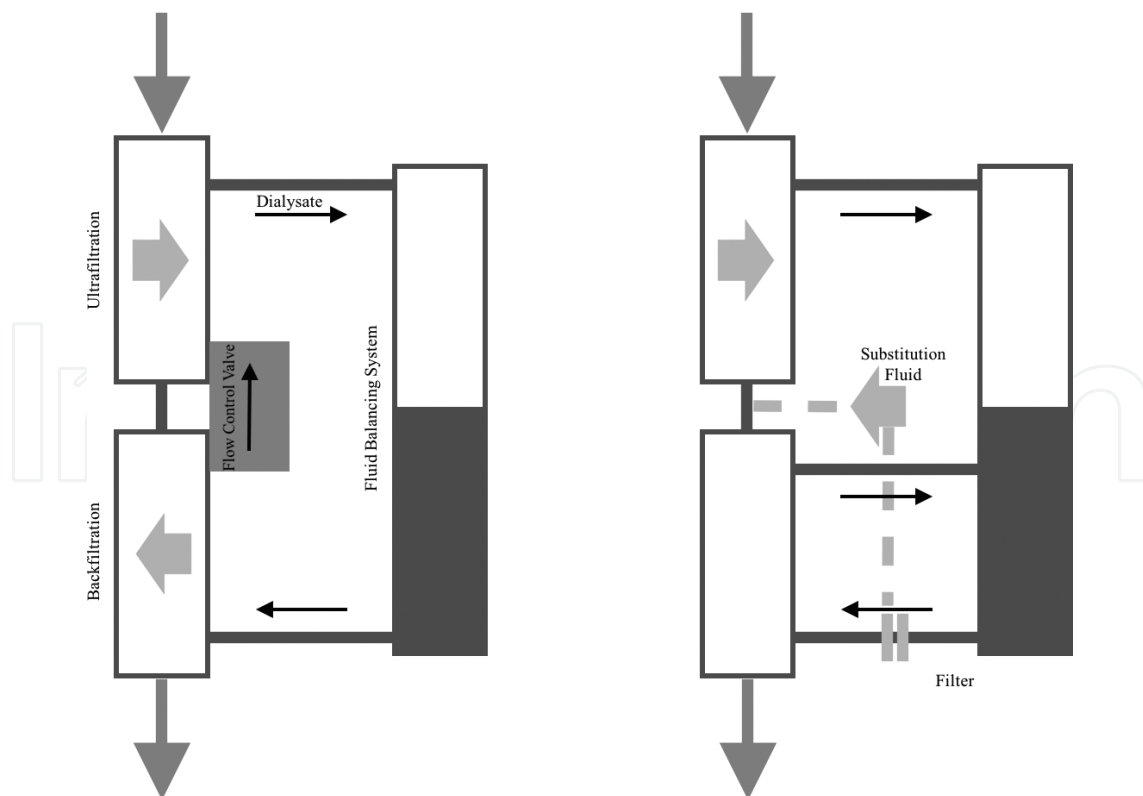


Figure 2. Double high-flux HDF and paired filtration dialysis with endogenous reinfusion.

3.1.5. Classic HDF

Classic HDF consists of a single dialyser which performs haemodiafiltration. The convection volume is replaced with packaged, commercially produced substitution fluid which is reinfused after the dialyser (**Figure 3**). This practice is associated with significant expense and obvious logistic issues [17]. These factors limit the volume of convection and therefore solute clearance.

