Level of renal function at which to initiate dialysis

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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)

- **Commence dialysis when GFR falls below approximately 10 mL/min/1.73 m^2 if there is evidence of uraemia or its complications such as malnutrition. In occasional patients it may be necessary to initiate dialysis at a higher GFR. (Level III evidence)**

- **If there is no evidence of uraemia or its complications including malnutrition, commence dialysis when GFR falls below approximately 6 mL/min/1.73 m^2. (Level III evidence)**

- **To encourage informed decision making, educate patients and staff about the strength of the evidence (at best, cohort studies) regarding the rationale for 'early' dialysis initiation.**

- **Monitor GFR quarterly from value of 15–20 mL/min/1.73 m^2 and monthly from < 10 mL/min/1.73 m^2 to avoid unintentional delay in initiation of dialysis.**

With regards to measurement of renal function:

- **GFR calculated as the mean of urea and creatinine clearance can be corrected for body surface area (BSA) by multiplying the uncorrected GFR by 1.73/BSA.**

- **BSA can be determined from the table in Appendix A, derived from the formula of Du Bois (1916), BSA = 0.007184 x [Height (cm)]$^{0.725}$ x [Weight (kg)]$^{0.425}$.**

- **Do not rely solely on creatinine clearance to determine the need for initiating dialysis, because of wide variations due to extrarenal creatinine clearance and renal creatinine secretion.**

- **Target urea clearance can be calculated from the formula:**
  C urea (L/wk) = 2.0 (target weekly Kt/V) x Weight (kg) x 0.58

V is calculated as (Weight (kg) x 0.58) in this equation. It can be more accurately determined from the table in Appendix B, derived from the formulae of Watson et al (1980):

- **for males V = 2.477 + [0.3362 x Weight (kg)] + [0.1074 x Height (cm)] - [0.09516 x age]**
- **for females V = -2.097 + [0.2466 x Weight (kg)] + [0.1069 x Height (cm)]**
- **for children V can be calculated using the Mellits-Cheek method (Mellits and Cheek 1970).***

*See also "*Use of estimated GFR to assess level of kidney function*" in CARI Evaluation of Renal Function guideline.

Background

This section examines evidence regarding the level of renal function at which maintenance dialysis should be commenced in patients with end-stage kidney disease (ESKD). Recommendations are opinion-based as there are no randomised controlled trials (RCTs) examining the issue. Excessive delay in the initiation of dialysis may expose the patient to life-threatening complications of uraemia and comorbid conditions, whereas initiation too early has the potential to increase costs of medical care, and expose the patient to the risks of the dialysis procedure itself, and potentially lead to acceleration of loss of residual renal function (RRF), premature exhaustion of the modality (especially with peritoneal dialysis [PD]) and patient fatigue.

Search strategy

Databases searched: Medline (1966 to April Week 2 2004). MeSH terms and text words for kidney disease were combined with MeSH terms and text words for renal replacement therapy and time factors. The results were then combined with the Cochrane sensitive search strategy for cohort and other prognostic studies.

Date of search: 28 April 2004.

What is the evidence?

There are no RCTs addressing these issues. Confounding influences in other studies include referral time bias, age, comorbidity, patient compliance and starting time bias.

In the CANUSA study (McCusker et al 1996), one- and two-year survival was greater for those starting CAPD with an initial GFR (mean of urea and creatinine clearance) greater than 38 L/week (95% and 82%) versus less than 38 L/week (91% and 74%, $p < 0.015$ by log-rank test). The apparent survival advantage of initial residual Kt/V greater than 0.71 was not statistically significant. The relative risk of death was 0.95 (95% CI 0.91–0.99) for a 5 L/week greater GFR at initiation (Cox proportional hazards model). This study was not designed to examine time of initiation of dialysis, and so this evidence in favour of earlier initiation is not strong.

In a prospective cohort study of 63 patients in 1991–92 (Tattersall et al 1995), hospitalisation length of stay was greater among those with residual Kt/V less than 1.05 versus greater than 1.05 at time of initiating dialysis. However, this result was difficult to interpret as hospital stay was also longer among those with increasing age and comorbidity. Mean Kt/V was 0.63 among the 6 patients who died, versus 1.05 among survivors. It was unclear whether the differences were due to time of referral or time of initiation.

