Dialysis membranes

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Authors: Peter Kerr and Nigel Toussaint

Guideline Recommendations

a. We recommend that either synthetic or cellulosic membranes be used for symptomatic intra-dialytic hypotension as synthetic membranes offer no benefit over cellulosic membranes (1C).
b. We recommend that high-flux membranes be used to remove molecules such as beta-2 microglobulin because they have been shown to achieve lower serum levels (1A).
c. We suggest there are possible survival benefits from high-flux membranes for some groups such as those on dialysis for more than 3.7 years, those with a serum albumin below 40 g/L and diabetics (1A).

UNGRADED SUGGESTION FOR CLINICAL CARE

- **The use of synthetic dialysis membranes is recommended over cellulosic membranes as they offer benefits in terms of biocompatibility (ungraded).**

Implementation and audit

The type of dialyser membrane used and the relationship to mortality and patient outcomes should be assessed using the ANZDATA Registry.

Background

Dialysis membranes are composed of semi-permeable compounds, allowing the separation of solutes between the blood and dialysate. Predominantly, traffic is from blood to dialysate but may also occur from dialysate to blood, potentially in terms of unwanted compounds such as endotoxin fragments contaminating dialysate. Traditionally, membranes were cellulose-based and developed as variations of this, mostly with varying numbers of acetate molecules per hexose repeat. Subsequent membranes were developed from more 'synthetic' compounds such as polyacrilonitryl and polysulfone (polysulphone). Synthetic membranes are typically much thicker than the thin cellulosic membranes.

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 are capable of being manufactured in low-flux or high-flux format. The latter format results in the ability to clear larger molecules, especially molecules of interest, 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 trans-membrane 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 and because of this, 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, interleukin-1 (IL-1), tumor necrosis factor (TNF), interleukin-6 (IL-6) and C-reactive protein (CRP). Some components of this cascade of events may also 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 offering some protection for the host from exposure to these compounds.

The issue of which membrane may be 'best' for a patient receiving haemodialysis centres on whether the membrane offers optimal small solute clearance, and/or middle molecule clearance and whether it offers the best biocompatibility profile. Central to this discussion is whether individual toxins and the clearance of these toxins can be related to patient outcomes. Thus, 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 death).

Search strategy

Databases searched: MeSH terms and text words for dialysis and dialysis solutions were combined with MeSH terms and text words for membranes and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The latest search was carried out in Medline (1950 – October Week 4, 2011). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of searches: 8 August 2008; 10 November 2011.

What is the evidence?

The composition of the dialyser membrane may influence the outcome of the dialysis process in several ways, for example molecular weight of cleared solute, biocompatibility and transmission of bacterial products from the dialysate. Despite determined study, much debate remains regarding the importance, the cause, and the outcome ensuing from the use of individual membranes.[1]

Cellulose acetate/diacetate, Cuprophan® and Hemophan® (modified cellulose) membranes now account for a minority of dialysis treatments, with the use of synthetic membranes being approximately 95% in this region. [2]

Membrane type has been linked in observational studies to patient survival,[3,4] cause of death (especially infection/cardiac),[5] recovery from acute renal failure[6] and complications associated with beta-2 microglobulin accumulation.[7-9]

Biocompatibility

Evidence of biocompatibility is limited by difficulties with selection of appropriate measures, and in establishing significant effect on patient outcome.[10]

The influence of various membranes on inflammatory markers is concisely reviewed in the European Best Practice Guidelines (EBPG) on dialysis strategies documents.[11,12] In short, synthetic membranes are generally more biocompatible than cellulosic membranes, depending on

the metric used. Cellulose membranes have no known advantages over synthetic membranes, and given unmodified cellulose membranes can markedly activate complement and bring about other potentially adverse effects in the blood, it would be recommended that patients be dialysed with more biocompatible and less complement-activating membranes.

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.[11]

A Cochrane review found that symptomatic hypotension during dialysis was no different between synthetic and cellulosic membranes.[13]

Advanced glycosylation end-product (AGE) production, as measured by pentosidine level, was lower in polysulfone low- and high-flux membrane-treated patients than in other synthetic or cellulosic membrane-treated patients.[14] However, a small cross-over study of 29 patients could find no benefit in terms of pre-dialysis serum levels after 6 weeks of therapy.[15]

In one randomised controlled trial (RCT) of 40 patients, high-flux membranes resulted in improved insulin resistance.[16]