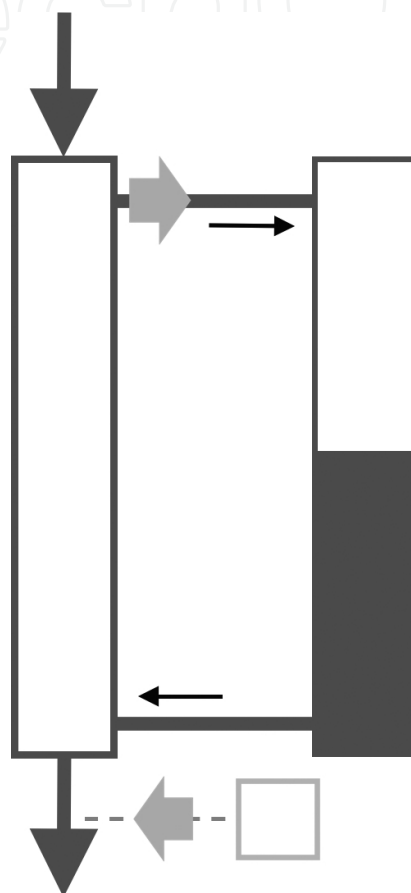


Figure 3. Classic HDF.

3.1.6. Online HDF

Online HDF relies on the ability of modern dialysis machines to generate unlimited quantities of ultrapure dialysis fluid, which can be reinfused directly into the circulation. In this system, dialysis fluid is prepared by the proportioning of ultrapure water and a concentrated electrolyte solution. This fluid is then used as both dialysate and substitution fluid (**Figures 6 and 7**). The integrity of the chemical composition is monitored using conductivity measurements. First described in the 1970s, the development of online fluid generation has facilitated the evolution of HDF from low-volume to high-volume practice [18]. It has been commercially available for over a decade and comes at minimal additional cost compared to high flux HD. This modality is the most widely utilised HDF technique in contemporary dialysis. It is well established in

Europe and Japan, and is experiencing escalating use in Australia and New Zealand (currently representing 16% of haemodialysis modalities) [19].

3.2. Biological safety

Since significant quantities of substitution fluid are being reinfused directly into the blood circuit, strict biological safety is essential. Many countries have specific policies outlining the technical requirements and water monitoring processes that dialysis units must comply with to practice HDF. Additionally, international guidelines exist which underpin the minimum standards for microbiological and chemical quality [20]. These technical requirements include the use of specific HDF machines and the ability to generate ultrapure water and dialysis fluid (Table 3). Generation of ultrapure water involves a pre-treatment system (microfiltration, softeners, activated carbon) followed by two reverse osmosis modules connected in series (Figure 4). In some water treatment systems, the reverse osmosis modules will be followed by a storage tank.

	Regular water	Ultrapure water	Ultrapure dialysate
<i>Microbial contamination</i>	<100 CFU/ml	<0.1 CFU/ml	<0.1 CFU/ml
<i>Bacterial endotoxins</i>	<0.25 IU/ml	<0.03 IU/ml	<0.03 IU/ml

Table 3. Water purity definitions.

