

Dialyser Membrane Prescription and Choosing HDF (Haemodiafiltration)

St. George Renal Department Protocol

Bottom line

All patients should be placed on high flux membranes as the minimum standard.

Indications and Evidence for advantages of use of high flux membranes includes

- 1. Patients on haemodialysis >3 years*
- 2. Albumin <40g/L*
- 3. Diabetes?*
- 4. Cardiac Disease?*

Indications and Evidence for advantages of use hemodiafiltration (HDF)

- 1. As for high flux above BUT,*
- 2. Aiming for increased removal of small- and medium-large sized solutes, and concern about amyloidosis*
- 3. If require lower Cr, urea and phosphate levels (10-15%). Less inflammatory stimulation, lower microbiological cfu; better lipid control (this is mainly with daily HDF)*
- 4. Better hemodynamic stability and particularly an advantage in elderly population and/or heart-compromised patients prone to dialytic hypotensive episodes*
- 5. Definite need for more evidence (awaiting results from the Italian, Dutch and French RCTs)*

The unit has funding for 10% of patients to be given haemodiafiltration, allocation will be done as requested.

If all places are full then discussion will take place through the HD committee and with consultants.

Note: it is important to check the 'Dialysis of Drugs' guideline when prescribing medication with high flux dialysers and during HDF as this may differ from low flux dialysers

The CARI Guidelines (July 2005)

No recommendations possible based on Level I or II evidence

SUGGESTIONS FOR CLINICAL CARE

(Suggestions are based on Level III and IV evidence)

There is inadequate randomised controlled trial (RCT) evidence to recommend (or not) the use of high-flux dialysers for the benefit of mortality or morbidity.

Careful consideration should be given to the use of high-flux membranes for patients expecting prolonged dialysis (> 5 years). (Level III evidence)

What other Guidelines Say

Hemodialysis Adequacy 2006 Work Group: Increase high flux dialyser use fuelled in part by the resurgence of single use practices, as well as the promotion of substituted cellulose and synthetic dialyzers (that are more likely to have high-flux properties) by clinical practice guidelines. (Hemodialysis Adequacy 2006 Work Group)

Kidney Disease Outcomes Quality Initiative: CLINICAL PRACTICE RECOMMENDATION 5: DIALYZER MEMBRANES - 5.3 The use of poorly biocompatible, unmodified cellulose dialyzer membranes for HD is discouraged.

British Renal Association: Dialysis Membranes. The balance of evidence supports the use of low flux synthetic and modified cellulose membranes instead of unmodified cellulose membranes. (Good Practice)

The balance of evidence supports the use of a dialysis regimen with enhanced removal of middle molecules in incident patients who are predicted to remain on haemodialysis for several years and prevalent patients who have been on haemodialysis for more than 3.7 years. Such patients are at risk of developing symptoms of dialysis-related amyloidosis. (Good practice) (BRA 2007 <http://www.renal.org/pages/pages/guidelines/current/haemodialysis.php>)

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines (EBPG guideline on dialysis strategies): Guideline 2.1 - The use of synthetic high-flux membranes should be

considered to delay long-term complications of haemodialysis therapy. Specific indications include; To reduce dialysis-related amyloidosis (III); To improve control of hyperphosphataemia (II); To reduce the increased cardiovascular risk (II); To improve control of anaemia (III); Guideline 2.2 - In order to exploit the high permeability of high-flux membranes, on-line haemodiafiltration or haemofiltration should be considered. The exchange volumes should be as high as possible, with consideration of safety. (Evidence level II). (EBPG 2007).

International Guidelines: No recommendation.

Background¹

Low Flux – High Flux and Biocompatibility

Dialysis membranes are composed of semi-permeable compounds, allowing the separation of solutes between the blood and dialysate. Membranes technology has improved with more biocompatible properties. The cellulosic membranes were predominantly low-flux, a term referring to the porosity of the membranes such that they effectively had a molecular weight cut-off below 5,000 D. The synthetic membranes were capable of being manufactured in low-flux or high-flux format. High flux dialysers results in the ability to clear larger molecules, especially molecules such as beta-2 microglobulin (MW 11,800 D). The flux rating may also be taken to relate to the ultrafiltration characteristics of the membrane, such that high-flux membranes have a higher K_{UF} (ultrafiltration co-efficient) than low-flux membranes (this relates to the amount of fluid moving across the membrane at a given transmembrane pressure).

