

Renal function should be reported as GFR equivalent (ml/min/1.73 m²).
(Evidence level: C)

Dialysis terms such as Kt/V and weekly creatinine clearance should be avoided.
(Evidence level: C)

Guideline I.1.3

A. GFR should only be estimated using a method, which has been validated in patients with advanced renal failure. The preferred method for calculating GFR in advanced renal failure is the mean of urea and creatinine clearance. The latter is best calculated from a 24-h urine collection and normalized to 1.73 m².
(Evidence level: C)

B. Other examples of validated GFR estimations are:

- MDRD equation
- Indicator decay methods (e.g. iohexol, iothalamate, EDTA, inulin)
- Creatinine clearance after oral cimetidine

Guideline I.1.4

A. To assist in the standard reporting of renal function in advanced renal failure, the preferred methods of estimating GFR in advanced renal failure are EITHER:

MDRD equation

(Evidence level: B) (*Appendix I*)

OR

The mean of urea and creatinine clearance, calculated from 24-h urine collections and normalized to 1.73 m²; preferably using the Gehan and George method for calculating surface area.

(Evidence level: B) (*Appendix I*)

Guideline I.1.5

A. To assist in the detection and timely referral of patients with renal failure, laboratories should be encouraged to report the GFR using the MDRD equation when serum creatinine above the normal

I.1 Measurement of renal function

Guideline I.1.1

A. Renal function should not be estimated from measurements of blood urea or creatinine alone. Cockcroft and Gault equation or reciprocal creatinine plots should not be used when the glomerular filtration rate (GFR) is <30 ml/min or to determine the need for dialysis.

(Evidence level: A)

Guideline I.1.2

A. To reduce confusion when communicating with general physicians and to encourage timely referral of patients with renal failure:

range is measured and there is insufficient data to calculate GFR more directly.

(Evidence level: C)

B. If creatinine clearance is requested from a 24-h urine collection, the laboratories should also report GFR calculated from the mean of urea and creatinine clearance. The report should indicate that this GFR is not normalized for surface area and should show indicative normal ranges for different sized patients.

(Evidence level: C)

Commentary on Guidelines I.1.1–I.1.5

Serum creatinine or reciprocal serum creatinine in patients with advanced renal failure are an unreliable measure of renal function and progression of renal failure [5–16]. This is due to differences in muscle mass associated with age, gender, race, nutrition, activity, and disease. Creatinine generation rate declines as renal disease progresses and the serum creatinine may not predictably reflect renal function [17].

The serum concentrations of both urea and creatinine have been shown to relate to mortality—the lower the concentration, the higher the mortality [18–21]. This is probably because, in patients with renal failure, a lower serum creatinine is more a marker of inactivity and malnutrition than it is of adequate renal function. On the other hand, low renal clearance at initiation of dialysis is significantly related to high dialysis mortality, independent of nutrition [22,23].

GFR normalized to surface area and expressed in units of ml/min/1.73m² is recognized as the standard measurement of renal function [24].

Numerous different methods for quantifying renal function have been validated against ‘gold-standard’ GFR measurements. The most accurate and direct measurements of GFR require timed blood sampling after administration of a tracer. This is often impractical for routine use in the nephrology clinic and is unrealistic as a standard for general practice. More practically, an estimate of GFR can be calculated from timed urine collections and a blood sample. As creatinine is secreted into the urine by the renal tubules, creatinine clearance overestimates GFR in advanced renal failure by as much as 70% [5,25]. By chance, the renal tubules absorb urea so that the mean of urea and creatinine clearance is close to GFR (actually underestimating GFR by ~10%) [5,26,27]. In CAPD, the standard method of quantifying residual renal function is by 24 h urine collection, calculating GFR as the mean of urea and creatinine clearance and normalizing to 1.73 m² surface area. This method has been the most well studied in advanced renal failure both before starting dialysis and after starting CAPD [22].

Alternatively, tubular creatinine secretion may be blocked by oral cimetidine, so that GFR can be estimated directly from creatinine clearance [5,25].

The accuracy of urine-based GFR estimation is dependent on the patient collecting the urine properly over a defined time. Common sources of error include; failing to empty the bladder at the start of the collection, failing to collect all urine passed during the collection interval, and errors in timing the interval. In theory, these errors can be minimized if the patient is carefully and consistently instructed and if duplicate measurements are made.

