HEMODIALFILTRATION
LITERATURE REVIEW AND PRACTICE CONSIDERATIONS

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This document was prepared at the request of the BC Hemodialysis Committee to provide a brief overview of the literature and to identify practice considerations with respect to the types of patients most likely to benefit from hemodialfiltration (HDF). Upon review of this document, the BC Hemodialysis Committee concluded there was insufficient evidence to create provincial recommendations around the appropriate use of HDF at this time. However, they felt the information provided in this document would be helpful in guiding health authorities and clinicians in planning and decision making in the area of HDF.

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1.0 PRACTICE CONSIDERATIONS

1.1 Patients to consider for online post-dilution hemodialfiltration

1. Patients who have clinical signs and symptoms of under-dialysis and require higher dialysis dose and don't have the option of increasing frequency or time.
2. Patients with refractory intra-dialytic hypotension (e.g. patients with end stage heart disease who cannot tolerate rapid large volume fluid removal due to hypotension) despite conventional measures on current HD prescription (including use of low dialysate temperature)
3. Patients who are likely going to have a long dialysis vintage (unlikely to be kidney transplant candidates)
4. Patients who have carpel tunnel syndrome and increased beta 2 microglobulin deposition (likely seen in patients with a very long dialysis vintage or poor clearance)
5. Patients with multiple myeloma (e.g. high serum free light chain levels) who are at risk for myeloma kidney and who require extracorporeal treatment

1.2 Other considerations for online post-dilution hemodialfiltration

1. <u>Key message:</u> It is important to achieve a target convection volume of 23 liters corrected for body surface area, per treatment, in order to derive any clinical benefit from HDF therapy (please see the monogram included on the last page).
2. Staff education on performing a high convection volume HDF is very important.
3. A decent vascular access is required, achieving a minimum blood pump speed of 300 ml/min each run.

2.0 CURRENT LITERATURE REVIEW

2.1 Summary of the literature

Hemodiafiltration (HDF) is an alternative chronic dialysis therapy for patients with end stage renal disease. HDF increases solute clearance by adding convective clearance to diffusive clearance provided by conventional HD. It increases clearance of both small and middle molecules but the improvement in middle molecule clearance is more pronounced. In convective therapy, a large volume of plasma water is ultrafiltered, and this requires the administration of a substitution fluid back to the patient in order to maintain patient's fluid balance. This substitution fluid is often administered post-filter to maximize solute clearance (e.g. post-dilution HDF). Convection volume refers to the total volume of the substitution fluid and net ultrafiltration fluid.

Online HDF is a modern HDF therapy where a substitution fluid is continuously produced from sterilization of ultrapure dialysate fluid inside HDF-capable dialysis machines during each treatment. A current standard is to use a high flux dialyzer membrane for HDF. There is a growing interest in offering this therapy to our patients, and the scope of this document is to discuss an updated literature review assessing clinical benefits of HDF compared to conventional hemodialysis therapy (HD).

2.1 Specific studies/publication

Hemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. Peters et al. NDT. 2016.

It is a pooled individual participant data analysis of four large randomized controlled trials comparing online HDF with HD (three published RCTs described below and one unpublished RCT). One of the criticisms of these well-known RCTs was informative censoring. There was a significant number of patients who discontinued the study and were censored as alive (no recording of follow-up data); kidney transplantation was one of their main reasons for leaving the study. Such an incomplete follow-up data on those patients and missing data on mortality were tracked down and included in this re-analysis, improving power and bias of those previous RCTs.

In this study of a median follow-up of 2.5 years, 769 out of 2793 participants died (292 cardiovascular deaths). Online HDF was associated with improved survival with a reduction of all-cause mortality by 14% (95% CI 1-25%) and a reduction of cardiovascular mortality by 23% (95% CI 3-39%) compared to HD. Survival benefit was greatest in the HDF group receiving the highest delivered convection volume (>23L per 1.73m^2 body surface area per session) with a multivariable-adjusted HR of 0.78 (95% CI 0.62-0.98) for all-cause mortality and 0.69 (95% CI 0.47-1.00) for cardiovascular disease mortality.

*Please see the nomogram in **Appendix 1** (can be used to determine a target convection volume based on patient's height and weight, in order to achieve a minimum 23 liters of convection volume per 1.73m^2 per treatment, convection volume=substitution volume + net ultrafiltration volume).

CONTRAST study: Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. Grooteman et al. JASN.2012

The following RCT of a mean follow up of 3 years did not show survival benefit of online HDF (n=358) compared to low flux HD (n=356). There was no difference in all cause-mortality (121 deaths per 1000 person years in online HDF versus 127 deaths per 1000 person years in low flux HD, HR 0.95 CI 0.75-1.20). An average delivered convection volume per session was 20.7 liters (below a target convection volume of 6 liters per hour or 24 liters per session). A post hoc analysis showed a positive association between all-cause mortality and a delivered convection volume (>21.95 liters per session) even after adjusting for potential confounders and dialysis facility (unadjusted HR 0.62, 95% CI 0.41-0.93).

