

Renal Medicine

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Management of mild to moderate chronic renal failure

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Chronic renal failure (CRF) is defined as a reduced glomerular filtration rate (GFR) which develops over a period of months or years and which is, at least in part, irreversible:

- mild: GFR 50–80 ml/min
- moderate: GFR 25–50 ml/min
- severe: GFR below 25 ml/min.

End-stage renal failure (ESRF) is reached when the GFR is insufficient to maintain health. In Western societies, most patients start renal replacement therapy (RRT), either dialysis or transplantation, when the GFR is below 10 ml/min but months before death is imminent; the start of RRT is then taken as the time of development of ESRF. RRT is a complex and costly process, and patients with ESRF have a high mortality (10–20% per year). Late referral of

patients for treatment is associated with increased mortality, morbidity and expense.¹

The prevalence of CRF rises dramatically with age: at age 50 less than 100 per million of the population have impaired renal function, rising to over 2,000 per million by age 75. The causes of CRF vary in different societies (Table 1). Diabetes is a much commoner cause of ESRF in the USA, but it is likely that the UK, with an ageing and increasingly obese population, will catch up. Some causes of CRF (eg obstruction, acute vasculitis) are relatively uncommon, but important preventable, causes of ESRF.

The treatment of patients with CRF has several components:

- assessment of renal function and diagnosis of the cause
- treatment of the underlying disease
- management of the systemic and metabolic consequences of reduced renal function.

Some, but not all, patients with CRF will progress to ESRF and require RRT.

The aim of much of the management of CRF is therefore to recognise patients whose renal function will deteriorate and then to delay or even prevent this deterioration.

Investigation of patients with suspected renal disease

Glomerular filtration rate

The first consideration in the management of any patient with suspected renal disease is GFR assessment. The simplest measure is serum creatinine (SCr) concentration which is determined by the creatinine clearance and the rate of creatinine production. Creatinine is excreted via the kidneys; at normal GFR, 85–90% of urinary creatinine arises from glomerular filtration, with only a small percentage coming from tubular secretion of creatinine. The creatinine clearance therefore closely approximates the GFR. Creatinine production is largely determined by skeletal muscle mass and is constant from day to day. However, muscle mass varies widely between individuals and SCr in isolation gives only an approximate estimate of GFR. A number of formulae take account of a patient's weight, age and sex (as measures of skeletal muscle mass) to calculate creatinine clearance from SCr. These have been shown to be more accurate than timed urine collections at estimating creatinine clearance/GFR. The most widely used is the Cockcroft-Gault formula (Box 1), application of which indicates the range of GFRs for a given SCr (Fig 1).

Cockcroft-Gault formula:

$$\text{GFR (ml/min)} = \frac{1.23 \times [140 - \text{age (years)}] \times \text{weight (kg)}}{\text{plasma creatinine } (\mu\text{mol/l})}$$

(multiply by 0.85 in women for lower muscle mass)

Examples:

70 kg 20-year-old man, creatinine
100 $\mu\text{mol/l}$ – GFR = 108 ml/min

50 kg 75-year-old woman, creatinine
100 $\mu\text{mol/l}$ – GFR = 36 ml/min

Table 1. Causes of end-stage renal failure in the UK and the US (percentage of total).

	UK (1998–2001) ²	USA (1996–2000) ³
Diabetes	17.6	44.3
Glomerulonephritis	11.8	12.1
Hypertension	6.6	23.4
Pyelonephritis/Obstruction	9.7	3.9
Renovascular disease	7.1	3.1
Polycystic kidney disease	6.5	2.3
Aetiology uncertain	18.6	4.0

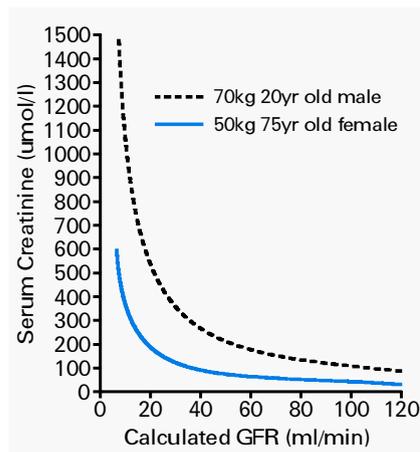


Fig 1. Plot of serum creatinine versus glomerular filtration rate (GFR) (calculated according to the Cockcroft-Gault formula) for a 70 kg, 20-year-old man and a 50 kg, 75-year-old woman.

As muscle mass changes only slowly, serial SCr measurements provide a simple yet accurate assessment of changes in renal function and will identify patients whose GFR is deteriorating.

The most accurate estimation of GFR involves measurement of clearance of radiolabelled EDTA or iohexol, a non-

ionic contrast medium. Both necessitate an injection followed by several blood samples.