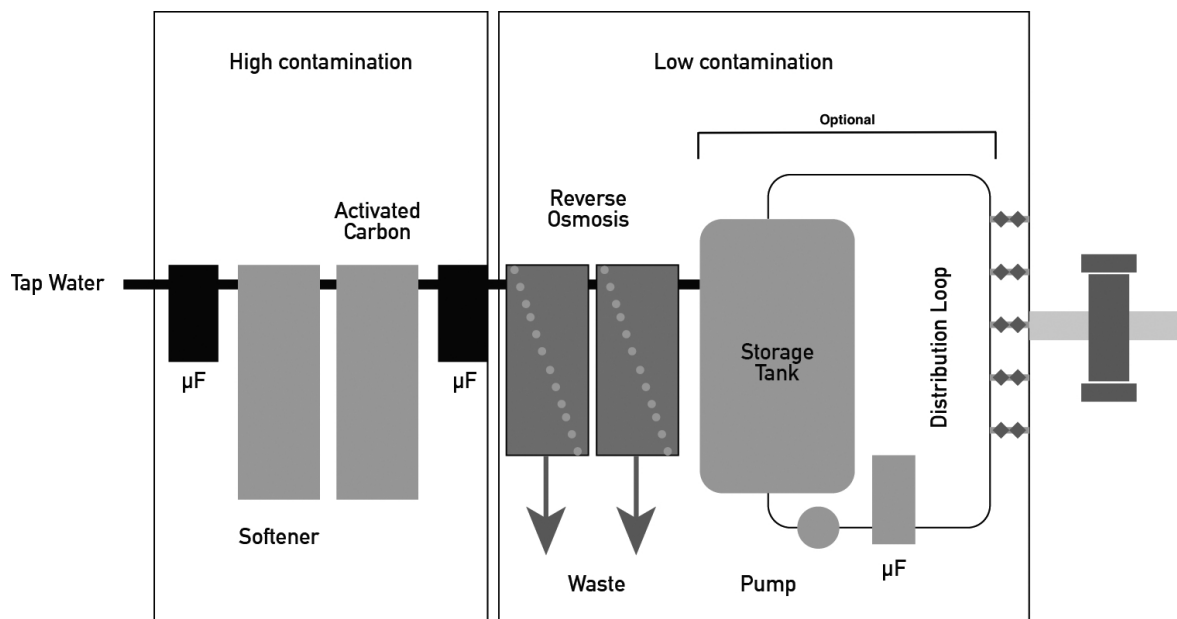


Figure 4. Conversion of tap water to ultrapure water.

Ultrapure water is converted to ultrapure dialysis fluid by combination with an electrolyte concentrate. The fluid then undergoes cold sterilisation, a process involving a series of filters with bacterial and endotoxin retentive properties at intermediate points in the circuit. An

inbuilt infusion pump diverts a proportion of ultrapure dialysate through another safety filter prior to being directly infused into the patient's bloodstream as replacement fluid (**Figure 5**).

