**targets needs to be assessed in the clinical context of the patient's wellbeing, fluid status, nutritional status as well as tolerance of dialysis prescription.**

## Background

As with any medical treatment, there are significant uncertainties associated with the prescription of peritoneal dialysis, including patient compliance, dialysis reliability, individual patient response to therapy and modification of membrane characteristics by the procedure. These uncertainties mandate the performance of some objective measurements of the adequacy of dialysis delivery. Unfortunately, there has been a tendency in the renal literature and in other guidelines to equate adequacy with small solute clearance measurements. Such an approach runs the risk of treating a laboratory result rather than the whole patient. Small solute clearance must not be considered in isolation, but interpreted in the more global context of clinical and laboratory assessments of all the other manifold aspects of dialysis adequacy, such as hydration status, blood pressure and lipid control, bone disease, anaemia and nutrition.



## Search strategy

**Databases searched:** MeSH terms and text words for peritoneal dialysis were combined with text words for renal clearance, peritoneal clearance and small solute clearance and then combined with the Cochrane highly sensitive search strategy for randomised controlled trials. The search was carried out in Medline (1966 – October Week 2 2003). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

**Dates of searches:** 18 November 2003; 25 November 2003.

## What is the evidence?

There have been two randomised controlled clinical trials (RCTs) to study the effects of increased peritoneal small solute clearances on clinical outcomes among patients with end-stage kidney disease (ESKD) who were being treated with PD.

The ADEMEX trial (Paniagua et al 2002) randomly assigned 965 Mexican patients to control (4 daily exchanges with 2 L of standard PD solution) or intervention groups (modified prescription to achieve a peritoneal clearance of 60 L/wk per 1.73 $m^2$). Randomisation was from a central randomisation centre and analysis was by intention to treat. The primary endpoint of death was no different in each group. Mortality rates remained similar for each group after adjustment for factors associated with survival in PD patients. No clear survival advantage was obtained with increases in peritoneal small solute clearances within the range achieved in this study. Secondary endpoints of hospitalisation, therapy-related complications, correction of anaemia and effects on nutritional status were no different (Paniagua et al 2002). Peritoneal Kt/V urea in the control group was 1.62 ± 0.01 compared with

2.13 ± 0.01 in the intervention group. These findings suggest that the survival benefit of PD is obtained with peritoneal Kt/V urea of ≥ 1.6 (Level II evidence).

Lo and colleagues (2003) enrolled 320 new Chinese continuous ambulatory peritoneal dialysis (CAPD) patients in an open label prospective randomised trial to total Kt/V targets of 1.5 to 1.7; 1.7 to 2.0; and > 2.0. The analysis of results was by intention to treat. There was no significant difference in patient survival. However, a significant number of patients in group A (Kt/V 1.5–1.7) were withdrawn by physicians due to inadequate ultrafiltration and clinically inadequate dialysis. The authors recommended a minimum target of total Kt/V > 1.7 (Level II evidence).

A number of uncontrolled, non-randomised cohort studies have demonstrated an association between total (peritoneal and renal) small solute clearance and outcome. (Teehan et al 1990, Blake et al 1991, Blake et al 1992, De Alvaro et al 1992, Lameire et al 1992, Teehan et al 1992, Genestier et al 1995, Maiorca et al 1995, Churchill et al 1996) (Level III evidence).

The CANUSA study (Churchill et al 1996), which was based on statistical modelling derived from non-randomised correlations, found a linear dose-outcome relationship for weekly Kt/V urea ranging from 1.5 to 2.3 and total $C_{cr}$ measurements ranging between 40 and 95 L/1.73 $m^2$ (Level III evidence).

Maiorca et al (1995) observed the best survivals if total Kt/V was > 1.96 (Level III evidence). Most studies demonstrate that a better outcome on CAPD is related to residual renal function at the time of commencement of CAPD. Residual renal function has a significant impact on the indices of adequacy (Maiorca et al 1995, Tattersall et al 1995, Churchill et al 1996) (Level III evidence).

No study has shown that a decline in residual renal function is compensated by an equal increase in peritoneal clearance. One prospective study demonstrated that a 22% increase in dialysis prescription only produced a 12% increase in $Kt/V_{urea}$ and weekly $C_{cr}$ by 10%. There was no associated improvement in nutritional parameters (Harty et al 1997) (Level III evidence).

There are no studies relating small solute clearance measurements to outcomes in patients treated with APD. Although the peak urea hypothesis argues that higher small solute clearances are required in nightly intermittent peritoneal dialysis (NIPD) and continuous cycling peritoneal dialysis (CCPD) than in CAPD (of the order of 4%–8% higher), these differences are small (Keshaviah 1994, Blake 1996). For the sake of simplicity and in the absence of strong evidence suggesting otherwise, the same targets and the same approach should be used for APD as for CAPD (Level III evidence).