Urine analysis

The cause must be determined in patients who have impaired renal function. All patients need a urine analysis, including stick tests for protein and blood, a culture of a midstream specimen and urine microscopy, particularly if the patient has haematuria. If there is proteinuria, this needs to be quantified with either a timed urine collection (eg 8 or 24 hours) or measurement of an albumin/creatinine ratio (ACR) on a random urine specimen. Measurement of ACR is simpler and corrects for the concentration of the urine. Daily urinary creatinine excretion is constant in a patient with stable renal function – measurement of urinary creatinine in a timed collection therefore permits the completeness of the collection to be estimated. A normal individual will have a maximum of 100–150 mg of protein per 24 hours and an ACR less than 3 mg albumin/mmol creatinine. Proteinuria of less than 1.5 g/day can be of either glomerular or tubular origin, whereas higher quantities always indicate a glomerular cause. Patients with higher levels of proteinuria are more likely to develop deteriorating renal function and therefore require closer monitoring.⁴

Assessment of tubular function includes:

- urinary concentrating ability
- presence of bicarbonate, glucose and amino acids in the urine, and
- urinary acidification tests.

Other important laboratory investigations are listed in Table 2.

Renal biopsy

A renal biopsy may be necessary to diagnose glomerular disease and other conditions causing diffuse renal injury.

Renal imaging

Renal ultrasound provides information on renal size, dilatation of the collecting system (indicating obstruction) (Fig 2) and evidence of scarring or increased echogenicity in diffuse renal disease. Further imaging can be undertaken with intravenous urography (IVU), providing greater anatomical detail particularly of the renal pelvis and ureters. Radiocontrast used in X-ray imaging (IVU and computed tomography (CT) scans) is potentially nephrotoxic, particularly in patients with CRE, diabetes or myeloma. The risk of nephrotoxicity can be minimised with adequate hydration and salination and probably by the use of oral N-acetyl cysteine. Nuclear medicine scans (eg DTPA, MAG3 and DMSA) are useful in determining relative function of the kidneys and the presence of partial obstruction or renal scarring. CT scanning is most useful

Table 2. Laboratory investigations for the assessment of renal function.

Haematology

FBC, clotting screen, Hb electrophoresis, vitamin B12, folate, ferritin, antiphospholipid screen, ESR

Biochemistry

U&E, creatinine, calcium, phosphate, LFTs, PTH, serum protein electrophoresis, urinary light chains (Bence Jones protein), lipids, glucose, Hb1Ac

Immunology

Autoantibodies (including ANCA, DNA binding, antiGBM), complements C3 and C4, immunoglobulins

ANCA = antineutrophil cytoplasmic antibody; ESRF = end-stage renal failure; FBC = full blood count; GBM = glomerular basement membrane; Hb = haemoglobin; HbA1c = glycated haemoglobin; LFT = liver function test; PTH = parathyroid hormone; U&E= urea and electrolytes.



Fig 2. Renal ultrasound showing dilated pelvis and calyces consistent with obstruction in a 65-year-old man with bladder outflow obstruction.

for the investigation of renal masses, whereas digital subtraction angiography or magnetic resonance angiography will diagnose large vessel renal artery stenosis. Nuclear medicine scans, with or without the coadministration of angiotensin-converting enzyme inhibitors (ACEI), are not sufficiently sensitive to rule out renal artery stenosis.

Treatment of specific diseases

Glomerulonephritis

All forms of glomerulonephritis result from an immune-mediated injury to the glomerulus. The rate of development of irreversible glomerular injury varies; some diseases such as antglomerular basement membrane disease can produce a devastating glomerular injury over days or weeks (Fig 3), whereas other conditions such as immunoglobulin A (IgA) nephropathy usually progress slowly.

The pathophysiology of many forms of glomerulonephritis is poorly understood and treatment depends upon the empirical use of immunosuppressive agents. In some cases, immunosuppression is effective at preventing further glomerular injury and the loss of renal function. The renal vasculitides, including the antineutrophilic cytoplasmic antibody associated diseases (Wegener's and microscopic polyangiitis), antglomerular basement disease and lupus nephritis respond well to immunosuppression if given before the glomerular injury is too severe. Some forms of acute glomerulonephritis, for example post-streptococcal glomerulonephritis, usually resolve spontaneously and immunosuppression is unnecessary. In chronic glomerulonephritis such as IgA nephropathy and membranous nephropathy, immunosuppression appears to protect some patients against progressive renal damage.

