Received: 19 February 2022 | Accepted: 5 March 2022

DOI: 10.1111/sdi.13073

SPECIAL ISSUE ARTICLE

Seminars in Dialysis WILEY

Basic prerequisites for on-line, high-volume hemodiafiltration

Richard A. Ward

Nelson, New Zealand

Correspondence
Richard A. Ward, Ph.D., 451 Suffolk Road, Nelson 7011, New Zealand.
Email: richard.ward@louisville.edu

Abstract

High-volume hemodiafiltration involves filtration of >23 L/treatment and its replacement by sterile non-pyrogenic substitution fluid, while maintaining the patient's fluid balance. That volume of substitution fluid precludes the use of prepackaged sterile fluid. Instead, substitution fluid must be prepared on-line using machines that incorporate a series of bacteria- and endotoxin-retentive filters. The sterilizing ultrafilters are validated to deliver sterile, non-pyrogenic fluid to the patient when operated according to the machine manufacturer's instructions and in compliance with international standards and regulatory oversight. A successful hemodiafiltration program also places important responsibilities on the user. Specifically, the user is responsible for ensuring that the dialysis water or dialysis fluid delivered to the sterilizing filters of the hemodiafiltration machine meets the machine manufacturer's specifications and is consistent with the quality used in the sterilization validation process. The user is also responsible for ensuring that the treatment prescription allows a filtration volume >23 L/treatment to be achieved by careful selection of a dialyzer, blood flow rate and treatment time. Questions related to assurance that the substitution fluid will routinely be sterile and non-pyrogenic have limited the uptake of on-line hemodiafiltration as a therapeutic option in some countries, such as the United States.

1 | INTRODUCTION

Solute removal in conventional high-flux hemodialysis (HD) occurs mainly by diffusion, which limits the removal of larger molecular weight solutes.[1] Hemodiafiltration (HDF) addresses that limitation by adding enhanced convection to diffusion. Convective solute removal is achieved by ultrafiltering a volume greater than that required to return the patient to their dry weight and replacing the excess by infusion of substitution fluid. High-volume HDF, defined by a convective volume of more than 23 liters per treatment,[2] is associated with better patient outcomes compared to conventional hemodialysis.[3] The volume of substitution fluid needed to achieve a convective volume greater than 23 liters precludes the use prepackaged bags of substitution fluid. Instead, substitution fluid is prepared online from dialysis fluid using HDF machines designed specifically for that purpose. The following sections outline the prerequisites for machines used to perform post-dilution HDF and discuss the role of the machine manufacturer and the user in assuring a safe and effective treatment.

2 | HDF MACHINES

Machines for HDF are based on conventional hemodialysis machines with three additional components: (1) a means of producing sterile, non-pyrogenic substitution fluid; (2) a pump for delivering that substitution fluid to the patient; and (3) a system for maintaining fluid and electrolyte balances while exchanging the required volumes of ultrafiltrate and substitution fluid. Incorporation of a means of processing non-sterile dialysis fluid and delivering it to the patient as sterile substitution fluid, priming fluid, or rinse-back solution is what differentiates HDF machines from conventional HD machines from a functional and regulatory perspective.[4]

2.1 | Substitution fluid

HDF machines prepare dialysis fluid from dialysis water and concentrates in the same manner as conventional hemodialysis machines. The dialysis fluid then undergoes further processing to produce substitution fluid compliant with international standards for sterility and non-pyrogenicity.[5] Since the substitution fluid is used extemporaneously, it is not possible to demonstrate compliance with standards by prior laboratory testing. Instead, the substitution solution must be produced by a process validated to produce sterile, non-pyrogenic substitution fluid when the system is used according to the manufacturer's instructions.

The process used to produce substitution fluid in current HDF machines is based on ultrafiltering dialysis fluid through a series of bacteria- and endotoxin-retentive filters. The sterilizing ultrafilters typically provide a six-log reduction in the number of incoming bacteria and a three-log reduction in incoming endotoxin.[6] The process is validated to produce substitution fluid meeting the applicable quality standard when supplied with dialysis water or dialysis fluid of a specified quality for a specified filter lifetime, including all anticipated disinfection cycles. The filters form an integral part of the dialysis fluid pathway and are disinfected when the HDF machine is disinfected. Safety is ensured by a filter integrity test performed automatically before each treatment, by including redundant ultrafilters, or by including an additional sterile single-use ultrafilter in the disposable substitution fluid tubing set. At the end of their specified lifetime, the filters are replaced according to the manufacturer's instructions.