In a 6-week, randomised cross-over study, triglycerides, remnant-like particle cholesterol and oxidised low-density lipoprotein (LDL) were all significantly improved with polysulfone high-flux membranes, compared with low-flux membranes.[17]

Bacterial products in dialysate pose uncertain risk with high-flux dialysis membranes that may permit passage of small molecular weight toxins or cytokines into the blood compartment of the dialyser. Significant consequences from any such putative contamination have yet to be demonstrated.[18]

In the setting of acute kidney injury (AKI), the effect of biocompatibility of dialysis membranes has also been studied. A meta-analysis involving 7 studies (n = 722), designed to assess the impact of biocompatible membranes on patients with AKI revealed a non-significant relative risk for mortality of 0.92 (95% CI 0.76 – 1.13), although a subgroup analysis suggested that cellulose membranes may offer a survival advantage compared with synthetic membranes.[19]

Another membrane type designed to improve biocompatibility are those coated with an additional compound such as vitamin E. Vitamin E plays a central role in reducing lipid peroxidation and inhibiting the generation of reactive oxygen species. Vitamin E-coated membranes have potential benefits in terms of oxidative stress, although the benefits seem relatively minor and no survival benefits have been demonstrated.[20] One randomised cross-over study of 62 patients demonstrated improvement in haemoglobin levels (and less erythropoietin resistance) and reduction in CRP and IL-6 with vitamin E-coated polysulfone membranes.[21] Another prospective observational study also reported reduction in inflammation and oxidative stress markers with vitamin E-coated membranes.[22]

Beta-2 microglobulin and amyloid

The influence of various membranes on beta-2 microglobulin and amyloidosis is concisely reviewed in the EBPG documents.[11,12] High-flux membranes, because of their greater porosity, remove larger molecules such as beta-2 microglobulin to a greater extent than do low-flux (cellulose or synthetic) membranes, often decreasing serum levels.[23–25]

High-flux dialysis using polysulfone membranes has been reported in one study to postpone clinical manifestations of dialysis-related amyloidosis.[26] This small RCT (n = 20) demonstrated beta-2 microglobulin amyloid in 8/10 patients on low-flux membranes and 0/10 for those on high-flux membranes.

An Italian study demonstrated a fall in beta-2 microglobulin levels only with high-flux membranes.[27,28]

Accumulation of beta-2 microglobulin in high concentrations promotes its polymerisation to cause beta-2 microglobulin amyloidosis. The incidence of beta-2 microglobulin-related amyloidosis is declining, which may be due to the increased use of synthetic membranes but may also relate to 'cleaner' dialysate.[8] In one study, prolonged use of high-flux synthetic membranes led to improvement in carpal tunnel syndrome and patient mortality.[9]

Recent developments in membrane technology have included a generation of 'superflux' membranes. These have larger pores that allow the passage of larger molecules, especially proteins. Although they tend to allow the loss of some albumin during dialysis, they may have benefits in terms of further preventing the development of amyloidosis. The small amount of albumin loss is probably not of nutritional concern, as demonstrated in one short-term study.[29]

Mortality

Several retrospective analyses have reported reduced mortality for patients treated with high-flux dialysers.[30-33] Quoting the larger examples of these, Woods and Nandakumar showed an increase in 5-year survival from 60% to 90% in 715 patients in Singapore treated with high- vs. low-flux polysulfone dialysers,[30] and Port et al reported on a USRDS analysis which demonstrated a 24% increased mortality amongst nearly 13,000 patients treated with low- vs. high-flux (synthetic) membranes.[31] On the other hand, Locatelli et al reported from the Lombardy Registry (Italy) over the period 1983-1995 and only showed a non-significant 10% improvement in mortality in 6640 patients.[27] A French observational study of 650 patients demonstrated a 38% improvement in survival in patients treated with high-flux dialysers.[32]

The US-based Hemodialysis Study (HEMO) was the first significant RCT to assess patient outcome related to high-flux membranes. This study was a factorial RCT that included an arm comparing low- versus high-flux dialysers while a separate arm compared different degrees of urea clearance, in a two-by-two design (n = 1846).[34] Flux was determined according to K_{UF}. Predominantly, prevalent patients were enrolled in this study, with the mean duration of dialysis therapy being 3.7 years. As a substantial proportion of patients were on high-flux dialysers before inclusion (60%), some bias may have been introduced by carry-over effects and lead time bias. The study was also criticised by some for allowing re-use of dialysers, as re-use can be associated with a decrease in large molecule clearance.