Diabetic nephropathy

Excellent diabetic control delays the development and progression of diabetic nephropathy (DN) in both type 1 and type 2 diabetes.^{5,6} Hypertension is almost always present in individuals with DN; blood pressure (BP) control, particularly

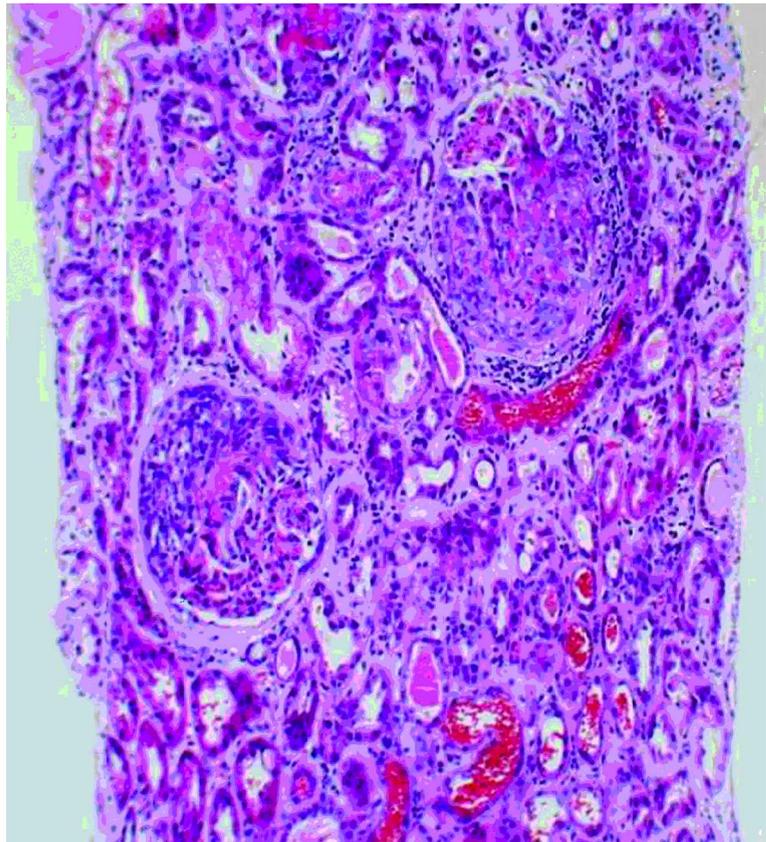


Fig 3. Renal biopsy showing severe crescentic glomerulonephritis from a 72-year-old woman with antglomerular basement membrane disease.

Key Points

Serum creatinine (SCr) is determined by glomerular filtration rate (GFR) and skeletal muscle mass; GFR may be reduced even with a normal SCr

Calculated creatinine clearance using a formula incorporating age, weight and sex provides an accurate estimate of GFR

GFR decreases in old age: by age 80, most patients will have a GFR 50% or less of the peak value

The main aim in the management of chronic renal failure (CRF) is to prevent, or at least delay, loss of renal function

Serial SCr measurements are an accurate method of monitoring renal function

Higher proteinuria levels increase the likelihood of a progressive deterioration in renal function in most renal diseases

Control of hypertension slows progression of CRF in all renal diseases – target blood pressure is lower than for nonCRF patients

Angiotensin-converting enzyme inhibitors (and angiotensin receptor blockers) are particularly effective in slowing progressive loss of GFR in patients with moderate to severe proteinuria (>1.0 g per day)

CRF is associated with an increased risk of cardiovascular disease

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with ACEI and angiotensin receptor blockers (ARBs), delays progression. Target BP should be 130/85 mmHg or less, but a diastolic pressure of 80 mmHg or less is ideal.⁷ DN usually, but not invariably, occurs in individuals with coexistent diabetic retinopathy.

Obstruction

Obstruction to urinary drainage is a relatively uncommon but important cause of CRF as early detection and treatment are always effective at preserving renal function.

General measures

Hypertension

Hypertension is present in most patients with CRF. BP control is undoubtedly the most important intervention in the large majority of patients with CRF; it is important in all patients and all renal diseases in delaying progression to ESRF. Target blood pressures in CRF are 130/85 mmHg or less. ACEIs (and probably ARBs) help to preserve renal function in nondiabetic as well as diabetic renal disease,⁸ particularly in patients with higher levels of proteinuria (>1g/day),⁹ although most patients require combination therapy to produce good BP control.

Diet

Glomerular hyperfiltration (increased GFR in functioning glomeruli) contributes to progressive renal injury and is reduced by a low protein diet. A low protein diet has a protective effect on GFR in patients with CRF,¹⁰ although the effect is slight and less important than hypertension control.

Infection

Urinary tract sepsis is associated with progressive renal injury in children. In adults, repeated pyelonephritis almost certainly produces renal scarring. Infections usually respond to appropriate antibiotics, but repeated or unresponsive infections should prompt a

search for an anatomical cause such as obstruction or calculi.