The levels of electrolytes in the dialysis fluid used for high-volume HDF might need to be adjusted from those used in conventional hemodialysis to avoid electrolyte imbalances. For example, it may be necessary to reduce the bicarbonate concentration in the dialysis fluid to avoid over-correction of the metabolic acidosis seen in hemodialysis patients.[7] It might also be necessary to adjust the dialysis fluid sodium concentration. The Gibbs-Donnan effect causes ultrafiltrate to have a lower sodium concentration than the plasma water from which it is derived, leading to an increase in plasma water sodium concentration along the length of the dialyzer. In conventional hemodialysis, the concomitant diffusion of sodium into the dialysis fluid limits any tendency for sodium to accumulate in the patient. However, at the higher ultrafiltration rates used in post-dilution HDF, the diffusive loss of sodium can be insufficient to counter the increase in concentration arising from the Gibbs-Donnan effect, resulting in an increased sodium burden for the patient.[8] Since that increase would be proportional to the convection rate, the effect would be more pronounced with high-volume post-dilution HDF. The impact of the Gibbs–Donnan effect can be negated by using a dialysis fluid sodium concentration lower than that of the plasma water. A recent study comparing sodium removal in post-dilution HDF and high-flux hemodialysis showed no difference between the two modes of treatment when a dialysis fluid sodium concentration 1 mmol/L lower than the pre-dialysis plasma sodium concentration (138 and 139 mmol/L, respectively) was used.[9]

2.2 | Substitution fluid infusion

HDF machines incorporate a pump to infuse substitution fluid into the extracorporeal circuit. While the most common point of infusion for high-volume HDF is in the venous line (post-dilution HDF), substitution fluid may be infused into the arterial blood line (pre-dilution HDF) or into the blood compartment of the dialyzer (mid-dilution HDF). This discussion is limited to post-dilution HDF.

2.3 | Maintenance of fluid balance

The large volumes of fluid exchanged with the patient during an HDF treatment require a precise fluid balancing system in the HDF machine. The balancing chamber systems developed for conventional hemodialysis with high-flux dialyzers can maintain fluid balance with a precision of ±100 mL/treatment and, thus, are well suited for HDF.

3 | DIALYSIS WATER FOR HDF

HDF machines used to produce substitution fluid on-line are validated to produce a sterile, non-pyrogenic fluid and deliver it to the patient under specified operating conditions. An important component of those operating conditions is the quality of the input dialysis water, and the dialysis fluid prepared from it, as specified by the HDF machine manufacturer. Dialysis water is produced from potable water using a dedicated water treatment system. While local conditions can influence the design of a water treatment system, in general the design of a system for HDF does not differ from that of one used to provide dialysis water for conventional hemodialysis.[10] Both systems will comprise a series of purification devices usually based on reverse osmosis to remove chemical and microbial contaminants and a piping loop to distribute the treated water to its points of use.[11,12] While there are no differences regarding the removal of chemical contaminants between the two applications, systems used for HDF can require more rigorous controls for microbial contaminants than systems used for conventional hemodialysis. For example, the quality requirements for dialysis water in current regulations published by the United States Center for Medicare and Medicaid Services[10] are not as stringent as those in international standards[5] and an upgrade in the design and operation of the water treatment and distribution system might be necessary to routinely comply with the specifications of the HDF machine manufacturer.