Urine-based GFR estimation requires normalization to surface area. The Gehan and George [28] method for calculating surface area is preferred, as it has been validated in 400 subjects [29]. It is recognized that the alternative Dubois and Dubois equations [30] for predicting surface area are widely used (including in the MDRD study) although were based on only nine subjects.

In order to avoid these practical difficulties, many nephrologists estimate the GFR using the Cockcroft and Gault method, which uses serum creatinine. Age, gender, and body weight are used to correct for the differences in muscle mass, and hence creatinine generation rate. This method gives reasonable agreement with GFR in mild degrees of renal failure (GFR ~50 ml/min) but overestimates GFR by up to 100% when GFR is 10 ml/min [5] or less. This is presumably because the relative malnutrition and inactivity in advanced renal failure results in additional decline in creatinine generation rate. As there is a better alternative (see below), the Cockcroft and Gault method should no longer be used.

The MDRD study [5] demonstrated that GFR could be estimated reliably in advanced renal failure using blood and demographic data. The MDRD method requires age, gender, race (black or white), and serum urea, creatinine and albumin. A simplified version of the MDRD method dispenses with the urea and albumin with a slight reduction in accuracy. Clinical chemistry laboratories generally have access to all the data apart from race. If race is unavailable and white race may be assumed, GFR will be underestimated by 18% if the patient is black (Afro-Caribbean). In the MDRD study, the equation predicted GFR at least as precisely as the mean of urea and creatinine clearance in 24-h urine collections.

The GFR calculated using the MDRD method is already corrected for surface area and requires no measurement of weight or additional normalization.

It should be noted that the MDRD equation has only been validated in American black and white racial groups. A patient categorized as black had a higher creatinine generation rate than one categorized as white and the equations reflect this difference. It is not yet clear how well the MDRD equations predict GFR in Asians or other racial groups. Until the method has been validated in other non-white racial groups, the MDRD equation should be used assuming white race and the resulting GFR prediction interpreted with caution.

The MDRD study based its conclusions on measurement of serum creatinine by the enzymatic

method, which is specific for creatinine. The commonly used Jaffe method for measuring creatinine is known to be subject to interference from certain drugs, glucose, and ketoacids. The Jaffe method may overestimate creatinine by ~8%, depending on the clinical and laboratory factors. Ideally, creatinine should be measured by a specific method such as the enzymatic method. If creatinine is measured by the Jaffe method the results should be corrected in consultation with the laboratory and interpreted with caution.

I.2 When to refer to a nephrology clinic

Guideline I.2.1

A. Referral to nephrology should be considered when the GFR is < 60 ml/min and is mandatory when the GFR is < 30 ml/min.

B. If a GFR prediction or measurement is not available, patients with chronic renal failure should be referred to a nephrologist when on two consecutive measurements, plasma creatinine exceeds 150 mmol/l in men and 120 mmol/l in women, corresponding to a GFR of ~ 50 ml/min. These patients should be referred whether or not there are other indications of chronic renal disease, such as proteinuria.

Guideline I.2.2

A. Patients with a GFR < 60 ml/min should have a treatment strategy aimed at:

- Reducing the mortality and morbidity of renal failure. In general, this is similar to the strategy in dialysis patients with respect to management of renal anaemia, nutrition, acid-base, calcium, phosphate homeostasis, and blood pressure control. (*Evidence level: B*)
- Delaying or preventing the progression of renal failure. This will include specific treatment of the underlying renal condition, regular GFR and protein excretion measurements to guide therapy, strict blood pressure control, ACE inhibition in patients with diabetes mellitus and those with protein excretion > 3 g/day, strict blood glucose control in diabetes, and modification of risk factors (including smoking, lipid abnormalities, excessive protein intake). (*Evidence level: B*)
- Referral to a nephrologist should be considered in order to implement this therapy.
- At a GFR of 60 ml/min the serum creatinine is ~ 140 $\mu\text{mol/l}$ for men and 105 $\mu\text{mol/l}$ for women.

Guideline I.2.3

A. Patients whose GFR is < 30 ml/min and declining despite therapy should be under the care of a nephrologist and be prepared for the onset of end-stage renal failure. This preparation includes:

- Choosing the most appropriate location (e.g. home or hospital) and form of treatment (e.g. HD, CAPD, pre-emptive transplantation or conservative treatment). This choice will involve discussion between patients, their families and nephrology staff. This process may need support from specialist renal counsellors and social workers. (*Evidence level: C*)
- Preparing appropriate dialysis access in a timely manner. (*Evidence level: B*)
- Hepatitis vaccinations should be considered. The effects must be assessed regularly.
- When GFR has fallen to 15 ml/min/1.73 m² the assessments should be intensified to about once monthly with special attention to control of hypertension, fluid overload, biochemical abnormalities, and management of malnutrition.