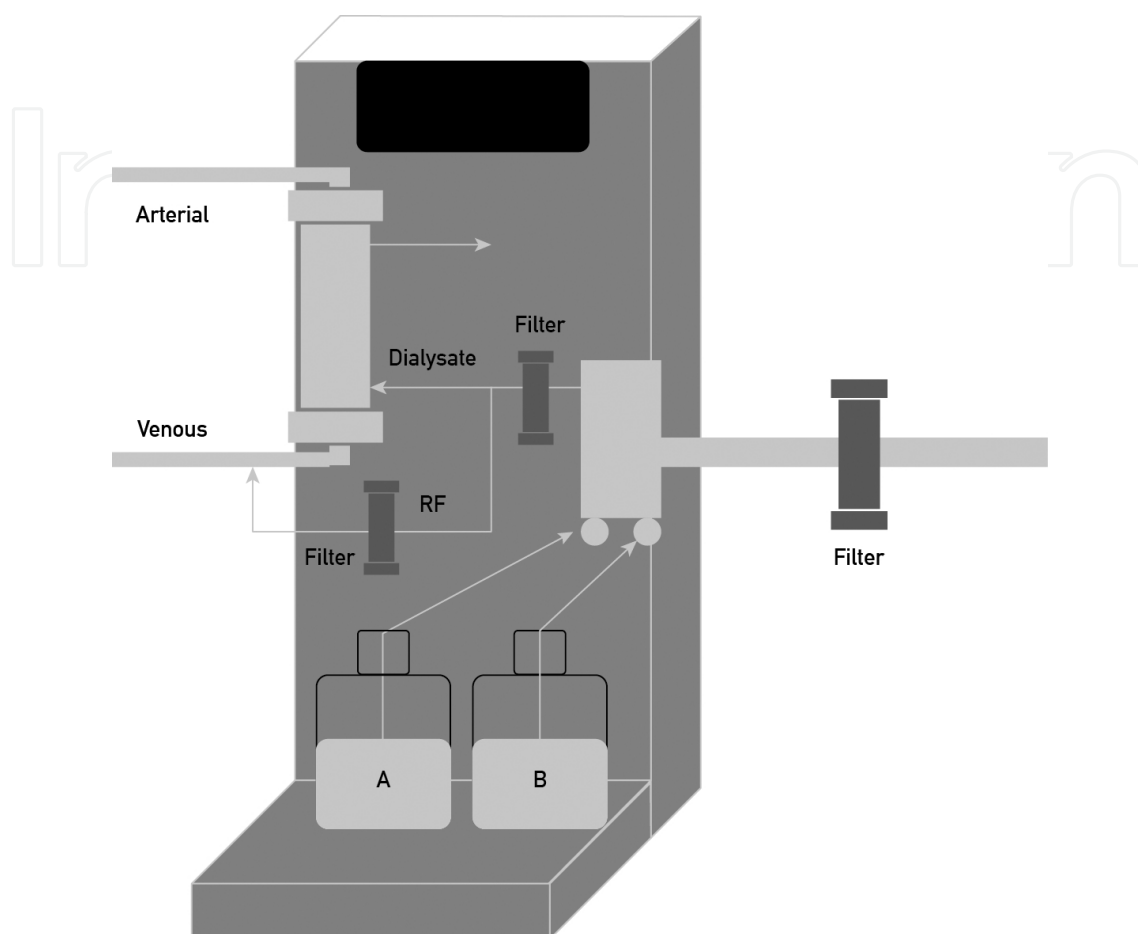


Figure 5. Conversion of ultrapure water to ultrapure dialysate.

Beyond the actual production of ultrapure dialysate, frequent disinfection of the water treatment system and dialysis machine, Thermochemical destruction of the biofilm, regular change of filters and maintenance of a permanent circulation of water are essential. Microbiological and endotoxin monitoring must also be carried out.

Several clinical studies have confirmed the safety of online HDF provided that appropriate CE marked and certified HDF machines are used and the best clinical practices are applied [21]. The three largest RCTs comparing HDF to HD did not demonstrate any higher incidence of infectious complications using online fluid generation [4, 8, 9].

4. Site of fluid reinfusion

Online HDF modalities are classified according to the location at which the replacement fluid is administered in the extracorporeal circuit. The replacement fluid has traditionally been

reinfused either before (pre-dilution) or after (post-dilution) the dialyser. Simultaneous pre- and post-dilution HDF techniques (mixed- and mid-dilution) have gained popularity in recent years. Each has relative advantages and disadvantages (**Table 4**). Other novel hybrid modalities have been proposed including ‘pre-dilution on demand’ and ‘backflush on demand’.

	Post-dilution	Pre-dilution	Mixed-dilution	Mid-dilution
<i>Small-solute clearance</i>	+++	+	+++	++
<i>Medium solute clearance</i>	++	+	+++	+++
<i>Protein-bound solute clearance</i>	++	+	+++	++