Turkish study: Mortality and cardiovascular events in online haemodiafiltartion (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF study. Ok et al. NDT. 2013.

In this RCT of a mean follow up of 2 years, there was no survival advantage of online HDF (n=391) compared to high flux HD (n=391). A post hoc analysis showed that a substitution volume above 17.4 liters per session (or likely 21 liters of convection volume, a median substitution volume of the study) was associated with improved all-cause and cardiovascular mortality compared to high flux HD (substitution volume <17.4 liters per session, p values 0.03 and 0.002 respectively). A target convection volume was a minimum of 15 liters per session, and a mean substitution fluid volume was 17.2 liters per session (95% of the patients were treated with >15 liters of substitution fluid).

ESHOL study: High efficiency post-dilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. Maduell F et al. JASN. 2013.

The following RCT of a mean follow up of 2 years, showed a statistically significant survival benefit of online HDF (n=456) compared to HD (n=450, 92% of which received high flux HD). The online HDF group had 30% lower risk of all-cause mortality (HR 0.70, CI 0.53-0.92, p=0.01), 33% lower risk of cardiovascular mortality (HR 0.67, CI 0.44-1.02, p=0.06, statistically significant reduction in stroke) and 55% lower risk of infection-related mortality (HR 0.45, CI 0.21-0.96, p=0.03) compared to HD group. The online HDF group also had lower rates of intradialytic hypotension and all-cause hospitalizations.

A *post hoc* analysis showed a lower morality risk in the highest delivered convection group (>23 liters per session, excluded for this post hoc analysis if achieved convection volume <18 liters per session) compared to HD group (in delivered convection volume of 23.1 to 25.4 liters per session, HR 0.6, CI 0.39-0.90, in delivered convection volume greater than 25.4 liters per session, HR 0.55, CI 0.34-0.84). A target substitution volume is a minimum of 18 liters per session, and a mean delivered convection volume was 23.7 liters per session.

Hemodiafiltration versus hemodialysis and survival in patients with ESRD: The French renal epidemiology and information network (REIN) registry. Mercadal et al. AJKD. 2016.

It is a large observational study based on the national registry assessing 28,407 incident hemodialysis patients who started chronic dialysis hemodialysis therapy between January

2008 and December 2011. 5526 of these patients received online HDF for a median of 1.2 years while 2254 patients received online HDF exclusively. Exclusive online HDF was associated with better outcomes as suggested by HR 0.77 (95% CI 0.67-0.87) for all-cause mortality and HR 0.66 (95% CI 0.50-0.86) for cardiovascular mortality. A positive correlation between survival benefit and online HDF was also observed when the data were analyzed at a facility level, which was performed to minimize a potential indication bias rising from different uptake of HDF among different centers. This study did not suggest the use of ultrapure dialysate fluid as a main contributing factor for benefits of HDF as there was no survival advantage seen in HD patients dialyzing in centers offering online HDF, compared to other HD patients dialyzing in centers not offering online HDF. Another interesting observation of the study was that online HDF was more likely to be offered to patients who were likely to have a long lifetime on hemodialysis and less likely to receive a kidney transplant. Information on delivered convection volumes was not available in the registry.