In a post-hoc analysis of the MDRD study (Beddhu et al 2003), higher MDRD GFR (but not creatinine clearance) at initiation was associated with an increased risk of death (HR 1.27 for each 5 mL/min increase). The authors contend that this might "reflect an erroneous GFR estimation by the MDRD formula," rather than evidence that sicker patients were commenced on dialysis at a higher GFR. Rather than argue against early initiation, the data emphasise the need to control for comorbidity, particularly in studies not primarily designed to examine timing of initiation.

In a prospective cohort study from Holland (Korevaar et al 2002), 38% of 237 incident dialysis patients commenced dialysis late, as defined by the K/DOQI guidelines. Compared with patients who have timely initiation, the health-related quality of life among late starters was worse during the first 6 months after initiation, but no different at 12 months.

A retrospective chart review was used in a study from Glasgow (Traynor et al 2002) to control for the influence of lead-time bias by calculating survival from the time point at which creatinine clearance was 20 mL/min. From a total of 275 patients, those with creatinine clearance less than the median of 8.3 mL/min at dialysis initiation survived longer than those with creatinine clearance greater than 8.3 mL/min, even after adjusting for baseline characteristics known or purported to influence survival.

In a retrospective analysis (Bonomini et al 1978) of 90 patients, those who commenced dialysis early (mean creatinine clearance 13 mL/min; n = 82) versus late following dietary management (mean creatinine clearance 2.1 mL/min, n = 308) had a higher mean 12 year survival (77% vs 51%), less hospitalisation (7 vs 16 d/yr) and greater employment (72% vs 42%). The differences were not explained by age, renal disease or starting time bias. Among a subset of patients who were subsequently transplanted (Bonomini et al 1986), there was a patient survival advantage for those who commenced dialysis early (n = 50) versus later (n = 96), as well as less vascular calcification, bacterial infection, dyslipidaemia and hospitalisation.

Of studies examining the influence of referral time, in two studies – one retrospective cohort (Jungers et al 1993) and one prospective cohort (Sesso and Belasco 1996) – creatinine clearance at initiation was slightly lower in those referred late, being 4.4 versus 6.4 mL/min (Jungers et al 1993) and 5.7 versus 7.4 mL/min (Sesso and Belasco 1996).

In the CANUSA study (Churchill et al 1996), there was a survival advantage for higher total (residual plus dialysis) Kt/V up to 2.0, and possibly up to 2.3. Based on these data in patients on peritoneal dialysis (PD), many authors have argued that it is logical to start dialysis at a level of residual renal function equivalent to the target total Kt/V. There are no data in non-dialysis patients to support this opinion, which

without evidence assumes equal clinical efficacy of renal and dialysis clearance. These opinion-based recommendations may be responsible, at least in part, for a recent worldwide trend towards initiating dialysis at a higher GFR than previously.

In a retrospective cohort study (Cooper et al 2003), nutrition as assessed by nitrogen index and serum albumin, was significantly worse in patients commencing dialysis at creatinine clearance of <10 versus >10 mL/min. A prospective study will be required to determine if this influences survival. A substudy of the IDEAL trial (Cooper et al 2004; see below) will examine this issue.

Opinion-based recommendations that dialysis should be initiated in an otherwise well patient at GFR < 5–6 mL/min are based on the high frequency of uraemic symptoms at that level of GFR, the possibility of life-threatening complications within 6 months at average rates of progression of renal dysfunction, and the increased likelihood of and morbidity associated with emergent dialysis. Balanced against this are the costs and risks of early initiation of dialysis, including complications of dialytic therapy, potential acceleration of loss of residual renal function, premature exhaustion of the modality (especially with PD) and patient fatigue.

The IDEAL trial (Cooper et al 2004) is a multicentre RCT that aims to determine whether it is better to commence dialysis with a creatinine clearance of 10–14 or 5–7 mL/min/1.73 m^2. Randomisation of 800 patients should be completed by mid-2005, with a 3-year follow-up at the end of the recruitment period.