While there was no overall mortality benefit from high-flux membranes in the HEMO study (HR 0.92, 95% CI 0.81 - 1.05), there was a mortality benefit observed for the subgroup of patients treated with dialysis for more than 3.7 years at study entry. In addition, in all patients in the study, high-flux membranes were associated with a decrease in cardiac deaths and cardiac hospitalisations,[35] as well as mortality from cerebrovascular disease (in those without known cerebrovascular disease)[36] but not infection-related deaths or hospitalisations.[37] Although no overall mortality benefit was seen with high-flux membranes, pre-dialysis serum beta-2 microglobulin levels were found to be a good predictor of mortality, as well as being correlated with deaths from infectious causes.[38] The latter observation may offer an alternative hypothesis to biocompatibility to explain the apparent difference in infectious complications between patients treated with dialysers containing cellulose versus synthetic membranes.

A post-hoc analysis of the 4-D study (a German RCT of statins in diabetic haemodialysis patients) demonstrated a 59% increased mortality in patients treated with low-flux membranes compared with high-flux membranes.[39] In this analysis, there was also a significant survival advantage for patients treated with low-flux synthetic and modified cellulose membranes compared with low-flux cellulose membranes over the 4-year follow-up period. However, another RCT comparing low-flux cellulose and low-flux synthetic membranes reported no difference in morbidity over 24 months.[40]

The European Membrane Permeability Outcome (MPO) study was an RCT of high- vs. low-flux membranes in incident dialysis patients (n = 738) conducted in 59 centres across 9 countries, with a minimum follow-up of 3 years.[41] Patients were stratified according to serum albumin (≤ 40 g/L and >40 g/L) and dialysis prescription was adjusted throughout the study to maintain Kt/V_{urea} above 1.2. A total of 647 patients completed the study, which demonstrated a 24% improvement in survival for the high-flux group which was not quite significant but a 37% significant survival advantage in those patients with a serum albumin at enrolment of ≤ 40 g/L. Diabetics also demonstrated a significant survival advantage.[41]

In an analysis of European centres in the Dialysis Outcomes and Practice Patterns Study (DOPPS) registry, the use of high-flux compared with low-flux membranes was by itself not associated with improved outcomes, although only 21% of patients in this analysis had diabetes and the mean serum albumin was 39.6 g/L.[42] Therefore, the patients in this analysis were predominantly not the at-risk patient group that may benefit from high-flux membranes as suggested by the MPO study.

Finally, removal of large solutes may also be enhanced by haemofiltration or haemodiafiltration (whereby some or all solute removal occurs by convection as opposed to haemodialysis, which is based on diffusion). The combination of high-flux membranes and therapies with a significant convective component may result in increased levels of large molecule removal. Several studies support the hypothesis that outcomes are improved with these latter therapies compared with standard haemodialysis but no RCT has been completed that assesses any survival benefit.[42-44]

Summary of the evidence

Much has been written about the potential benefits of high-flux membranes, particularly in terms of biocompatibility and clearance of beta-2 microglobulin (the latter with the end-point of the appearance of amyloid deposits). However, amyloidosis seems to be on the decline and biocompatibility is probably less relevant than long-term survival. In the short term, dialysis hypotension may not be significantly better with high-flux membranes.

A Cochrane review of dialysis membranes was published in 2005.[13] As the MPO study had not been published, little evidence was available to comment on mortality advantages. Significant benefits for synthetic membranes (not necessarily high-flux membranes) were found in the areas of beta-2 microglobulin clearance, incidence of amyloidosis, and triglyceride levels.

Only two randomised trials have examined mortality. The HEMO study supported the use of high-flux membranes in a limited subgroup of patients only (those on dialysis for more than 3.7 years).

The MPO study has more recently been published.[45] This study also supported the use of high-flux membranes in two subgroups: those with a serum albumin below 40 g/L and diabetics. In the overall group, the 95% confidence interval for the HR for death just crossed 1.0 – thus suggesting but not able to confirm a benefit.

The results of these two RCTs suggest that larger molecules are clinically important and that the use of high-flux membranes may confer an outcome advantage compared with low-flux membranes. However, the results are not unequivocal and questions remain regarding the relative importance of high-flux membranes to overall outcomes. The benefit on patient outcomes of high-flux membranes in association with dialysis therapies involving convection, such as haemodiafiltration, is also yet to be fully established.

The main downside to high-flux membranes relates to their cost, which was initially prohibitive, but now has approached the cost of low-flux membranes.