At a GFR of 30 ml/min the serum creatinine is ~ 180 $\mu\text{mol/l}$ for men and 150 $\mu\text{mol/l}$ for women.

Commentary on Guideline I.2.1–I.2.3

Patients with chronic renal failure and a GFR < 30 ml/min generally progress (evidence level: B) [31–34], irrespective of the underlying renal condition. Progression of renal failure may be prevented or significantly slowed by various means including:

- Strict blood pressure control [36–39].
- Certain drugs (ACE inhibitors, calcium channel blockers) [36,38,40,41].
- Strict blood glucose control in patients with diabetes mellitus [42].
- Revascularization procedures in selected patients with renovascular disease [43–46].

Progression of renal failure has been associated with additional potentially modifiable risk factors, including lipid abnormalities [58] and smoking [60].

Specific treatment of any underlying renal condition may also be required.

Patients with a GFR < 60 ml/min are prone to complications similar to dialysis patients, including:

- Renal anaemia [47,48].
- Fluid overload, hypertension, and left ventricular hypertrophy [49–51].
- Abnormalities in calcium and phosphate metabolism [52,53].
- Malnutrition [54–57].
- Lipid abnormalities [58,59].

Most of the deaths in dialysis patients are related to cardiovascular disease and/or malnutrition [61]. The cardiovascular disease and/or malnutrition may be preventable by appropriate pre-dialysis care and timely initiation of dialysis. Morbidity and mortality once dialysis starts may be reduced by timely placement of appropriate access and psychological preparation of the patient. Vaccination against hepatitis B

[66] should be included in the management of these patients as well as regular vaccinations against influenza [67] and possibly also against pneumococcal pneumonia [68].

The diagnosis of the underlying renal condition should be performed by a nephrologist. Also, general preventative measures require careful monitoring of renal function and protein excretion and are best undertaken under nephrology supervision. The earlier this prevention is performed, the greater the chance of avoiding the need for dialysis.

In order to maximize the preventative potential, and to reduce the morbidity and mortality associated with chronic renal failure, the EBPG group feels that referral to the nephrologist should be made as soon as the GFR drops to <60 ml/min. This requires the nephrology departments to shift their focus from providing dialysis and transplantation to prevention and disease management. This will be more ethical and may be cost-effective in the long-term. The NHANES III study in the USA determined a GFR is <60 ml/min in 12.3% of the population [70]. At present, nephrology services have insufficient capacity to cope with so many patients.

In recognition of current nephrology capacity, the EPBG group recommends referral at a GFR between 30 and 50 ml/min. Patients with a GFR <60 ml/min who are not under the care of a nephrology service should still receive preventative treatment and monitoring by a general practitioner or internist.

By the time the GFR has declined to 30 ml/min, the patient will require preparation for dialysis and specific renal failure care which can only be performed in a nephrology department with access to dialysis. The NHANES III study determined that 0.2% of the US population have a GFR <30 ml/min and are not on dialysis. Nephrology services should have the capacity to manage at least this number of patients, which is similar to the number of patients on dialysis.

In population studies, serum creatinine has been demonstrated as effective in screening for early chronic renal failure. The cut-off value for a clearance of <60 ml/min/1.73 m² was 137 μ mol/l for men and 104 μ mol/l for women. For a clearance of <30 ml/min/1.73 m², the cut-off value was 177 μ mol/l for men and 146 μ mol/l for women [35].

B. High-risk patients e.g. diabetics may benefit from an earlier start.

(Evidence level: C)

C. To ensure that dialysis is started before the GFR is < 6 ml/min, clinics should aim to start at 8–10 ml/min.

(Evidence level: C)

Commentary on Guideline I.3

The timing of initiation of dialysis is controversial as it has major cost and practical implications. There is currently no definitive (evidence level: A) evidence on this issue. Dialysis is currently started when the GFR is at a mean of ~6 ml/min but there are wide variations with some groups advocating starting with a GFR of 15 ml/min. The rationale for starting dialysis earlier, despite the cost and inconvenience to the patient, is that it may reduce the currently unacceptably high morbidity and mortality of dialysis patients.