Summary of the evidence

There are no RCTs on this topic.

What do the other guidelines say?

There are no differences of substance between the above CARI Suggestions for Clinical Care, and the other published guidelines, each of which is opinion-based.

Kidney Disease Outcomes Quality Initiative: Guideline 1. CPG for PD Adequacy. Commence dialysis when weekly Kt/V (urea) falls below 2.0 (or C urea 7 mL/min, C creatinine 7–14 mL/min/1.73 m^2, GFR 10.5 mL/min/1.73 m^2), unless stable or increasing lean body weight and no evidence of malnutrition (including nPNA > 0.8 g/kg/d) and no symptoms or signs of uraemia. This recommendation is opinion-based, and extrapolated from PD data (Churchill et al 1996).

British Renal Association: No recommendation.

Canadian Society of Nephrology: Guideline 1.3. Initiation of Dialysis. Commence dialysis when GFR < 12 mL/min (C creatinine < 18 mL/min) if evidence of uraemia or malnutrition; this recommendation is based on evidence from cohort studies (as above). Commence dialysis when GFR < 6 mL/min if no evidence of uraemia or malnutrition; this recommendation is opinion-based.

European Best Practice Guidelines: Guideline I.3. When to Start Dialysis. Commence dialysis when GFR is < 15 mL/min and there is one or more of the following: symptoms or signs of uraemia, inability to control hydration status or blood pressure, or a progressive deterioration in nutritional status. In any case, dialysis should be started before the GFR has fallen to 6 mL/min/1.73 m^2, even if optimal pre-dialysis care has been provided and there are no symptoms. High-risk patients (e.g. diabetics) may benefit from an earlier start. To ensure that dialysis is started before the GFR is < 6 mL/min, clinics should aim to start at 8–10 mL/min.

Implementation and audit

There are no guidelines to implement. Audit of the uptake of the above suggestions for clinical care could involve ANZDATA collection of entry GFR (mean urea and creatinine clearance) for all new patients commencing dialysis.

Suggestions for future research

An RCT of outcome of patients commencing dialysis at GFR 10–14 versus 5–7 mL/min/1.73 m^2 is underway in Australia and New Zealand (Cooper et al 2004). This trial will not conclude until 2008. Included in this are patients with no evidence of uraemia or malnutrition.

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Appendices

Appendix A: Body surface area (BSA)