<i>Albumin loss</i>	++	+	+	+++
<i>Filter clotting</i>	++	+	+	+++
<i>High TMP</i>	++	+	+	+++

Table 4. Relative advantages and disadvantages of fluid reinfusion site.

4.1. Post-dilution HDF

Post-dilution HDF is regarded as the most efficient form of HDF in terms of solute clearance and is the most common format used in contemporary clinical practice. By reinfusing fluid after the dialyser, a continuous concentration gradient is maintained along the entire course of the dialyser (**Figure 6**). This approach has been shown to be superior to both high-flux HD and pre-dilution HDF in terms of small-solute and middle-molecule clearance [11, 22].

The efficiency of solute clearance in this system occurs at the expense of escalating haemoconcentration, which increases the risk of filter clotting, membrane pore occlusion and a subsequent increase in TMP. In extreme cases, red cell damage and protein denaturation may occur. There is also an increased risk of albumin loss as a result of the high TMP. The potential for haemoconcentration means that the filtration fraction must be limited which in turn necessitates a high blood flow rate to achieve adequate convection (typically >350 ml/min). Therefore, in patients with poor vascular access, inadequate blood flow may compromise the ability to achieve satisfactory clearances. Similarly, the risk of filter clotting means that patients with high haematocrit, cryoglobulinemia or gammopathy should be preferentially managed with pre-dilution or mixed-dilution HDF.