Other measures

CRF and ESRF are associated with hyperlipidaemia and a substantially increased risk of cardiovascular disease.¹¹ Lipid lowering may preserve renal function and reduce proteinuria;¹² this is now being addressed in suitably designed large studies. Smoking increases cardiovascular risk, and patients with CRF who smoke are more likely to progress to ESRF. All patients should be encouraged to stop smoking.¹³

Systemic and metabolic consequences of chronic renal failure

Anaemia

This is discussed in the accompanying article by Stevens *et al.*

Calcium, phosphate and parathyroid hormone

Patients with CRF develop hyperphosphataemia, hypocalcaemia and elevated parathyroid hormone due to deficient vitamin D activation and reduced urinary phosphate excretion. In some patients this starts to occur with minimal reduction of GFR (eg 70–80 ml/min) but becomes clinically important when the GFR is below 30 ml/min. Treatment with active vitamin analogues (alphacalcidol and 1,25-dihydroxycholecalciferol), reduction of dietary phosphate intake and oral phosphate binders (usually calcium containing) usually prevents the development of hyperparathyroidism and renal bone disease.

Acidosis

Patients with CRF develop a metabolic acidosis due to the defective acid excretion resulting from a reduced GFR. The metabolic acidosis which occurs in proximal or distal renal tubular acidosis may occur with a normal GFR and is the result of impaired bicarbonate reabsorption or defective urinary acidification.

Metabolic acidosis in CRF usually becomes apparent only when the GFR falls below 30 ml/min. Correction of the acidosis with oral sodium bicarbonate improves nutrition and growth in children with CRF; its role in adults is less clear.

Drugs

Many drugs are largely, or exclusively, cleared via the kidneys so doses need to be adjusted in patients with a reduced GFR. This is true both for patients with known CRF and also for those in whom it is unsuspected, particularly the elderly. The risk of nephrotoxicity is increased in CRF and certain drug classes should be avoided (eg nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase 2 inhibitors).

Conclusions

The management of CRF depends on:

- elucidation of the cause
- treatment of the underlying disease process (if possible)
- correction of the metabolic consequences of a reduced GFR and, most importantly,
- measures to prevent or delay progression to ESRF.

Although most patients with CRF will not progress to ESRF, early recognition of CRF is important in preventing further loss of renal function. This is particularly true as ESRF affects increasing numbers of patients and its treatment consumes more healthcare resources.¹⁴ A rising SCr, higher levels of proteinuria and elevated BP are indicators of more severe renal disease. The most effective measure in the majority of patients is excellent BP control.

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Clinical management of anaemia

pre-endstage renal failure

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Anaemia is an early complication of chronic renal failure (CRF) and part of the growing public health problem presented by chronic kidney disease (CKD). Solutions to public health problems require strategies for early identification and prevention of the associated adverse outcomes; these in turn require an understanding of those adverse outcomes and their prevalence. The National Kidney Foundation-Kidney Dialysis Outcomes Quality Initiative (NKF-KDOQI) recommends a target haemoglobin (Hb) range for renal anaemia treatment of 11–12 g/dl.¹ The European Best Practice Guidelines (EBPG) recommend that 85% of patients with CRF should attain an Hb level of above 11 g/dl.² Despite these recommendations, surveys demonstrate that less than a quarter of pre-endstage renal failure (pre-ESRF) patients in the USA and less than a third in Europe receive active anaemia management. Management of renal anaemia is further compli-

cated by the role played by iron, and the concept of functional iron deficiency. This article will review the following:

- the definition of pre-ESRF, renal anaemia and iron deficiency
- the pathogenesis, prevalence and adverse outcomes of anaemia in this patient group
- the investigation and treatment of anaemia
- target levels of Hb, and
- the adverse effects of treatment.

Definition of pre-endstage renal failure, renal anaemia and iron deficiency

Pre-endstage renal failure

A recent KDOQI workshop clearly defined five stages of CKD related to glomerular filtration rate (GFR) corrected for body surface area (Table 1).³ For the purposes of this article, patients with pre-ESRF are considered to be those with stage 3–4 CKD or stage 5 CKD not requiring renal replacement therapy. In evaluating patients with kidney disease it is essential to think in terms of renal function rather than to rely on measurements of serum creatinine (SCr) alone. An estimate of renal function may be obtained by either the Cockcroft-Gault calculation of creatinine clearance (CrCl) or the modified Modification of Diet in Renal Disease (MDRD) equation for GFR (Box 1).

Renal anaemia

Anaemia in CKD is currently defined as Hb less than 11 g/dl in premenopausal women and prepubertal patients, and

Table 1. Stages of chronic kidney disease.

Stage	GFR (ml/min)	Descriptor
1	>90	Kidney disease with normal or increased GFR
2	60–89	Kidney disease with mildly reduced GFR
3	30–59	Moderately severe renal failure
4	15–29	Severe renal failure
5	<15	End-stage renal failure

GFR = glomerular filtration rate.