2 The initiation of dialysis

This guideline is an adaptation of Guideline I from the first wave of the European Best Practice Guidelines for haemodialysis (Nephrol Dial Transplant 2002; 17 [Suppl 7]: 7–15) and was developed in concert with the Work Group responsible for this first wave of the haemodialysis guidelines.

Guidelines

A. Patients with chronic renal failure should be referred to a nephrologist when, on two consecutive measurements, plasma creatinine exceeds 150 µmol/l (1.7 mg/dl) in men or 120 µmol/l (1.4 mg/dl) in women or if there is proteinuria, to assess renal function more precisely and initiate treatment and dietary counselling. (Evidence level C)

B. Renal function should never be estimated from measurements of plasma urea or creatinine alone, but should include an assessment of GFR. (Evidence level B)

C. The preferred method for calculating the GFR in advanced renal failure is the mean of urea and creatinine clearance. This value is best calculated from a 24 h urine collection and normalized to 1.73 m². (Evidence level B)

D. Conservative treatment should be aimed at slowing the progression of renal failure, decreasing proteinuria, strict control of blood pressure, prevention of overhydration, and treatment of anaemia, renal bone disease and metabolic acidosis. Detection of protein-energy malnutrition requires active dietary counselling.

In patients with diabetes mellitus, tight blood glucose controls should be encouraged. Hepatitis vaccinations should be considered. The effects must be assessed regularly. The various options of renal replacement therapy have to be discussed in a timely fashion with the patients. (Evidence level C)

When the GFR has declined 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. Access surgery should be planned. (Evidence level C)

E. Dialysis should be instituted whenever evidence of uraemia is present, or blood pressure and hydration status cannot be controlled, or when a deterioration of the nutritional status is noticed. In any case, dialysis should be started before the GFR is <6 ml/min/1.73 m² (creatinine clearance 8 ml/min/1.73 m²). (Evidence level C)

To ensure that dialysis is not started at a GFR of <6 ml/min/1.73 m², initiation at the level between 8 and 10 ml/min should be considered. Diabetic patients may require an earlier start. (Evidence level C)

Commentary on Guideline 2: the initiation of dialysis

Guideline A. Plasma creatinine

The plasma creatinine concentration is commonly used for the assessment of the glomerular filtration rate (GFR). This may give unreliable results, because plasma creatinine is dependent not only on GFR, but also on muscle mass, which varies with age, gender, weight, race, nutrition, activity and disease [1]. In the case of paraplegia or muscle diseases, plasma creatinine is low because of reduced muscle mass [2,3]. In patients with liver cirrhosis, muscle mass is reduced and, in addition, a decreased ability to produce creatinine is important [4–7]. Conversely, a high protein intake can lead to a 10% increase in creatinine production, and the ingestion of large amounts of cooked muscle meat increases plasma creatinine because of absorption of ingested creatinine in the bowel [8,9]. Furthermore, a marked reduction in GFR can be present before it is reflected in a plasma creatinine concentration above the upper limit of the normal range. This is due to four causes: (i) the creatinine generation rate declines as renal disease progresses [10]; (ii) the exponential relationship between the GFR and plasma creatinine [11]; (iii) an increase of plasma creatinine within the normal range in an individual patient; and (iv) tubular secretion of creatinine, which is relatively more important when the GFR is lower [12]. Moreover, in severe chronic renal failure, creatinine can be excreted or...
metabolized by extrarenal pathways, probably the intestinal microflora [13–15].

It follows from the above considerations that a plasma creatinine concentration exceeding the normal laboratory range usually indicates a severe impairment of the GFR. Several studies have shown that late referral of patients with chronic kidney disease to a nephrologist is associated with high mortality and morbidity [14–17]. This is the basis for the plasma creatinine values given in guideline 2.A. The nephrologist should decide on further investigations and treatment. These investigations must include a better assessment of GFR than plasma creatinine. Based on the results of these investigations, a decision should be made as to whether the patient requires chronic kidney disease care by a nephrologist, or can be temporarily referred back to the referring physician with guidelines for treatment and re-referral.