	Height (cm)																
Wt (kg)	**120**	**125**	**130**	**135**	**140**	**145**	**150**	**155**	**160**	**165**	**170**	**175**	**180**	**185**	**190**	**195**	**200**
36	1.06	1.09	1.12	1.15	1.19	1.22	1.25	1.28	1.31	1.33	1.36	1.39	1.42	1.45	1.48	1.51	1.53
38	1.08	1.12	1.15	1.18	1.21	1.24	1.27	1.31	1.34	1.37	1.4	1.43	1.45	1.48	1.51	1.54	1.57
40	1.11	1.14	1.17	1.21	1.24	1.27	1.30	1.33	1.37	1.40	1.43	1.46	1.49	1.52	1.55	1.58	1.61
42	1.13	1.17	1.20	1.23	1.27	1.30	1.33	1.36	1.39	1.43	1.46	1.49	1.52	1.55	1.58	1.61	1.64
44	1.15	1.19	1.22	1.26	1.29	1.32	1.36	1.39	1.42	1.45	1.49	1.52	1.55	1.58	1.61	1.64	1.67
46	1.18	1.21	1.25	1.28	1.32	1.35	1.38	1.42	1.45	1.48	1.51	1.55	1.58	1.61	1.64	1.67	1.70
48	1.20	1.23	1.27	1.30	1.34	1.37	1.41	1.44	1.48	1.51	1.54	1.57	1.61	1.64	1.67	1.70	1.73
50	1.22	1.26	1.29	1.33	1.36	1.40	1.43	1.47	1.50	1.53	1.57	1.60	1.63	1.67	1.70	1.73	1.76
52	1.24	1.28	1.31	1.35	1.39	1.42	1.46	1.49	1.53	1.56	1.59	1.63	1.66	1.70	1.73	1.76	1.79
54	1.26	1.30	1.33	1.37	1.41	1.44	1.48	1.52	1.55	1.59	1.62	1.66	1.69	1.73	1.76	1.79	1.82
56	1.28	1.32	1.36	1.39	1.43	1.47	1.50	1.54	1.58	1.61	1.65	1.68	1.72	1.75	1.78	1.82	1.85
58	1.30	1.34	1.38	1.41	1.45	1.49	1.53	1.56	1.60	1.63	1.67	1.71	1.74	1.78	1.81	1.85	1.88
60	1.32	1.36	1.40	1.43	1.47	1.51	1.55	1.59	1.62	1.66	1.69	1.73	1.77	1.80	1.84	1.87	1.91
62	1.34	1.38	1.41	1.45	1.49	1.53	1.57	1.61	1.64	1.68	1.72	1.76	1.79	1.83	1.86	1.90	1.93
64	1.35	1.39	1.43	1.47	1.51	1.55	1.59	1.63	1.67	1.70	1.74	1.78	1.82	1.85	1.89	1.92	1.96
66	1.37	1.41	1.45	1.49	1.53	1.57	1.61	1.65	1.69	1.73	1.77	1.80	1.84	1.88	1.91	1.95	1.99
68	1.39	1.43	1.47	1.51	1.55	1.59	1.63	1.67	1.71	1.75	1.79	1.83	1.86	1.90	1.94	1.97	2.01
70	1.41	1.45	1.49	1.53	1.57	1.61	1.65	1.69	1.73	1.77	1.81	1.85	1.89	1.92	1396	2.00	2.04
72	1.42	1.47	1.51	1.55	1.59	1.63	1.67	1.71	1.75	1.79	1.83	1.87	1.91	1395	1399	2.02	2.06
74	1.44	1.48	1.53	1.57	1.61	1.65	1.69	1.73	1.77	1.81	1.85	1.89	1.93	1.97	2.01	2.05	2.08
76	1.46	1.50	1.54	1.59	1.63	1.67	1.71	1.75	1.79	1.83	1.87	1.91	1.95	1.99	2.03	2.07	2.11
78	1.47	1.52	1.56	1.60	1.65	1.69	1.73	1.77	1.81	1.85	1.89	1.94	1.98	2.01	2.05	2.09	2.13
80	1.49	1.53	1.58	1.62	1.66	1.71	1.75	1.79	1.83	1.87	1.92	1.96	2.00	2.04	2.08	2.12	2.15
82	1.50	1.55	1.59	1.64	1.68	1.72	1.77	1.81	1.85	1.89	1.94	1.98	2.02	2.06	2.10	2.14	2.18
84	1.52	1.56	1.61	1.65	1.70	1.74	1.79	1.83	1.87	1.91	1.96	2.00	2.04	2.08	2.12	2.16	2.20
86	1.53	1.58	1.63	1.67	1.72	1.76	1.80	1.85	1.89	1.93	1.98	2.02	2.06	2.10	2.14	2.18	2.22
88	1.55	1.60	1.64	1.69	1.73	1.78	1.82	1.87	1.91	1.95	1.99	2.04	2.08	2.12	2.16	2.20	2.24
90	1.56	1.61	1.66	1.70	1.75	1.79	1.84	1.88	1.93	1.97	2.01	2.06	2.10	2.14	2.18	2.22	2.27
92	1.58	1.63	1.67	1.72	1.77	1.81	1.86	1.90	1.95	1.99	2.03	2.08	2.12	2.16	2.20	2.25	2.29
94	1.59	1.64	1.69	1.74	1.78	1.83	1.87	1.92	1.96	2.01	2.05	2.09	2.14	2.18	2.22	2.27	2.31
96	1.61	1.66	1.70	1.75	1.80	1.84	1.89	1.94	1.98	2.03	2.07	2.11	2.16	2.20	2.24	2.29	2.33
98	1.62	1.67	1.72	1.77	1.81	1.86	1.91	1.95	2.00	2.04	2.09	2.13	2.18	2.22	2.26	2.31	2.35
100	1.64	1.69	1.73	1.78	1.83	1.88	1.92	1.97	2.02	2.06	2.11	2.15	2.20	2.24	2.28	2.33	2.37
102	1.65	1.70	1.75	1.80	1.84	1.89	1.94	1.99	2.03	2.08	2.12	2.17	2.21	2.26	2.30	2.35	2.39
104	1.66	1.71	1.76	1.81	1.86	1.91	1.96	2.00	2.05	2.10	2.14	2.19	2.23	2.28	2.32	2.37	2.41
106	1.68	1.73	1.78	1.83	1.88	1.92	1.97	2.02	2.07	2.11	2.16	2.20	2.25	2.30	2.34	2.38	2.43
108	1.69	1.74	1.79	1.84	1389	1.94	1.99	2.03	2.08	2.13	2.18	2.22	2.27	2.31	2.36	2.40	2.45
110	1.70	1.75	1.81	1.86	1.91	1.95	2.00	2.05	2.10	2.15	2.19	2.24	2.29	2.33	2.38	2.42	2.47
112	1.72	1.77	1.82	1.87	1.92	1.97	2.02	2.07	2.11	2.16	2.21	2.26	2.30	2.35	2.40	2.44	2.49
114	1.73	1.78	1.83	1.88	1.93	1.98	2.03	2.08	2.13	2.18	2.23	2.27	2.32	2.37	2.41	2.46	2.50