Dialysis membranes, by coming into contact with blood elements, may incite an inflammatory response in the host. The older, cellulosic membranes generally incite a greater inflammatory response than the newer synthetic membranes. Hence, the synthetic membranes are said to be more biocompatible.

Biocompatibility can be measured in many different ways such as induction of activated complement, neutrophil superoxide, IL-1, TNF, IL-6 and CRP. Some components of this cascade of events may be induced by contaminants in the dialysate rather than by the membrane itself. The synthetic membranes have a sponge-like supporting wall which may be adsorptive for contaminants such as endotoxin fragments, thus protecting the host from exposure to these compounds.

Thus, the issue of which membrane may be 'best' for a patient receiving haemodialysis centres around whether the membrane offers optimal small solute clearance, and/or middle molecule clearance and whether it offers the best biocompatibility profile. Further, argument continues whether these factors actually impact on patient outcome, especially in the long term. The impact of using different membranes can be measured in the short term (e.g. acute reactions, fever, shortness of breath) or the long term (as development of amyloidosis, atherogenesis or more importantly, death).

Haemodiafiltration (HDF)

HDF increases the dialysis efficacy by enlarging the molecular weight spectrum of uremic toxins up to middle and large solutes; second, HDF ameliorates the clinical tolerance of sessions and the quality of life; and third, HDF improves the biocompatibility of the HD system by combining the use of high flux synthetic membranes and ultrapure dialysis fluid purity.

This modality is approved in Europe provided that specific EU-certified HDF machines are used and water purity comply with the level of microbiological purity as defined in the European Best Practice Guide (Canaud 2006).

Current Evidence

High Flux Dialysis Membranes

Modified cellulose membranes (Cellulose acetate/diacetate, cuprophan and haemophan) now rarely used due to associated increase in mortality and morbidity compared with with more biocompatible synthetic membranes (polyacrilonitryl and polysulfone (or polysulphone).

Membrane type has been linked in observational studies to patient survival (Allon 2003), cause of death (especially infection/cardiac causes) (Owen et al 1993), recovery from acute renal failure (Covic et al 1998) and complications associated with b-2-microglobulin accumulation (Van Ypersele de Strihou et al 1991, Schwalbe et al 1997, Koda et al 1997). One meta-analysis suggested membranes had little influence on survival in acute renal failure (Jaber et al 2002).

Biocompatibility and/or flux may influence nutritional status via a catabolic response and amino acid losses, susceptibility to infection, atherogenesis via oxidative stress and lipid profile, residual renal function, and possibly mortality (EBPG 2002). Biocompatible membranes may beneficially influence the rate of loss of residual renal function compared with incompatible membranes (McKane et al 2002, McCarthy et al 1997), however, this has only been reported in observational studies and has not been the subject of a randomised trial.

Some evidence exists that the accumulation of middle-molecular-weight uremic solutes might contribute to the observed mortality. A study of uraemic solute suppression of appetite (and nutrition) by Anderstam et al (1996) may provide scientific support for the benefits of membrane middle-molecule clearance.