**Guideline B. Measurement or estimation of GFR**

Numerous different methods for assessment of the GFR have been validated against ‘gold standard’ GFR measurements. The most accurate ones, besides insulin clearance, require the administration of a tracer with timed blood and urine samplings. Measurement of the GFR with these methods is unrealistic as a standard for general practice, but also not without technical problems. First, incorrect urine collections obtained by spontaneous voiding will lead to an inaccurate GFR when renal clearance is measured. Secondly, when a plasma clearance is calculated, the GFR will be overestimated due to extrarenal clearance of the tracer. In clinical nephrology practice, the 24 h endogenous creatinine clearance is often used. However, creatinine is not only filtered, but also secreted in the proximal tubules. Therefore, the endogenous creatinine clearance overestimates the GFR. In normal renal function, this accounts for 10–40% of the GFR [16,17], but it can increase to >100% in patients with a GFR of ~40 ml/min/1.73 m² [12,18–21]. The accuracy of the creatinine clearance can be improved either by inhibition of tubular secretion by, for example, cimetidine, or by taking the mean of the creatinine and urea clearance. A high dose cimetidine has been shown to improve the assessment of the GFR by creatinine clearance in healthy volunteers [22], in patients with kidney diseases [12,18,23–24], in those with a renal transplant [25,26] and during continuous ambulatory peritoneal dialysis (CAPD) [27]. Filtered urea is partly absorbed in the collecting tubule. Consequently, renal urea clearance will underestimate the GFR. The mean value of creatinine and urea clearance gives a good estimation of the GFR in patients with renal failure [27,28] and has therefore been used in studies on the contribution of residual GFR to adequacy of dialysis treatment [29,30].

Normalizing the GFR for body surface area is useful in children and common practice in adults. The accuracy of all urine-based GFR estimations is dependent on the accuracy of urine collections. Inaccuracies can be due to failing to empty the bladder at the start of the urine collection, failing to collect all urine passed during the collection interval, and errors in timing the interval. In theory, these errors can be minimized when the patient is carefully and consistently instructed and when duplicate urine collections are made. To avoid these practical difficulties, formulae have been developed to estimate the GFR or creatinine clearance from plasma creatinine, age, gender and body weight. The first formula to estimate creatinine clearance was developed by Cockcroft and Gault [1] and is still widely used. It will overestimate the GFR in the low range. Since then, many new formulae have been developed either for estimating creatinine clearance by correcting plasma creatinine for age, gender and weight, or to estimate the GFR. The latter formulae were either obtained from multiple regression analysis and also contained plasma urea and/or albumin, or were based on the Cockcroft and Gault formula after inhibition of tubular creatinine secretion by cimetidine. The various formulae, their accuracy and precision have been reviewed [31]. The most recently published formula is that of the MDRD study [21]. Besides demographics, it includes plasma urea and albumin. The accuracy and precision were better than those of the Cockcroft and Gault formula and it has been validated over a wide range of GFRs [21]. However, no separate validation has been done for very low GFR values. It should also be noted that the validation has been done in American black and white racial groups. It is unclear how well the MDRD equation predicts the GFR in Asians or other racial groups.

It is concluded that the preferred method for calculating the GFR in advanced renal failure is the mean of urea and creatinine clearance. When accurate urine collections are impossible, a formula based on plasma creatinine can be used. The Cockcroft and Gault equation after cimetidine [31] or the MDRD formula are likely to give the best estimates. An additional problem is the lack of calibration of creatinine assays.

**Guideline D. Conservative treatment of chronic kidney disease**

Patients with a chronic kidney disease and a GFR <30 ml/min generally progress to end-stage renal failure, irrespective of the underlying renal condition [32–35]. The progression can be slowed by a number of means, including strict blood pressure control [36–39] and certain drugs, e.g. angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers [36,38,40,41]. Strict blood glucose control is important in patients with diabetes mellitus [42]. Specific treatment of any underlying renal condition may also be required, such as revascularization procedures in selected patients with renovascular disease [43–46]. Hyperlipidaemia [47] and smoking [48] have been associated with an increased progression to end-stage renal failure.
Besides attempts to slow the progression to end-stage renal failure, the treatment of patients with chronic kidney disease should be directed at prevention and treatment of other complications that can occur, such as anaemia [49, 50], fluid overload, hypertension and left ventricular hypertrophy [51–53], abnormalities in calcium and phosphate metabolism [54, 55], malnutrition [56–59] and lipid abnormalities [47, 60]. Also vaccinations should be done (hepatitis B [61], influenza [62], or considered (pneumococcus [63]).