4.2. Pre-dilution HDF

In pre-dilution HDF, the substitution fluid is reinfused before the entry of blood into the dialyser (**Figure 6**). This avoids complications relating to haemoconcentration which extends filter life and lowers TMP. Because of the lower risk of clotting, heparin dose can be minimised and heparin-free dialysis for high-risk patients is possible [23]. In Japan, where this technique is used most widely, improvements in shear stress, blood pressure and haematological parameters (especially neutrophil and lymphocyte function) have also been reported [24, 25].

This same group have described improvements in dialysis-related symptom burden including itch, restless legs syndrome and insomnia compared to the post-dilution HDF.

Pre-dilution HDF has obvious deleterious effects on the efficiency of solute clearance. The reduced efficiency of this system means that ultrafiltration rates must be at least twofold higher than those in post-dilution HDF to achieve equivalent solute clearance. In fact, ultrafiltration rates of up to 100% of the blood flow rate are often used.

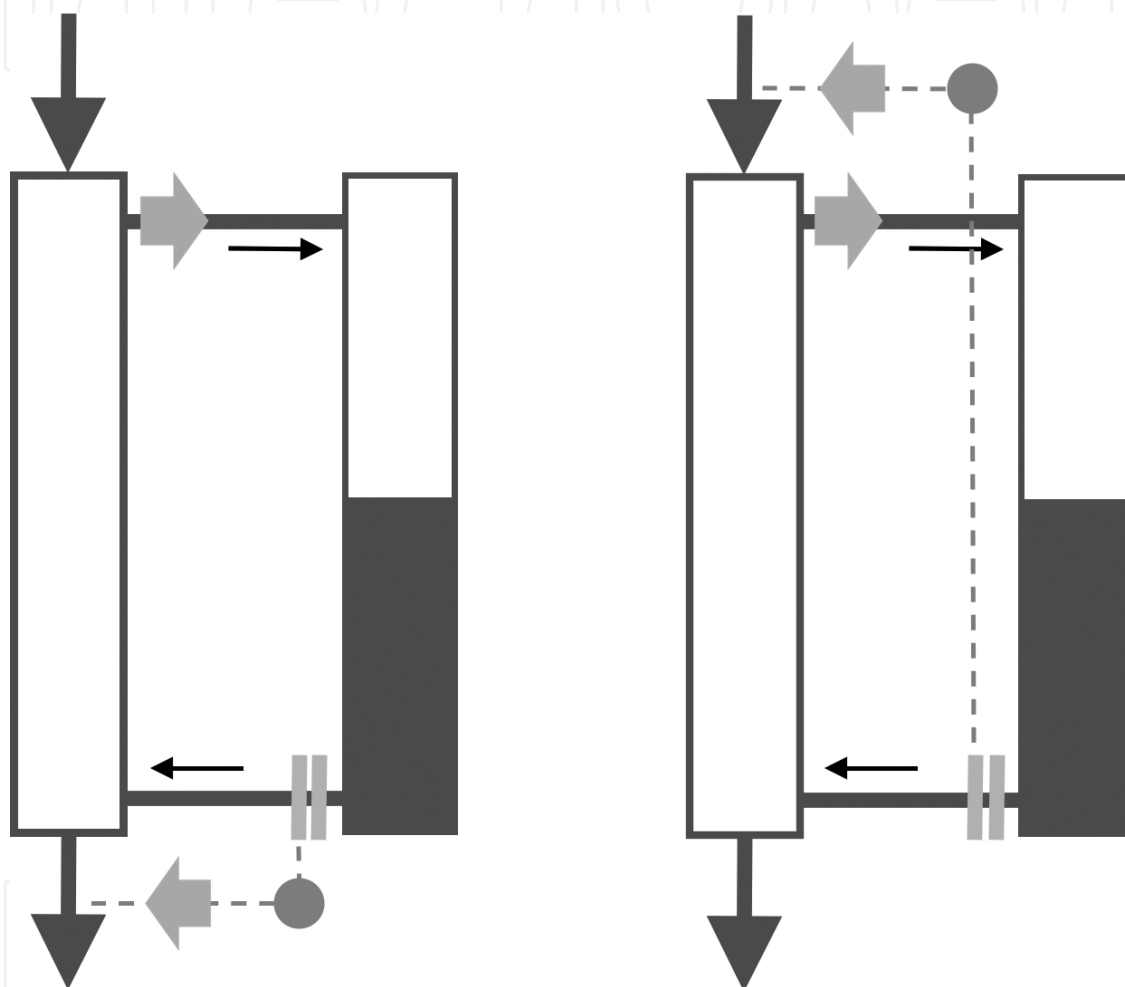


Figure 6. Post-dilution HDF and pre-dilution HDF.

4.3. Mixed-dilution HDF

In mixed-dilution HDF, fluid is simultaneously reinfused both before and after the dialyser in a ratio that is automatically regulated by the TMP and ultrafiltration feedback (Figure 7). An internal feedback mechanism maintains the TMP between 250 and 300 mmHg and ensures a maximum filtration fraction after considering the blood and dialysate flow, internal pressure and hydraulic permeability of the dialyser. Convection volume tends to be 30–40 L/session. TMP is calculated according to the pressure measured at four points in the system: blood entry

into the dialyser entry ($P_{\text{blood in}}$), blood exit from the dialyser ($P_{\text{blood out}}$), dialysate entry into the dialyser ($P_{\text{dialysate in}}$) and dialysate exit into the dialyser ($P_{\text{dialysate out}}$).