The DOQI guidelines advocate starting at a GFR of ~10 ml/min but the GFR may be ignored if there is no evidence of malnutrition. This is confusing as there is good evidence that nutritional indices are already compromised when GFR is <30 ml/min [55,57]. Early malnutrition is difficult to detect and any criteria for starting dialysis based on nutrition will favour starting dialysis earlier when there is intensive nutritional supervision.

Numerous (evidence levels: B or C) studies have suggested a reduced survival in patients starting dialysis later than at a GFR of 6 ml/min compared with starting dialysis earlier [22,23,62]. These studies may be criticized for failing to control for the effects of late referral, which may be an independent risk for dialysis mortality.

The Netherlands Cooperative Study on the Adequacy of Dialysis suggested that a patient survives ~2.5 months longer if started on dialysis according to the DOQI guidelines (GFR >10 ml/min or nPNA >0.8 g/kg/day) compared with a later start. This survival advantage was considered by the study authors to be due to the patients starting dialysis at an earlier stage in their disease, estimated at ~4 months [69]. The latter study was retrospective, the patients were relatively young and disease progression in the period before dialysis started was not studied. There is clearly a need for a prospective, randomized controlled study to clarify this issue. It is recognized that such a study would be very difficult to perform, as it would be almost impossible to enforce an unbiased subject allocation process.

There are also suggested and theoretical benefits of starting dialysis earlier than a GFR of 10 ml/min [63]. In the CANUSA study of CAPD patients a combination of renal and dialysis creatinine clearance of >10 ml/min was associated with a significantly improved survival [22]. As most of the variability in total clearance in the CANUSA study was due to the initial residual renal function, this suggests that

I.3 When to start dialysis

Guideline I.3

A. Dialysis should be instituted whenever the 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 m², even if optimal pre-dialysis care has been provided and there are no symptoms.

the higher the residual renal function at the start of dialysis, the better the outcome.

While the optimal level of GFR for starting dialysis remains controversial, there is no data supporting the safety of delaying dialysis until the patient is symptomatic with a GFR < 6 ml/min. It is the opinion of the EBPG group that a practice of delaying dialysis until the GFR is < 6 ml/min, whether or not the patient is symptomatic, is unsafe.

The issue of whether dialysis should be initiated at 'full dose' or in an incremental manner with dose adaptations according to progressive decrease of residual renal function remains open. Similarly the other important issue of the type of dialysis method (peritoneal dialysis (PD) or HD) that should be favoured as first therapy in a patient with some residual renal function is also unsettled at present; this will remain so at least until the concept of starting renal replacement therapy with PD in an 'integrative care approach', as recently put forward [64,65] gains stronger scientific support.

In conclusion, until the results of a randomized prospective trial evaluating the benefits of earlier start of dialysis are published, it is recommended that dialysis be initiated at any time after GFR has fallen to < 15 ml/min/1.73 m² if there is evidence of malnutrition, or fluid overload unresponsive to diuretics, or clinical signs and symptoms of uraemia. Based on opinion rather than evidence, the minimal level of GFR above which dialysis should be started regardless of symptoms is 6 ml/min/1.73 m².

made over the entire interdialytic interval (usually 2 days).

(Evidence level: C)

- **The mean blood urea and creatinine concentrations during the collection period should be estimated as the mean of the post-HD concentration immediately after dialysis (after rebound correction; see Appendix) and the pre-HD value immediately before the following dialysis.**

(Evidence level: C)

- **To convert GFR to Kt/V the Casino and Lopez [72] method should be used.**

(Evidence level: C)

Commentary on Guideline I.4

Currently, residual renal function is not routinely measured in HD. On the other hand, current guidelines and practice recognize the critical importance of residual renal function in CAPD [71,73–79].

In CAPD, residual renal function provides a significant and often crucial contribution to overall clearance, at least in the first 2 years of dialysis [71].

In the past, the renal contribution to clearance was ignored in both HD and CAPD. Residual renal function was assumed to fall to zero soon after starting dialysis. It was only after residual renal function was routinely measured in CAPD, that its true importance was discovered. There is now a well-validated and universally accepted method for quantifying residual renal function in CAPD, based on urine collections [71].

In HD, there is no validated and universally accepted method for measuring renal function. It has been considered to decline faster in HD compared with CAPD [80]. However, the rate of residual renal function decline may be less when patients are treated by biocompatible membranes (see Commentary on HD Guideline III.2), or by ACE inhibitors [81–84].