Calculated by the Dubois formula:
Body surface area = 0.007184 x (patient's height, cm)$^{0.725}$ x (patient's weight, kg)$^{0.425}$

Appendix B: Total body water (V) – adults

Female V= -2.097 + [0.2466 x Wt (kg)] + [0.1069 x Ht (cm)]

Female		Ht (cm) 120	130	140	150	160	170	180	190	200
	30	18.1	19.2	20.3	21.3	22.4	23.5	24.5	25.6	26.7
	40	20.6	21.7	22.7	23.8	24.9	25.9	27.0	28.1	29.1
	50	22.7	24.1	25.2	26.3	27.3	28.4	29.5	30.5	31.6
	60	25.5	26.6	27.7	28.7	29.8	30.9	31.9	33.0	34.1
Wt (kg)	**70**	28.0	29.1	30.1	31.2	32.3	33.3	34.4	35.5	36.5
	80	30.5	31.5	32.6	33.7	34.7	35.8	36.9	37.4	39.0
	90	32.9	34.0	35.1	36.1	37.2	38.3	39.3	40.4	41.5
	100	35.4	36.5	37.5	38.6	39.7	40.7	41.8	42.9	43.9
	110	37.9	38.9	40.0	41.1	42.1	43.2	44.3	45.3	46.4
	120	40.3	41.4	41.5	43.5	44.6	45.7	46.7	47.8	48.9

Male V= 2.477 + [0.3362 x Wt (kg)] + [0.1074 x Ht (cm)] – [0.09516 x age]

Male		Ht (cm) 120	130	140	150	160	170	180	190	200
	30	25.4	26.6	27.6	28.7	29.7	30.8	31.9	33.0	34.0
	40	28.8	29.9	33.0	32.0	33.1	34.2	35.3	36.3	37.4
	50	32.2	33.2	34.3	35.4	36.5	37.5	38.6	39.7	40.8
	60	35.5	36.6	37.7	38.8	39.8	40.9	42.0	43.1	44.1
Wt (kg)	**70**	38.9	40.0	41.0	42.1	43.2	44.3	45.3	46.4	47.5
	80	42.3	43.3	44.4	45.5	46.6	47.6	48.7	49.8	50.9
	90	45.6	46.7	47.8	48.8	49.9	51.0	52.1	53.1	54.2
	100	49.0	50.1	51.1	52.2	53.3	54.4	55.4	56.5	57.6
	110	52.3	53.4	54.5	55.6	56.6	57.7	58.8	59.9	60.9
	120	55.7	56.8	57.9	58.9	60.0	61.1	62.2	63.2	64.3

Use table, then subtract 1 for every decade of life (males only)