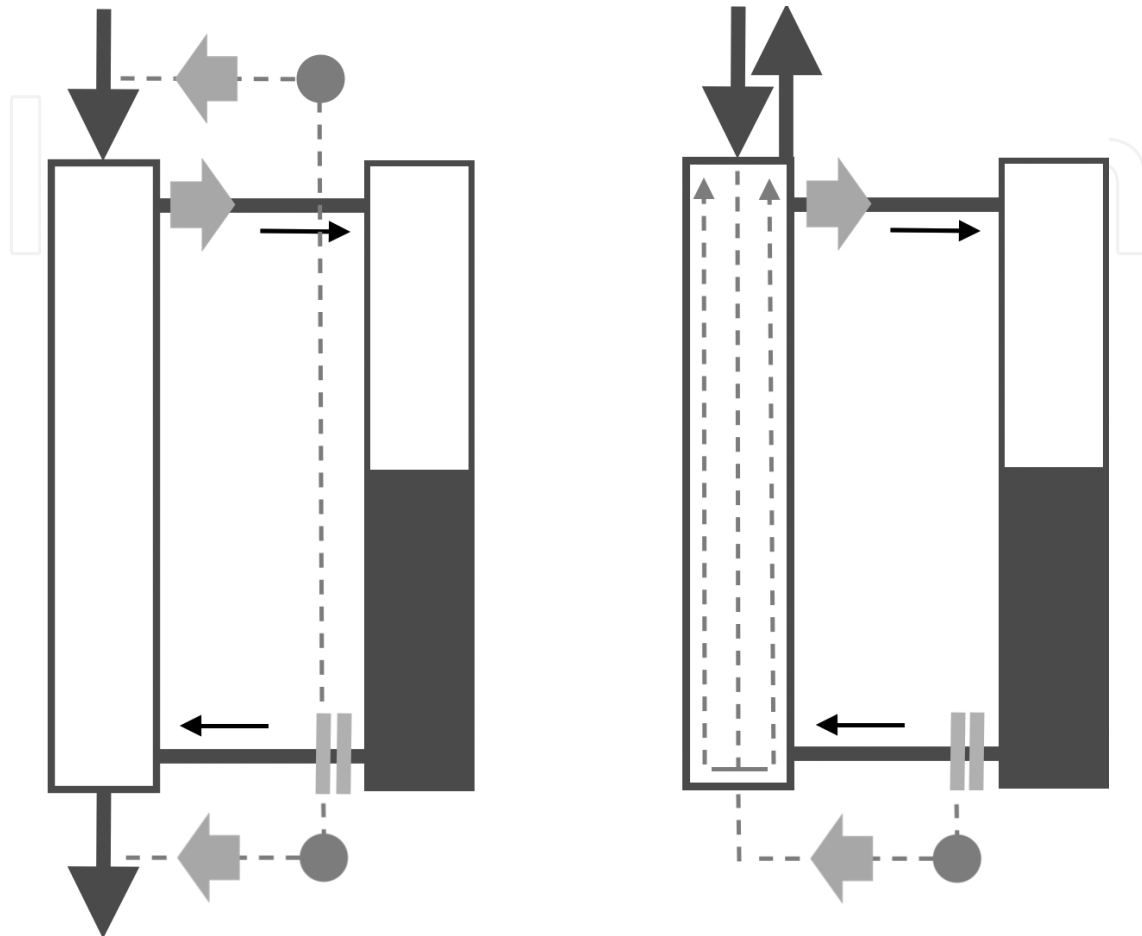


Figure 7. Representation of the mixed-dilution and mid-dilution HDF.

$$TMP = 0.5 \times [(P_{\text{blood in}} + P_{\text{blood out}}) - (P_{\text{dialysate in}} + P_{\text{dialysate out}})]$$

If the TMP rises beyond its maximum tolerated value, a fraction of infused dialysate is diverted from post- to pre-dilution, which decreases haemoconcentration and lowers the risk of membrane pore occlusion. Similarly, if the TMP falls below the target range, fluid is redirected towards the post-dilution mode to increase system efficiency.

Mixed dilution HDF has been shown to be non-inferior to post-dilution HDF in terms of small and protein-bound solute clearance and superior to post-dilution and pre-dilution HDF in terms of β_2 -microglobulin clearance ($\beta_2\text{-M}$) [26–29]. Whilst these were relatively small randomised trials which require larger studies to confirm their findings, mixed-dilution HDF appears to offer an attractive balance between efficiency of solute removal and minimisation of haemoconcentration-related complications. Specifically, it may be suitable for patients in

whom target convection volumes are not achieved by post-dilution HDF because of high haematocrit, high plasma protein, or inadequate vascular access and blood flow rate.

4.4. Mid-dilution HDF

Mid-dilution HDF similarly combines pre- and post-dilution fluid reinfusion into a hybrid system (**Figure 7**). It does so by utilising a specialised haemodiafilter, the Nephros OLpur MD 190. This filter is constructed in such a way that blood enters through the central core fibres of the dialyser and returns in the opposite direction peripherally. This model effectively comprises two dialysers in series. Substitution fluid is incorporated at the midpoint of the system, which creates an initial post-dilution stage followed by a pre-dilution stage. This enables a high-concentration gradient and encourages movement of small solutes in the first stage and maximal ultrafiltration of plasma water and convective removal of larger molecules in the second stage. Reinfusion rates up to 10–12 L/h are possible.