The other potential disadvantage of high-flux membranes is the concern about the back-filtration of dialysate contaminants to the patient, resulting from a putative shift of water contaminants from the dialysate into the patients' blood (both from convection and diffusion), which may stimulate

mononuclear cells to release cytokines. Most evidence suggests that synthetic dialysis membranes, with their thick walls and supportive 'honeycomb' are actually quite adsorptive for endotoxins and represent a significant barrier to endotoxin transfer from dialysate to blood. More attention to water quality has also reduced the micro-inflammatory state of dialysis patients.[46]

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: The use of poorly biocompatible, unmodified cellulose dialyser membranes for HD is discouraged. (KDOQI - 2006 Updates, section II, 5.3)[47]
UK Renal Association: BRA (4th edition, 2007). Suggests avoid using low-flux cellulosic membranes. These guidelines precede the MPO study and subsequently quote the HEMO study with its limitations re mortality benefit.[48]
Canadian Society of Nephrology*:* No recommendation.
European Best Practice Guidelines: Avoid bio-incompatible membranes. To achieve an improved clinical outcome regarding morbidity and mortality, the use of large pore/high-flux biocompatible dialysers should be preferred (2002).[11]
The use of synthetic high-flux membranes should be considered to delay long-term complications of haemodialysis therapy (2007).[12] Specific indications include: to reduce dialysis-related amyloidosis (level III); to improve control of hyperphosphataemia (level II); to reduce the increased cardiovascular risk (level II); to improve control of anaemia (level III).
A more recent position statement was also published advising that high-flux dialysers be used in the cases of high-risk patients (comparable to the low-albumin group of the MPO study).[49]
International Guidelines*:* No recommendation.

Suggestions for future research

There is a trend to even larger pore membranes, sometimes referred to as 'superflux' membranes. These need to be subjected to trial with meaningful outcomes, such as mortality or significant morbidity. Further large scale trials of current high-flux membranes assessing mortality benefits would require very large numbers of patients and would not be feasible in Australia (alone). They are unlikely to be performed. However, smaller trials assessing surrogate endpoints are more feasible. Endpoints could include serum markers (e.g. beta-2 microglobulin, or molecules such as fetuin) or markers of vascular disease progression (e.g. vascular calcification, arterial compliance, carotid intima-media thickness).

Conflict of interest

Peter Kerr has a Level II b conflict of interest according to the conflict of interest statement set down by KHA-CARI.

Nigel Toussaint has no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

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Table 1. Characteristics of key studies

Study ID	N	Study design	Description - Participants and Interventions	Follow up	Comments and results
MacLeod et al (2005) [13] Cochrane review	32 studies; 1,946 participants (median 24).	Systematic review of randomised controlled trials and quasi-randomised controlled trials.	Any patient maintained on or commencing haemodialysis. Comparison of any (or several) synthetic HD membranes with any (or several) cellulose or modified cellulose HD membranes. Outcomes: hypotension, adverse symptoms, significant infection, hospital admissions, adequacy of dialysis, pre-dialysis β_2 microglobulin, amyloidosis, nutritional status, QoL, mortality.	NA	Key outcomes: • Sessions with symptomatic hypotension: o RCTs (1 only) - RR: 1.22 (95%CI 0.8, 1.84) o Cross-over RCTs – 8 all no significant difference • Pre-dialysis β_2 microglobulin: o RCTs (4) MD -14.67 (95%CI -33.40, 4.05) – significant heterogeneity. • Amyloidosis: o RCTs (1 only) – RR: 0.03 (0.00, 0.54) – control rate 14/20. • Mortality: o Cellulose - RCTs (3) – RR: 1.18 (95%CI 0.63, 2.22) – control rate 16/227 o Sub cellulose – RCT (1 only) – RR 1.63 (95%CI 0.67, 3.99) – control rate 7/103 Limitations: Small numbers of trials for key outcomes with small number of participants. Variation in membrane flux across trials, differences in exclusion criteria particularly for comorbidity and heterogeneity. Limited trials including substituted cellulose.
Jaber et al (2002) [19]	7 studies (4 RCTs and 3 nonrandomised CTs); 722 participants (median 76)	Systematic review of randomised and non-randomised controlled trials.	Patients with Acute Renal Failure (ARF). Comparison of cellulose derived membranes with synthetic membranes. All cellulose derived classified as bioincompatible (BICM) and synthetic classified as biocompatible (BCM).	NA	Mortality: • BCM vs. BICM RR: 0.92 (95%CI 0.76,1.13) – overall control rate 46% significant heterogeneity. Limitations: Not able to account for use of high-flux and low-flux membranes in the BCM group. Low precision (i.e. large confidence interval).