4 | USER RESPONSIBILITIES

Dialysis fluid is produced from dialysis water and electrolyte concentrates meeting widely accepted quality standards.[5] While responsibility for the design and validation of an HDF machine, and specification of its input fluid quality, rests with the manufacturer of the machine and is subject to compliance with international standards[12] and

regulatory oversight, the user is responsible for ensuring that the quality of the input water or dialysis fluid meets the machine manufacturer's specifications on a day-to-day basis. That responsibility includes following all manufacturers' instructions for the operation and maintenance of the water treatment and distribution systems as well as the HDF machines, including regular testing to confirm compliance with the manufacturers' specifications. In the United States, that responsibility for the quality of dialysis water and dialysis fluid is clearly assigned to the Medical Directors of individual dialysis facilities[13]

5 | ENSURING A HYGIENIC INTEGRITY

A rigorous approach to cleaning (descaling) and disinfection is an important part of maintaining the quality of dialysis water and dialysis fluid. A disinfection schedule shown to routinely produce dialysis water of the requisite quality should be implemented and validated, with testing for bacteria and endotoxin used to confirm the adequacy of that schedule rather than being used to indicate when disinfection is needed. Where permitted under the manufacturer's instructions for use, thermal disinfection of the dialysis water storage and distribution system with hot water is preferred to chemical disinfection because the lack of residuals with the former allows daily disinfection, which is increasingly recommended in many jurisdictions. Descaling is used before disinfection to remove calcium deposits and help prevent biofilm formation. The two processes can be combined by using citric acid in conjunction with thermal disinfection. Detailed guidance on maintaining and monitoring water storage and distribution systems as well as HDF machines can be found in international standards for the preparation and quality management of fluids for hemodialysis and related therapies, including HDF.[5]

Concentrates should be obtained from commercial sources in a form ready to use, either as a liquid or sterile powder cartridges. Batch preparation of bicarbonate concentrates at the dialysis facility, a common practice in the United States and Japan, is not recommended because of their susceptibility to microbial contamination except when sterilizing ultrafiltration can be implemented as the final step of preparation.

6 | REGULATORY CONSIDERATIONS

HDF machines incorporating the features described above have been demonstrated to be highly reliable in large clinical studies.[14–16] Despite that, and the widespread use of such machines in Europe and Asia, on-line HDF is generally not available as a treatment option in the United States. Part of the reason is a lack of HDF machines that have received approval for use from the United States Food and Drug Administration (FDA). Machines for HDF that generate substitution fluid on-line are considered medical devices by the FDA and the agency has outlined a pathway for their regulatory approval.[4] To date, however, only one HDF system has cleared the FDA process, in part because of a perceived lack of clarity regarding what is required to complete certain aspects of that regulatory process, particularly those related to demonstrating the sterility and non-pyrogenicity of the substitution fluid.[6] While the fluid balancing systems and the pumps used for infusion of the substitution fluid are similar, and in some cases identical, to what can be found in standard hemodialysis machines, the infusion of large volumes of substitution fluid directly into the blood during HDF has no direct equivalent in hemodialysis. Although it is generally recognized that the internal filtration/back-filtration associated with high-flux hemodialysis is an uncontrolled form of HDF,[17] the FDA does not consider it to be a form of HDF.[6] That lack of a predicate has made it almost certain that, in addition to bench testing, clinical trials will be needed to demonstrate the safety of the systems used to prepare substitution fluid. While approaches to addressing the bench testing requirements of the FDA approval pathway have been suggested,[6] important questions remain about the design of the clinical trials and what data are required to satisfy the agency's concerns about the risks posed by on-line production of substitution fluid.[6] Examples of areas outlined in the FDA's guidance on the approval pathway that need clarification include how to demonstrate that the substitution fluid remains sterile and non-pyrogenic under conditions of routine clinical use and how to demonstrate that biofilm will not develop in the substitution fluid pathway.

7 | ACHIEVING HIGH-VOLUME HDF

7.1 | Choice of a dialyzer

Uremic toxins are thought to extend in size up to 55–60 kDa[18] and the benefits of high-volume HDF are thought to arise from its ability to remove larger uremic toxins.[19] Achieving the removal of larger uremic toxins requires the use of a dialyzer with a membrane permeability profile that permits the convective clearance of small peptides and proteins that would normally cross the glomerular basement membrane. The removal of larger uremic toxins, however, must be balanced against the possible loss of beneficial solutes, such as albumin. Currently available data suggest that long-term albumin loss should be limited to <12 g/week,[20] with a lesser amount (6–8 g/week) being favored by many. Therefore, attention needs to be paid to selecting a dialyzer for high-volume HDF that has a membrane permeability profile that allows the maximum removal of large sized uremic toxins while maintaining a low level of albumin loss.