Unfortunately, due to the nature of the specialised dialyser, mid-dilution HDF is associated with higher costs. There is also a higher degree of albumin loss, which is not insignificant. Concerns exist regarding generation of a high TMP, which could compromise membrane permeability. A TMP of up to 1000 mmHg has been reported as necessary to achieve the required minimum ultrafiltration of 6 L/h [30]. This high TMP is especially problematic in the first section of the dialyser where the post-dilution phase takes place and is thought to be the result of partial fibre clotting and increased resistance to blood flow due to the reduced capillary diameter in this segment [31]. Given the pro-coagulant effect of rapid convection, adequate anticoagulation is necessary to ensure device patency. Reversal of the configuration of the blood tubing (i.e. connecting the arterial line to the venous port of the dialyser and vice versa) has been successfully trialled in mid-dilution HDF without significant effect on plasma clearances if adequate infusion rates are maintained [32, 33]. Consideration should also be given to the use of larger-surface filters (e.g. Nephros OLpur MD 220) [34].

When compared to post-dilution HDF, mid-dilution HDF is associated with inferior small solute but superior middle-molecule clearance (β_2 M, myoglobin, prolactin, RTP) and similar clearance of protein-bound solutes [35–37]. With increasing molecular weight, differences in treatment efficiency between mid- and post-dilution HDF rise [36]. Phosphate clearance is similar between the two groups. Whilst few studies have compared mid- and mixed-dilution HDF, one small prospective randomised trial found greater small-solute and middle-molecule clearance with mixed-dilution HDF though differences in dialyser membranes may have confounded their outcomes [30]. Another small prospective crossover study compared ‘simple mid-dilution’ (using two dialysers in series, rather than the Nephros OLpur MD 190) and mixed-dilution HDF. They similarly found that mixed-dilution HDF provided significantly greater clearances of urea, creatinine and β_2 M compared To ‘simple mid-dilution’ HDF with equivalent phosphate clearances [38]. These outcomes require examination in larger trials.

4.5. Novel systems

Two novel systems, ‘*pre-dilution on demand*’ and ‘*backflush on demand*’, have recently been proposed as potential alternatives to the standard online HDF modalities [39]. These sys-

tems utilise inbuilt automated software to balance ultrafiltration against haemoconcentration. In pre-dilution on-demand mode, escalating TMP is managed by temporarily pausing ultrafiltration and diverting a proportion of filtered dialysate into the dialyser in pre-dilution mode as a bolus. This produces sudden haemodilution. In backflush on demand, rising TMP results in an automatic cessation of filtration and an infusion of ultrapure dialysate into the dialyser. This creates positive pressure in the dialysate compartment, which backflushes the membrane pores and reduces haemoconcentration. These modes are currently experimental but offer a novel and intuitive solution to some of the inherent technical barriers of the existing HDF modes. Of note, these machines and dialysers would carry additional expense, which would need to be considered.

5. Summary

Many questions remain unanswered in the field of fluid convection, generation and reinfusion in haemodiafiltration. Although convection volume appears to have a dose-dependent relationship with survival, randomised trials have failed to consistently demonstrate improved mortality in their primary analyses. Furthermore, the critical 'dose' required to improve patient outcomes is yet to be determined and may need to be individualised according to patient factors, including patient size and residual renal function. Online generation of ultrapure dialysate has revolutionised the practice of HDF by allowing large convection volumes, although this approach requires strict monitoring in terms of quality and safety. The preferred site of fluid reinfusion is not known and warrants careful consideration of the opposing factors of solute clearance efficiency and the consequences of haemoconcentration. Hybrid modalities appear to present a promising balance between the two. Given the lack of robust clinical trials confirming the benefits of HDF, the increasing uptake of HDF worldwide has largely been driven by industry. Lack of a harm signal, cost neutrality and optimism that patient benefits will arise from large convective volumes have facilitated acceptance amongst the Nephrology community. It is unclear whether high-quality data from randomised trials will be available to guide convection and reinfusion strategies and it is likely that practice will need to rely on the results of observational studies.

Author details

Emily J. See¹, Carmel M. Hawley¹, John WM. Agar² and David W. Johnson^{1*}

*Address all correspondence to: david.johnson2@health.qld.gov.au

1 University of Queensland at Princess Alexandra Hospital, Brisbane, Australia

2 University Hospital Geelong, Geelong, Australia

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