There is insufficient evidence to determine whether achieving a Kt/V target is more important than achieving a $C_{cr}$ target or vice versa. There are more studies, more experience and fewer methodological problems with Kt/V (Twardowski 1998) but $C_{cr}$ may be more discriminatory in terms of predicting outcome (Brandes et al 1992, Selgas et al 1993, Churchill et al 1996). For example, in the CANUSA study, $C_{cr}$ was more strongly associated with hospitalisation than Kt/V and only $C_{cr}$ was significantly associated with technique failure. This finding may simply reflect the fact that $C_{cr}$ is

disproportionately affected by residual renal function relative to Kt/V (Tzamaloukas et al 1998a). However, $C_{cr}$ is much less susceptible to therapeutic manipulation than Kt/V (Level III evidence).

Small solute clearance targets should be modified according to peritoneal membrane transport status, since this parameter has an independent influence on patient outcome (Fried 1997, Churchill et al 1998, Davies et al 1998) and differentially affects creatinine versus urea clearance (Blake et al 1996, Tzamaloukas et al 1998a, Tzamaloukas et al 1998b). Given that low- and low-average transporters, even with lower weekly peritoneal $C_{cr}$ measurements, have substantially increased survival and technique survival compared with higher transporters (Churchill et al 1998), it seems prudent to accept lower $C_{cr}$ targets for these patients. Failure to do so would otherwise invariably lead to the inappropriate transfer of a group of better prognosis patients to haemodialysis (Level III evidence).

No firm recommendations can be made regarding patients at the extremes of body size. Previous studies relating small solute clearance to patient outcome have primarily studied normal weight patients (BMI 20–27.5 kg/m$^2$). Formulae used to calculate total body water (TBW) and, to a lesser extent, body surface area (BSA) may be quite inaccurate at such extremes. Thus, malnourished underweight individuals may have misleadingly high clearance values after normalisation while obese patients may have misleadingly low clearance values (Level III evidence).

**Body size and total body fluid: potential problems**

Unrealistic estimates of V occur in subjects whose height and/or weight differ from the normal range (BMI < 20 or > 27.5 kg/m$^2$). In a recent study, TBW in men was approximately 2–6 L greater than previously reported using the above calculations and TBW in women was 2–5 L less than reported (Chumlea et al 1999). The mean ratio of TBW to weight declined with age as a function of increased body fatness (men > women).

The impact of larger body size has differing effects on determinants of normalised $C_{cr}$ compared with Kt/V. There tends to be a greater impact of V using 58% versus the Watson formula in large and often obese Maori and Pacific Islanders such that the recommended values for adequacy cannot be achieved. The parameters for defining underweight, normal or overweight in ethnically and racially diverse groups needs to be defined. Discrepancies in TBW and Kt/V occur with different body habitus and relative distribution of body fat.

Excess weight (BMI > 27.5 kg/m$^2$) in African Americans on haemodialysis is associated with a higher survival rate at 1 year, independent of Kt/V and urea reduction ratio (URR) (Fleischmann et al 1999) (Level III evidence).

## Summary of the evidence

Two RCTs have examined the role of small solute clearance in CAPD on patient survival. Survival benefit in PD is achieved if the peritoneal Kt/V urea is ≥ 1.6. Increasing clearances above this level did not enhance patient survival (Level II evidence). However, limitations of the ADEMEX trial include use of prevalent and

incident patients (probable under-representation of high-transporters) and smaller habitus Mexicans vs North Americans / Australians. Observational studies suggest that small solute clearances should be modified according to peritoneal membrane transport status (Level III evidence).

## What do the other guidelines say?

### 1. Adequate dose of peritoneal dialysis

**Kidney Disease Outcomes Quality Initiative:**
Guideline 15.
*Weekly Dose of CAPD (Evidence level not stated)*
For CAPD, the delivered PD dose should be a total Kt/Vurea of at least 2.0 per week and a total creatinine clearance (CCr) of at least 60 L/wk/1.73 $m^2$ for high and high-average transporters, and 50 L/wk/1.73 $m^2$ in low and low-average transporters.

Guideline 16.
*Weekly Dose of NIPD and CCPD (Opinion)*
For NIPD, the weekly delivered PD dose should be a total Kt/Vurea of at least 2.2 and a weekly total creatinine clearance of at least 66 L/1.73 $m^2$.
For CCPD, the weekly delivered PD dose should be a total Kt/Vurea of at least 2.1 and a weekly total creatinine clearance of at least 63 L/1.73 $m^2$.