Dialyzer membranes can be classified into low-flux or high-flux varieties in accordance with their ultrafiltration coefficient (Kuf) and large-molecule clearance. The HEMO Study suggested that membranes with β_2M clearance less than 10 mL/min be regarded as low flux, whereas those with β_2M clearance greater than 20 mL/min and Kuf of 14 mL/h/mm Hg or greater may be classified as high flux (Chueng & Levin, 2003) . Another classification recommended that dialyzers with Kuf between 4 and 8 mL/h/mm Hg be regarded as low flux, whereas those with Kuf greater than 20 mL/h/mm Hg be regarded as as high flux (Ronco, 2002)

Several retrospective analyses have reported reduced mortality for patients treated with high-flux dialyzers. Quoting the larger examples of these, Woods and

Nandakumar (2000) showed an increase in 5-year survival from 60% to 90% in 715 patients in Singapore treated with high- versus low-flux polysulfone dialysers. Port and colleagues also reported an 18% reduction in mortality among nearly 13,000 patients treated with high- versus low-flux membranes in the US (Port et al 2001). On the other hand, Locatelli and colleagues reported from the Lombardy Registry (Italy) over the period 1983–95 and only showed a non-significant 10% improvement in mortality in 1082 patients treated with high-flux, of 6444 patients who commenced dialysis in the study period (Locatelli et al 1999).

Only two randomised control studies -

Hemodialysis (HEMO) study (Cheung et al, 2003) - primary analysis did not show a significant effect of high-flux membrane use on all-cause mortality, high-flux dialysis was associated with a 32% mortality risk reduction in patients who had been on dialysis for more than 3.7 years before entering the study (Seabra et al, 2009).

In addition, in all patients, highflux membranes were associated with a decrease in cardiac deaths (20%) and cardiac hospitalisations (Cheung et al 2003) but not infection-related deaths or hospitalisations (Allon et al 2003).

Other findings from HEMO study included 52% risk reduction for cerebrovascular death in patients with vascular disease when starting dialysis (Delmez et al 2006). High flux dialysers were shown to lower β_2 -microglobulin levels which were associated with significantly less infectious deaths (Cheung et al 2003).

Membrane Permeability Outcome (MPO) study (Locatelli, 2009) - membrane choice did not significantly affect overall patient mortality, but patients with serum albumin \leq 40 g/l high-flux membrane was associated with a decrease of the risk of mortality (37%).

Both studies, HEMO and MPO, suggest possible benefit in patients with diabetes (Seabra et al 2009)

Haemodiafiltration (HDF)

Despite technological advances featuring online (ol)-HDF and favorable lawful environment, the prevalence of HDF-treated patients is less, and less than 10% of dialysis patients are receiving online convective therapies (Canaud et al, 2003)

Microbiological safety of the ol-HDF methods has been proved in several long-term clinical studies, if strict guidelines for water purification are followed (Penne et al, 2009). Assessment of HDF machines (CFU, ET) has confirmed that sterile dialysis fluid and/or infusate (CFU \leq 0.1 CFU/mL and ET \leq 0.03 IU/mL) preparation were regularly achieved in HDF-treated patients, despite infusions during dialysis. Low cytokine activity and CRP or inflammatory mediators (IL-6) were found in patients.

Dialysis efficacy and HDF provides significantly higher instantaneous body clearances than high flux HD both for small and middle molecule solutes. Urea and creatinine clearance increased by 10-15%. There is better phosphate (still require phosphate binders if 3x/week) and β_2 -microglobulin removal vs. high flux membrane dialysis. Improvement of hemodynamic stability was repeatedly reported in the elderly population and/or heart-compromised patients prone to dialytic hypotensive

episodes. Intradialytic symptomatology and post dialysis fatigue are reduced with HDF methods, particularly when they are applied on a daily basis. Blood pressure control is achieved similar to that obtained with high-flux HD, probably related to better hemodynamic stability. Prevention or delayed occurrence of β_2 M-amyloidosis in long-term-treated ESRD patients has been evidenced in several large retrospective database studies (Canaud et al, 2003). Dyslipidaemia profile, oxidative stress, and AGEs reported in dialysis patients contribute to accelerate atherosclerosis. The regular use of high-flux membranes in HD or in HDF has been shown to improve lipid profile (Blankestijn et al, 1995) and to reduce oxidative stress and AGEs concentrations (Chun-Liang et al, 2003). Controversially anemia may be improved and EPO needs reduced in patients treated.

DOPPS study has shown that patients receiving HDF treatment had a reduced risk of death compared with those treated by conventional HD (Canuad, 2003b).

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