3.0 CURRENT STATE OF ART

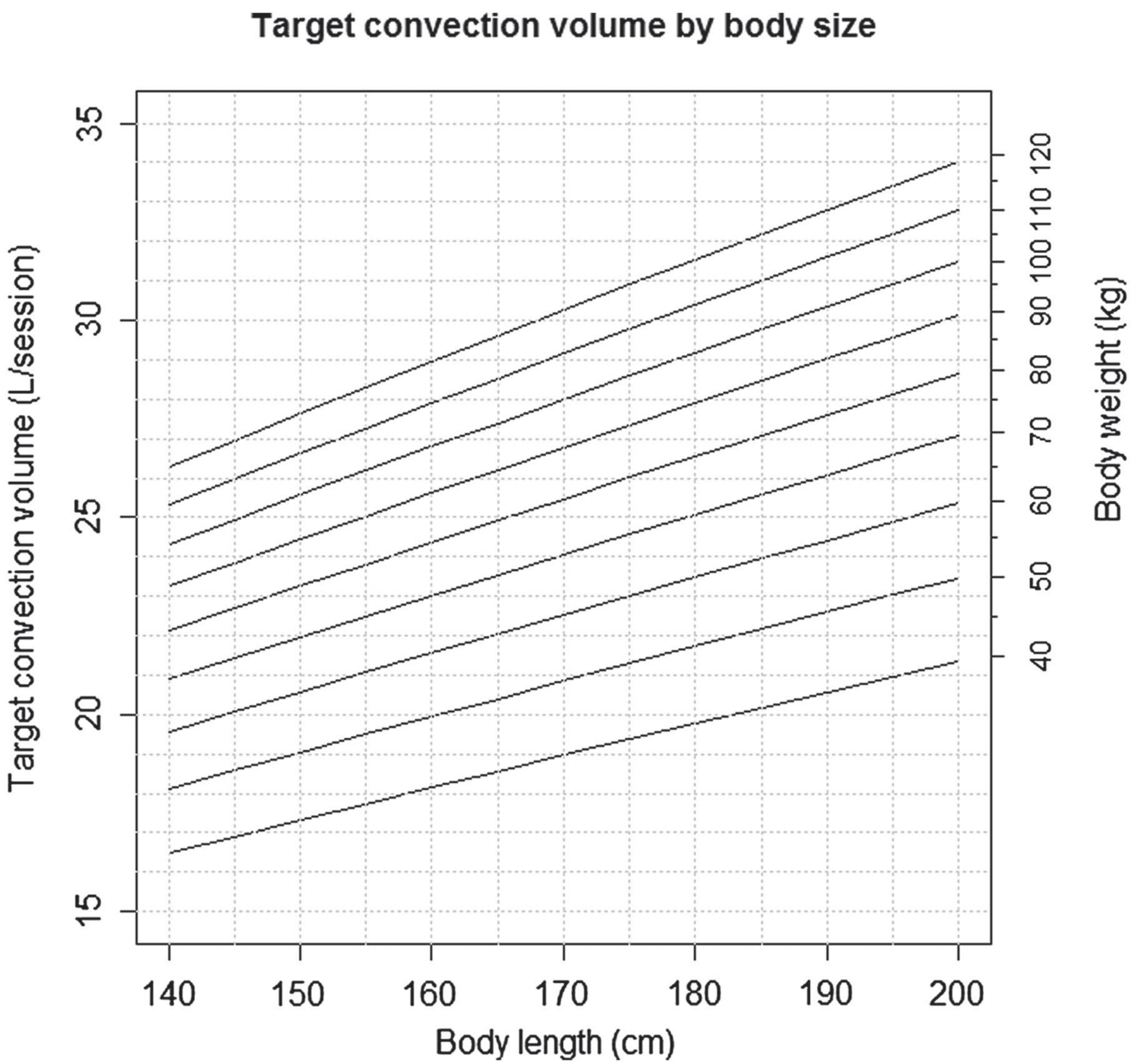
There is a different uptake of HDF therapy at an international level. It is related to the lack of conclusive evidence on a survival benefit of HDF compared to HD, increased treatment costs, and potential safety concerns regarding substitution fluids.

HDF experts suggest that there is a potential survival benefit associated with high volume HDF although more studies are needed to define minimum and limiting values. It may be related to improved intradialytic hemodynamic stability (suspected to be from cooling effect of substitution fluid replacement) and enhanced clearance of non-small molecules. A potential selection bias (e.g. high convection is likely to be achieved in healthier dialysis group who may have a lower mortality risk) cannot be ruled out in these observational studies. Therefore, there is a need to design a randomized control trial assessing different convection volumes, preferably in incident dialysis patients.

More observational studies demonstrate that a high volume convection HDF therapy is achievable in clinical practice. Key contributors of high convection volume deliverance can be patient specific (vascular access blood flow) or treatment specific (treatment time, filtration fraction) or center specific (staff practice patterns, Contrast study, ESHOL)

With respect to safety of HDF, an online produced substitution fluid should be sterile and non-pyrogenic. Every center offering online-HDF must follow strict standards and regulations regarding dialysis water treatment and monitoring, to ensure the safety of HDF although some of the details need to be further standardized at both national and international levels. It is reassuring that there has been no published studies or case reports on adverse patient outcomes of HDF.

Appendix 1:
Convection volume per session needed for an individual patient to have a BSA-adjusted convection volume of at least 23 L or above, based on measurements of height and weight of the patient.



Convection volume per session needed for an individual patient to have a BSA-adjusted convection volume of at least 23 L or above, based on measurements of height and weight of the patient. The formula used was: Convection volume needed = (23 × individual BSA)/1.73. Here BSA (m2) = 0.0235 × height (cm)0.42246 × weight(kg)0.51456.

Source: Sanne A.E. Peters et al. Nephrol. Dial. Transplant. 2016;31:978-984