Study ID	N	Study design	Description - Participants and Interventions	Follow up	Comments and results
HEMO Study [34,35,37]	1,846	Open randomised controlled trial. Multi-centre, US	Adult (18-80 years) in-centre 3 weekly haemodialysis patients (>3 months on dialysis). Exclusions included comorbidities, high residual urea clearance, low serum albumin (<2.6 g/dL) and failure to achieve high target dialysis dose in <4.5 hrs. Intervention: standard vs. high dialysis dose with low-flux or high-flux dialysis membrane. Primary outcome: All-cause mortality. Secondary outcome: First cardiac hospitalisation or all-cause death; first infection-related hospitalisation or all-cause death; and first declining albumin event or all-cause death.	Mean: 2.84 years	All-cause mortality: • High dose vs. standard dose: RR1.01 (95%CI 0.92,1.12) – control rate 48% • High-flux vs. low-flux: RR1.03 (95%CI 0.93,1.13) – control rate 48% Death due to cardiac causes: • High dose vs. standard dose: RR1.04 (95%CI 0.86,1.25) – control rate 18% • High-flux vs. low-flux: RR 0.84 (95%CI 0.69,1.02) – control rate 20% Death due to infection: • High dose vs. standard dose: RR1.04 (95%CI 0.80,1.35) – control rate 11% • High-flux vs. low-flux: RR 0.94 (95%CI 0.72,1.22) – control rate 11% All-cause mortality – interaction with years of dialysis prior to randomisation: • ≤3.7 yr - high-flux vs. low-flux: adjusted RR 1.05 (95%CI 0.89,1.24) • >3.7 yr - high-flux vs. low-flux: adjusted RR 0.68 (95%CI 0.53,0.86) Limitations: Strength of relationship between effect of flux years and years on dialysis varied in different analyses and is not conclusive. Limited power for subgroup analyses and secondary outcomes.
Locatelli et al (2009) MPO study [41]	647	Open randomised controlled trial. Multi-centre, Europe	Adult (18-80 years) in-centre haemodialysis patients (>2months on dialysis) with serum albumin ≤4 g/dL (modified during trial to include >4 g/dL). Exclusions include comorbidities, dialysis after transplantation, use of immunosuppressants. Patients terminated after 4 week run in if dialysis dose <1.2 Kt/V. High-flux vs. low-flux membranes Outcomes: Death and hospitalisation.	Mean 3.0 years (SD 1.9)	All-cause mortality: • High-flux vs. low-flux: RR 0.87 (95%CI 0.67,1.14) – control rate 27% Death due to cardiac causes: • High-flux vs. low-flux: RR 0.86 (95%CI 0.56,1.32) – control rate 12% Death due to infection: • High-flux vs. low-flux: RR 0.78 (95%CI 0.40,1.49) – control rate 6% Accumulation of β2-microglobulin 0 to 36 months: • High-flux vs. low-flux: MD -3.60 mg/L (95%CI -5.18,-2.02) [i.e. lower accumulation in high-flux group] Subgroup analysis of ≤4.0 g/dL serum albumin all-cause mortality: • High-flux vs. low-flux: Adjusted RR 0.63 (95%CI 0.45,0.90) – control rate 35.7% at 4 yrs Subgroup analysis of >4.0 g/dL serum albumin all-cause mortality: • High-flux vs. low-flux: Adjusted RR 1.82 (95%CI 0.86,3.82) – control rate 27.3% at 4yrs Limitations: High rate of dropout (42%) due primarily to transplantation. Ad-hoc subgroup analysis.

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Krane et al (2007) 4D study [39]	1,255 (648 able to be classified for subgroup analysis).	Subgroup analysis of randomised controlled trial. Multi-centre, Germany	Adult haemodialysis patients with type 2 diabetes. Dialysis membrane at discretion of centre. Atorvastatin vs. placebo. Primary outcome: Death from cardiac causes, nonfatal MI and stroke. Secondary outcome: All-cause death.	Mean 3.96 years	All-cause mortality: • Low-flux synthetic compared to high-flux synthetic: adjusted RR 1.59 (95%CI 1.22,2.07) – control rate 56% at 3 years. • Low- flux cellulose compared to low-flux synthetic: adjusted RR 2.61 (95%CI 1.80,3.79) – control rate 56% at 3 years. Limitations: Ad-hoc subgroup analysis. Differences in baseline conditions between membrane groups. Selection of membrane clinic dependent and limited availability of information on dialysis treatment delivery and dose.