Besides medical treatment, the various options of renal replacement therapy should be discussed with the patients, and often also with their family and partners. It is obvious that the above specific treatments should be prescribed and assessed by a nephrologist, who is fully trained in all aspects of nephrology, including the whole spectrum of renal replacement therapy, and who has access to all its modalities. The medical assessment should be intensified to about once monthly when the GFR has declined to 15 ml/min/1.73 m², because of imminent symptoms of uraemia and sometimes unsatisfactory results of medical treatment. Therefore, access surgery should also be planned in this period.

Guideline E. The initiation of dialysis

The timing of initiation of dialysis is a controversial issue because it has major implications on the patients’ lifestyle, dialysis capacity and costs. The opinion-based DOQI recommendations advised starting dialysis when Kt/V_urea falls to 2.0 per week, unless patients had stable or increased oedema-free body weight and a normalized protein equivalent of nitrogen appearance (nPNA) of ≥0.8 g/kg/day, and a complete absence of clinical signs or symptoms attributable to uraemia [64]. A renal Kt/V_urea of 2.0 per week is roughly equivalent to a GFR of 10 ml/min/1.73 m². The recommendation had to be opinion based, because no randomized controlled clinical trial has been published. Such a study is extremely difficult to conduct because it would be almost impossible to enforce an unbiased subject allocation process. Consequently, results from observational studies will have to be used. Bonomini et al. reported that an early start of dialysis was associated with reduced mortality and morbidity [65], but the control group was treated with a low protein diet for at least 2 years and no information was given on how the patients were selected for early start. Also, in a number of other studies, no distinction was made between late referral, causing a late start by definition, and early referrals with a late start [66]. Also the lead time bias was not taken into account. Lead time is the interval between the start of a study and a defined effect. Therefore, apparent prolonged survival may be due simply to earlier registration of patients, who start dialysis at an earlier phase in their life.

Well controlled prospective cohort studies are an alternative when no randomized controlled trials are available. The Netherlands Cooperative Study on the Adequacy of Dialysis is a prospective cohort study in which new dialysis patients are included at the time of the start of dialysis and are followed at regular intervals. In this study, a comparison was made between patients who started dialysis on time according to the DOQI recommendations and those who started late [67]. It appeared that the mean difference in survival time between timely and late starters during the first 3 years after the initiation of dialysis was 2.5 months with a 95% confidence of 1.1–4.0 months. It was estimated from the literature that the lead time bias could have ranged from 4.1 to 8.3 months. Consequently, the apparent gain in survival from a timely start was presumably due to the effect of lead time. These results have been confirmed in a large retrospective analysis from Scotland, where the lead time could be calculated [68].

The appearance of clinical symptoms of uraemia can occur at various levels of GFR, once it is below 15 ml/min/1.73 m². Therefore, the recommendation is based primarily on clinical criteria. Once the GFR is <15 ml/min/1.73 m², access surgery should be planned and dialysis should be instituted whenever evidence of uraemia is present, or blood pressure and hydration status cannot be controlled, or when deterioration of the nutritional status is noticed. Timely insertion of a peritoneal dialysis catheter will avoid the necessity of temporal haemodialysis by a central venous line. To prevent a too late start, a threshold level of a GFR of 6 ml/min/1.73 m² is recommended. To avoid starting at a level of <6 ml/min/1.73 m², initiation of dialysis should be considered when the GFR level has fallen to 8–10 ml/min.

References


61. Dukes CS, Street AC, Starling JF, Hamilton JD. Hepatitis B vaccination and booster in predialysis patients: a 4-year analysis. *Vaccine* 1993; 11: 1229–1232 (A)


**Appendix**

**Calculation of GFR from urine collections**

\[
GFR = \frac{Uvol}{2 \times t} \times \left( \frac{Urea + Ucreat}{purea + pcreat} \right) \times 1.73 \times \frac{BSA}{BSA}
\]

Cockcroft and Gault

**Estimation of creatinine clearance from plasma creatinine, age, body weight and gender**

\[
\text{Creatinine clearance} = \frac{(140 - \text{age}) \times \text{BW}}{\text{Pcreat}}
\]

Multiply by 1.23 when the patient is male.

**Estimation of GFR from age, gender, race and plasma urea, creatinine and albumin (MDRD equation)**

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

Albumin in g/dl, age in years. GFR in ml/min/1.73 m². Validated in US white and black (Afro-Caribbean) patients. Multiply by 1.18 if patient is black. Multiply by 0.762 if female.

**Estimation of GFR from urine collections**

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