In HD, it is becoming increasingly recognized that residual renal function is an important contributor to solute clearance, has a favourable effect on outcome [85,86], and may be crucial for phosphate homeostasis [87].

For these reasons, the EBP group consider that it is now time for guidelines on how to measure residual renal function in HD. For practical reasons, and to standardize between HD and CAPD, we are recommending the same method as used in CAPD as far as possible.

In HD, unlike in CAPD, the blood urea and creatinine concentrations vary over the weekly dialysis cycle. There is also evidence that the GFR also may vary over the dialysis cycle, being lower during and immediately after dialysis and higher before the next dialysis [88]. Therefore, the urine should be collected over a complete dialysis cycle, starting (with an empty bladder) at the start of one dialysis and ending at the start of the next. In order to compensate for

I.4 Measurement of residual renal function in HD

Introduction

Measurement of residual renal function is well established in CAPD but there is no current recommended method for measuring residual renal function in HD. To address this, these guidelines also include a recommendation for a standard method for measuring and reporting residual renal function in HD.

Guideline I.4

A. To assist in the standard reporting of residual renal function in HD:

- **Residual renal function should be reported as GFR and expressed in ml/min/1.73 m² as in pre-ESRD.**
(Evidence level: C)
- **GFR should be estimated as the mean of urea and creatinine clearance using urine collections as in CAPD and pre-ESRD.**
(Evidence level: C)
- **Because residual renal function may vary over the interdialytic period, the urine collections should be**

fluctuations in blood urea and creatinine concentrations, the mean of the concentrations immediately after the end of dialysis and immediately before the next dialysis should be used. As there is a significant rebound in concentration after dialysis, especially for creatinine, the post-dialysis concentrations should be corrected using the equation in Appendix II.

Another reason why residual renal function in HD has not been measured routinely is that there is uncertainty on how to include residual renal function in the overall estimation of clearance in a patient on dialysis. It is hard to equate the continuous residual renal function with the intermittent clearance of HD. Dialysis clearance is quantified by Kt/V , an exponential function of cleared mass, whereas renal clearance is a linear function of cleared mass. Recently, a kinetic estimate of a time-averaged clearance, derived from a urea kinetic model has been proposed to relate renal and dialysis clearance (see Commentary on Guideline II. 3.1). The Casino and Lopez method relates Kt/V to the 'equivalent renal urea clearance' (EKR). For simplicity, a chart can be used to equate renal clearance to Kt/V and vice versa (see Appendix II).

It should be noted that the Casino and Lopez method is based on renal urea clearance rather than GFR. This would have the effect of reducing the value of the residual renal function compared with dialysis (as urea clearance is 30–50% less than GFR). If GFR is used instead of renal urea clearance, an equilibrated Kt/V of 1.2 (the recommended minimum) equates to a GFR of 13 ml/min. This seems more probable than a renal urea clearance of 13 ml/min, which is approximately equal to a GFR of 19 ml/min. For this reason and to standardize with CAPD, the EBPG group recommends GFR as a measure of renal function, rather than renal urea clearance.

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Appendix I

Calculation of GFR from urine collections

GFR = glomerular filtration rate in ml/min/m², SA = surface area in m², t = duration of collection in minutes (usually 1440), U_{vol} = urine collection volume in millilitres, U_{urea} , U_{creat} = urine urea, creatinine concentration. S_{urea} , S_{creat} = serum urea, creatinine concentrations.

Urea and creatinine concentrations must be in same units for urine and serum.

$$GFR = \frac{U_{vol}}{2 \times t} \times \left(\frac{U_{urea}}{S_{urea}} + \frac{U_{creat}}{S_{creat}} \right) \times \frac{1.73}{SA}$$

Calculation of surface area: preferred method (Gehan and George) [28]

SA in m², weight in kg, height in cm.

$$SA = 0.0235 \times Wt^{0.51456} \times Ht^{0.42246}$$

Calculation of surface area: alternative method (Dubois and Dubois) [28]

SA in m², weight in kg, height in cm.

$$SA = 0.007184 \times Wt^{0.425} \times Ht^{0.725}$$

Calculation of GFR from age, gender, race and blood urea nitrogen (BUN), creatinine, and albumin (MDRD equation) [5]

Albumin in g/dl, age in years. GFR in ml/min/1.73m². Validated in US white and black (Afro-Caribbean) patients.

Multiply by 1.18 if patient is black. Multiply by 0.762 if patient is female.