In addition to a favorable membrane permeability profile, dialyzers intended for high-volume HDF should incorporate design features which favor convective solute removal. Dialyzers best suited for HDF should have fibers with an increased internal diameter compared to those used for hemodialysis to reduce the resistance to blood flow and allow the filtration fraction to be maximized. Ultrafiltration rates and, hence, rates of convective solute removal are low in conventional hemodialysis compared to HDF. To partially offset that difference, dialyzers intended for hemodialysis frequently have fibers with a reduced internal diameter and an increased length to promote internal

ultrafiltration and back-filtration, thereby increasing large solute removal.[21] These design features are undesirable in dialyzers intended for HDF because they can increase viscosity and oncotic pressure and, thus, limit the filtration fraction that can be achieved, as well as reducing individual fiber flow and increasing the risk of clotting.[22]

7.2 | Blood flow rate

Prescribing and routinely achieving an adequate blood flow rate (Q_B) is critical for successful implementation of high-volume HDF. The Q_B must be high enough to provide the necessary filtrate flow rate while limiting the filtration fraction to <30%. A filtration fraction greater than 30% can lead to a high hematocrit in the dialyzer, which increases pressures, membrane fouling, increased albumin loss, and risk of clotting. In practice, the actual filtration fraction that can be achieved for a given patient is limited by that patient's hematocrit.

The high filtration fraction used in high-volume HDF leads to the development of a secondary protein layer at the surface of the dialyzer membrane, which compromises both the hydraulic and solute permeability profile of the membrane. The extent to which that secondary protein layer forms is dependent on the shear rate and shear stress within each hollow fiber. To maintain an adequate shear rate and make best use of the dialyzer, Q_B should be >200 mL/min-m^2.

7.3 | Achieving the desired convective volume

Changes in blood flow rate and hematocrit during a treatment can require regular adjustment of the ultrafiltration rate if the target convective volume is to be achieved without triggering repeated transmembrane pressure (TMP) alarms. Some HDF machines now incorporate an ultrafiltration control system that automatically adjusts the TMP to optimize the ultrafiltration rate in response to changes in hematocrit and viscosity while maintaining a safe filtration fraction.[23–25]