**British Renal Association:** A total weekly $C_{Cr}$ (dialysis + residual renal function) of 50 L/week/1.73 $m^2$ and/or a weekly dialysis $Kt/V_{urea}$ of greater than 1.7 checked 6–8 weeks after beginning dialysis, should be regarded as minima; the mean Kt/V or clearance of a group of patients needed to achieve these minimum figures will need to be higher, e.g. Kt/V 1.9–2.0, $C_{Cr}$ 60–65 L/week/1.73 $m^2$. These studies should be repeated at least annually, or if suspicion arises that residual renal function has declined more rapidly than usual.
Values achieved using APD regimens are even less well defined, but almost certainly need to be higher than for CAPD: minima of Kt/V > 2.0 and weekly $C_{Cr}$ > 60 L should be aimed for.

**Canadian Society of Nephrology:** For CAPD and APD, the minimum weekly Kt/V clearance target would be 2.0 per week and minimum weekly $C_{Cr}$ 60 L/week in high and high-average peritoneal transporters and 50 L/week in low and low-average transporters. (Opinion)
Clearances less than a Kt/V of 1.7 per week and a corrected $C_{Cr}$ of 50 L/week would be considered unacceptable. (Opinion)
Apply all clearance targets in the context of the patient's personal and clinical circumstances. (Opinion)

**European Best Practice Guidelines:** No recommendation.

### 2. Body size and total body fluid

**Kidney Disease Outcomes Quality Initiative:** Estimating TBW and BSA. (Opinion)
V (total body water) should be estimated by either the Watson or the Hume method in adults using actual body weight (Watson et al 1980, Hume and Weyers 1971).
Watson method:
Men V = 2.447 + 0.3362*weight (kg) + 0.1074*height (cm) - 0.09516*age (years)
Women V = 2.097 + 0.2466*weight (kg) + 0.1069*height (cm).

**British Renal Association:** Du Bois method (Du Bois and Du Bois 1916):
BSA ($m^2$) = 71.84*weight (kg)$^{0.425}$*height (cm)$^{0.725}$

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

**European Best Practice Guidelines:** No recommendation.



## Implementation and audit

1. In reporting to ANZDATA, encourage measurements of residual renal function, peritoneal creatinine clearance, renal creatinine clearance, peritoneal Kt/V and renal Kt/V.

2. Encourage identification of patients with BMIs outside the accepted normal range to enable separate analysis of the impact of body size on clearances and outcome.

3. Identify peritoneal transporter status at the commencement of CAPD and in subsequent documentation of outcome.

4. Compare individual unit results with reported national averages.

5. Audit outcomes for CAPD versus APD at comparable weekly total small solute clearances.

## Suggestions for future research

1. It is proposed that a prospective randomised clinical trial to assess outcome (measured as death, hospitalisation rates, cardiovascular events and other co-morbidity) related to dialysis prescription and adequacy be instigated. Stratification for diabetes versus non-diabetes would be required.

2. Randomise after 6 months stable CAPD to two groups:
– manipulation and maintenance of Kt/V > 2.2
– maintenance of Kt/V of 1.8.

3. Power calculations indicate that 176 patients would be required in each group to have at least an 80% probability of being able to detect a 50% reduction in mortality at the 5% level of significance. These calculations assume that the mortality rate of

patients on dialysis is 15 per 100 patient-years and that the study would extend over a 3-year period.

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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 |
|---|---|---|---|---|---|---|---|---|
| Lo et al, 2003 | 320 | Randomised controlled clinical trial | 6 dialysis centres in Hong Kong | New CAPD patients | 1.7–2.0 Kt/V | 1.5–1.7 Kt/V | 24 | Trial with three arms, including third arm > 2.0 Kt/V |
| Paniagua et al, 2002 | 965 | Randomised controlled clinical trial | 24 dialysis centres in 14 Mexican cities | 865 CAPD patients; 18–70 yrs | Modified PD regimen. Achieve $pC_{Cr}$ value of 60 L/wk per 1.73 $m^2$ | Standard PD regimen. 4 daily exchanges of 2 L PD solution. | 24 | |

**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) | | |
| Lo et al, 2003 | Adequate, sequential sealed envelopes | Unclear | Unclear | Unclear | Yes | 0.01 |
| Paniagua et al, 2002 | Central | No | No | No | Yes | 9.33 |

**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] |
|---|---|---|---|---|---|
| Lo et al, 2003 | All-cause mortality | 24/104 (Group B) | 20/104 (Group A) | 1.20 (95%CI: 0.71, 2.03) | 0.04 (95%CI: -0.07, 0.15) |
| | All-cause mortality | 26/112 (Group C) | 20/104 (Group A) | 1.21 (95%CI: 0.72, 2.03) | 0.04 (95%CI: -0.07, 0.15) |
| Paniagua et al, 2002 | All-cause mortality | 159/481 | 157/484 | 1.02 (95%CI: 0.85, 1.22) | 0.01 (95%CI: -0.05, 0.07) |