

## Dialysis membranes

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### GUIDELINES

**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)**

### 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 be dialysate to blood, often in terms of unwanted compounds such as endotoxin fragments contaminating dialysate. Traditionally, membranes were cellulose based and developed as variations of this, predominantly with varying numbers of acetate molecules per hexose repeat. Subsequent membranes were developed from more 'synthetic' compounds such as polyacrylonitril and polysulfone (or polysulphone).

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. The latter 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).

## **Search strategy**

**Databases searched:** MeSH terms and text words for dialysis were combined with MeSH terms and text words for membrane/s and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1966 – April Week 3 2003). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Date of searches:** 28 April 2003; 2 March 2004.

## **What is the evidence?**

The composition of the dialyser membrane may influence the outcome of the dialysis process in several ways, such as molecular weight of cleared solute or 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 (Hakim 1998).

Cellulose acetate/diacetate, cuprophan and haemophan (modified cellulose) membranes now account for a minority of dialysis treatments, with the use of synthetic membranes being approximately 70% in this region. The use of high-flux membranes has grown in recent years (Kerr 2003).

Evidence of biocompatibility is limited by difficulties with selection of appropriate measures, and in establishing significant effect on patient outcome (Klinkmann & Davison 1994).

Membrane type has been linked in observational studies to patient survival (Lowrie et al 1998), cause of death (especially infection/cardiac causes) (Owen et al 1993), recovery from acute renal failure (Covic et al 1998) and complications associated with  $\beta$ -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.

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.

Several retrospective analyses have reported reduced mortality for patients treated with high-flux dialysers. 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).

The HEMO study represents the only published RCT of low- versus high-flux dialysers. This study not only compared urea clearance but also 'low'- and 'high'-flux membranes, based on  $K_{UF}$ . While there was no overall mortality benefit from high-flux membranes, there was a benefit if the patients had been on dialysis for more than 3.7 years at study entry (Eknoyan et al 2002). In addition, in all patients, high-flux membranes were associated with a decrease in cardiac deaths and cardiac hospitalisations (Cheung et al 2003) but not infection-related deaths or hospitalisations (Allon et al 2003). The HEMO study has been criticised for primarily including prevalent patients, and including excessive numbers of small patients (< 100 kg) and African-Americans (62%).

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 (Pereira et al 1995).

Advanced glycosylation endproduct (AGE) production as measured by pentosidine level was lower in polysulphone low- and high-flux membrane-treated patients than in other synthetic or cellulosic membrane-treated patients (Jadoul et al 1999).

## **Summary of the evidence**

There is very little RCT evidence to support the use of high- or low-flux membranes. 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). There are other observational studies which tend to support high-flux, but not universally so. The

issue of biocompatibility alone is more difficult, as there are no long-term RCTs comparing outcomes in relation to biocompatibility.

An Italian/European study (the MPO study) is currently underway: This RCT will examine the influence of high-flux membranes on mortality and may help clarify this issue (Locatelli et al 2005).

## **What do the other guidelines say?**

**Kidney Disease Outcomes Quality Initiative:** These guidelines do not address membrane flux and membrane biocompatibility was excluded from the literature review.

**British Renal Association:** Dialysis Membranes. Those with a life expectancy of more than 7 years who are unlikely to receive a transplant should receive high-flux dialysis. Patients with symptoms of dialysis-related amyloidosis should also (where possible) receive high-flux dialysis (BRA 2002).

**Canadian Society of Nephrology:** No recommendation.

**European Best Practice Guidelines:** Guideline III.2. To achieve an improved clinical outcome regarding morbidity and mortality, the use of large pore/high-flux biocompatible dialysers should be preferred (EBPG 2002).

**International Guidelines:** No recommendation.

## **Implementation and audit**

ANZDATA: dialyser membrane use and relationship to mortality should be recorded.

## **Suggestions for future research**

1. Effects of membrane type on nutrition could be investigated.
2. Effects of membrane type on cardiovascular surrogate endpoints could be investigated.
3. A prolonged RCT could be run (depending on the outcome of the MPO study).

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## Appendices

**Table 1 Characteristics of included studies**

Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Comments
HEMO study - Allon 2003	1846	Randomised controlled trial	Multicentre 15 clinics, 72 dialysis units	Hemodialysis 18–80 yrs	High-flux membrane 32 $\beta_2$ -microglobulin clearance <10mL/min	Low-flux membrane 32 $\beta_2$ -microglobulin clearance >20mL/min	36	2 x 2 factorial design; including standard dialysis dose eKt/V 1.05 vs high dialysis dose eKt/V 1.45
HEMO study - Cheung 2003		As above						
HEMO study - Eknoyan 2002		As above						

*The CARI Guidelines – Caring for Australians with Renal Impairment*

**Table 2 Quality of randomised trials**

Study ID (author, year)	Method of allocation concealment	Blinding			Intention-to-treat analysis	Loss to follow up (%)
		(participants)	(investigators)	(outcome assessors)		
HEMO study - Allon 2003	Central	No blinding	No blinding	Yes	Yes	68.4
HEMO study - Cheung 2003						
HEMO study - Eknoyan 2002						

**Table 3 Results for dichotomous outcomes**

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
HEMO study - Allon 2003					
HEMO study - Cheung 2003					
HEMO study - Eknoyan 2002	All-cause mortality	429/921	442/925	0.97 (95%CI: 0.89, 1.07)	-0.01 (95%CI: -0.06, 0.03)
	First hospitalisation for cardiac cause or death from any cause	529/921	550/925	0.97 (95%CI: 0.89, 1.04)	-0.02 (95%CI: -0.07, 0.02)
	First hospitalisation due to infection or death from any cause	542/921	562/925	0.97 (95%CI: 0.90, 1.04)	-0.02 (95%CI: -0.06, 0.03)
	First >15% decrease in serum albumin level or death from any cause	490/921	521/925	0.94 (95%CI: 0.87, 1.03)	-0.03 (95%CI: -0.08, 0.01)
	Death due to infection	97/921	104/925	0.94 (95%CI: 0.72, 1.22)	-0.01 (95%CI: -0.04, 0.02)