REFERENCES

1. Leypoldt JK. Solute fluxes in different treatment modalities. *Nephrol Dial Transplant*. 2000;15(suppl_1):3-9. doi:10.1093/oxfordjournals.ndt.a027961
2. Blankestijn PJ, Fischer KI, Barth C, et al. Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol. *BMJ Open*. 2020;10:e033228. doi:10.1136/bmjopen-2019-033228
3. Peters SA, Bots ML, Canaud B, et al. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant*. 2016;31(6):978-984. doi:10.1093/ndt/gfv349
4. Food and Drug Administration. Guidance for the Content of Premarket Notifications for Hemodialysis Delivery Systems. Rockville, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 1998.
5. International Organization for Standardization. Preparation and quality management of fluids for haemodialysis and related therapies. Part 1: General requirements (ISO 23500-1:2019). Geneva: International Organization for Standardization; 2019.
6. Ward RA, Vienken J, Silverstein DM, Ash S, Canaud B, Workgroup KHIHDF. Regulatory considerations for hemodiafiltration in the United States. *Clin J Am Soc Nephrol*. 2018;13(9):1444-1449. doi:10.2215/CJN.12641117
7. Montagud-Marrahi E, Broseta J, Rodriguez-Espinosa D, et al. Optimization of dialysate bicarbonate in patients treated with online haemodiafiltration. *Clin Kidney J*. 2020;14(3):1004-1013. doi:10.1093/ckj/sfaa058
8. Pedrini LA, Ponti R, Faranna P, Cozzi G, Locatelli F. Sodium modeling in hemodiafiltration. *Kidney Int*. 1991;40(3):525-532. doi:10.1038/ki.1991.241
9. Rodriguez A, Morena M, Bargnoux A-S, et al. Quantitative assessment of sodium mass removal using ionic dialysance and sodium gradient as a proxy tool: Comparison of high-flux hemodialysis versus online hemodiafiltration. *Artif Organs*. 2021;45(8):E280-E292. doi:10.1111/aor.13923
10. Ward RA, Tattersall JE. Water treatment and safety requirements. In: Nubé MJ, Grooteman MPC, Blankenstijn PJ, eds. *Hemodiafiltration: Theory, Technology and Clinical Practice*. Springer; 2016:41–55. doi:10.1007/978-3-319-23332-1_3
11. Kasparek T, Rodriguez OE. What medical directors need to know about dialysis facility water management. *Clin J am Soc Nephrol*. 2015;10(6):1061-1071. doi:10.2215/CJN.11851214
12. International Electrotechnical Commission. *Medical Electrical Equipment - Part 2–16: Particular requirements for Basic Safety and Essential Performance of Haemodialysis, Haemodiafiltration and Haemofiltration Equipment (IEC 60601–2-16:2018)*. Geneva: International Electrotechnical Commission; 2018.
13. United States Department of Health and Human Services, Centers for Medicare and Medicaid Services. Conditions for coverage for end-stage renal disease facilities. *Final Rule Fed Register*. 2008;73:20370.
14. Grooteman MP, van den Dorpel MA, Bots ML, Penne EL, Van der Weerd NC, Mazairac AH, den Hoedt CH, Van der Tweel I, Lévesque R, Nubé MJ, Ter Wee PM, Blankestijn PJ, CONTRAST Investigators. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol* 2012;23:1087–1096. doi:10.1681/ASN.2011121140
15. Ok E, Asci G, Toz H, et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant*. 2013;28:192-202.
16. Maduell F, Moreso F, Pons M, et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol*. 2013;24(3):487-497. doi:10.1681/ASN.2012080875
17. Ronco C, Brendolan A, Feriani M, et al. A new scintigraphic method to characterize ultrafiltration in hollow fiber dialyzers. *Kidney Int*. 1992;41(5):1383-1393. doi:10.1038/ki.1992.203
18. Chmielewski M, Cohen G, Wiecek A, Carrero JJ. The peptidic middle molecules: is molecular weight doing the trick? *Semin Nephrol*. 2014;34:118-134. doi:10.1016/j.semnephrol.2014.02.005
19. Canaud B, Vienken J, Ash S, Ward RA, Kidney Health Initiative HDF Workgroup. Hemodiafiltration to address unmet medical needs ESKD patients. *Clin J Am Soc Nephrol*. 2018;13(9):1435-1443. doi:10.2215/CJN.12631117
20. Ward RA, Beck W, Bernardo AA, Alves FC, Stenvinkel P, Lindholm B. Hypoalbuminemia: a price worth paying for improved dialytic removal of middle-molecular-weight uremic toxins? *Nephrol Dial Transplant*. 2019;34(6):901-907. doi:10.1093/ndt/gfy236
21. Ward RA. Do clinical outcomes in chronic hemodialysis depend on the choice of a dialyzer? *Semin Dial*. 2011;24:65-71.
22. Bowry SK, Canaud B. Achieving high convective volumes in on-line hemodiafiltration. *Blood Purif*. 2013;35(Suppl 1):23-28. doi:10.1159/000346379

23. Joyeux V, Sijpkens Y, Haddj-Elmrabet A, Bijvoet AJ, Nilsson LG. Optimized convective transport with automated pressure control in on-line postdilution hemodiafiltration. *Int J Artif Organs*. 2008;31(11):928-936. doi:10.1177/039139880803101102
24. Marcelli D, Scholz C, Ponce P, et al. High-volume postdilution hemodiafiltration is a feasible option in routine clinical practice. *Artif Organs*. 2015;39:142-149. doi:10.1111/aor.12345
25. Panichi V, De Ferrari G, Saffioti S, et al. Divert to ULTRA: differences in infused volumes and clearance in two on-line hemodiafiltration treatments. *Int J Artif Organs*. 2012;35(6):435-443. doi:10.5301/ijao.5000106

How to cite this article: Ward RA. Basic prerequisites for on-line, high-volume hemodiafiltration. *Semin Dial*. 2022;1-5. doi:10.1111/sdi.13073