SI units (Creat in μ mol/l, Urea in mmol/l).

$$GFR = 170 \times (Creat \times 0.0113)^{-0.999} \times age^{-0.176} \times (Urea \times 2.8)^{-0.17} \times Alb^{0.318}$$

US units (Creat in mg/dl, Urea in mg/dl)

Table 1. Levels of renal function (based on MDRD data)

	Gender	GFR ml/min/1.73 m ²	Creatinine clearance ml/min/1.73 m ²	Serum creatinine	
				mg/dl	μ mol/l
Referral (latest)	Male	30	37	2.3–4.5	200–400
	Female	30	37	1.5–4.1	140–360
Start dialysis	Male	8	10	5.1–10.2	450–900
	Female	8	10	4.1–9.0	360–800

$$\text{GFR} = 170 \times \text{Creat}^{-0.999} \times \text{age}^{-0.176} \\ \times \text{BUN}^{-0.17} \times \text{Alb}^{0.318}$$

Table 1 provides levels of renal function

$$\text{GFR} = \frac{U_{\text{vol}}}{t} \times \left(\frac{U_{\text{urea}}}{\text{PreUrea} + \text{PostUrea}} + \frac{U_{\text{creat}}}{\text{PreCreat} + \text{PostCreat}} \right) \times \frac{1.73}{\text{SA}}$$

Appendix II

Calculation of GFR from interdialytic urine collections

GFR in ml/min/m², surface area in m², urea and creatinine concentrations must be in same units for urine and serum.

t = time in minutes between dialyses. PreUrea, PreCreat = pre-dialysis urea and creatinine concentrations in blood sample at the end of collection. PostUrea, PostCreat = post-dialysis urea and creatinine concentrations in blood sample at beginning of collection. U_{vol} = urine collection volume in millilitres. U_{urea} , U_{creat} = urea and creatinine concentrations. SA = surface area (see Appendix I).

For increased precision, the post-rebound concentration can be used instead of the post-dialysis concentration [89]. The post-rebound concentration can be calculated from dialysis time in minutes (td), pre- and immediate post-dialysis concentrations using;

$$\text{Rebound} = \text{pre} \times \left(\frac{\text{Post}}{\text{pre}} \right)^{\frac{td}{td+35}}$$

Use value 70 instead of 35 to calculate creatinine rebound.

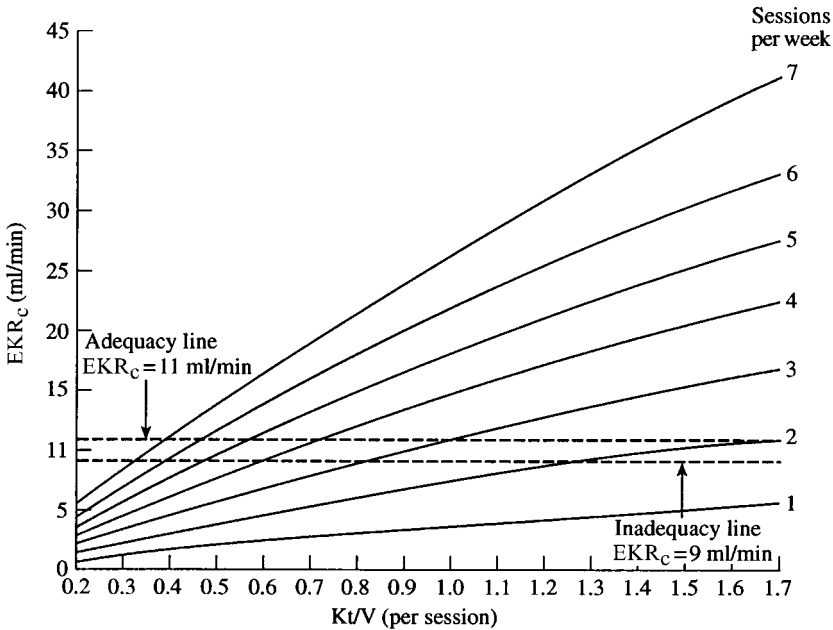


Fig. 1. The relationship between renal function and Kt/V (based on MDRD data) [5]. The graph can be used to convert any level of residual renal function to Kt/V. The Kt/V can be read from the x-axis at the intersection of the curve representing the dialysis frequency and a horizontal line drawn at the y-axis level corresponding to the GFR. For example, a GFR of 5 corresponds to a Kt/V of 4 for three sessions per week.