

# The new patient with renal failure

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## **Incidence and prevalence of kidney disease**

End-stage kidney disease (ESKD) is loss of renal function requiring treatment with any form of chronic dialysis or transplantation. Dialysis for acute kidney injury (AKI) is not considered ESKD unless renal function fails to recover. Data on the incidence and prevalence of renal failure are collected by various registries around the world, and in most countries the incidence is increasing. Mean incidence of ESKD across Europe rose from 79 to 117 new patients per million population (PMP) per year between 1990 and 2000.

### **UK renal registry data**

In the UK, 113 new patients PMP were dialysed in 2006 (annual acceptance rate). Median age was 65years (but lower for non-white patients), and 21% were >75years old. Diabetes now is the single most common renal diagnosis, at 22% for incident (but not prevalent) patients.

### **United States Renal Data System data**

In the USA, 351 new patients PMP/year were dialysed in 2005. Median age was 65. There is great ethnic variation, with incidences of 991 for African-Americans, 516 for Native Americans, 315 for Asians, and 268 for whites. In the USA, 1 in 1000 of the population were receiving treatment for ESKD. Overall prevalence of ESKD is 1585 PMP in the USA, but there is some evidence that the rate of growth is slowing. 16% of this population are ≥75years. Annual growth in prevalent patients is ~3%. Incidence of ESKD has doubled over the last decade. The average age of patients starting dialysis is increasing (median currently 63years), and more have diabetes.

Actual costs of renal replacement therapy (RRT) in 2005 were US\$21.3 billion, and this is expected to double to US\$53.6 billion by 2020. By 2020 it is predicted that just under 50% of all incident ESKD patients will have diabetes, and it will make up 37% of the prevalent population.

Taiwan reports the highest incidence rates for new patients starting RRT.

International comparisons		
ESKD	Incidence (PMP per year)	Prevalence (PMP)
USA	351	1585
Australia	109	741
Belgium	180	1015
Canada	160	1003
Chile	135	866
Denmark	120	783
Finland	94	710
Germany	203	1057
Hong Kong	173	965
Israel	174	639
Italy	121	755
Japan	267	1857
Malaysia	103	560
New Zealand	106	755
Norway	99	732
Russia	24	115
Spain	126	868
Taiwan	404	1830
Turkey	179	451
UK	113	689

## Definition and prevalence of chronic kidney disease

The Kidney Disease Outcomes Quality Initiative (K/DOQI) has developed a classification of chronic kidney disease (CKD) which is now widely used, despite some reservations.

Classification of CKD

Stage	Description	GFR (ml/min/ 1.73m <sup>2</sup> )	Prevalence (approximate % of US population)
1	Kidney damage with normal or ↑ GFR	>90	3.3%
2	Mild ↓ GFR	60–89	3%
3	Moderate ↓ GFR	30–59	4.3%
4	Severe ↓ GFR	15–29	0.2%
5	Kidney failure	<15 or dialysis	0.2%

- The figures for prevalence are probably an underestimate.
- Over 19 million of the adult US population have some form of CKD.
- A population survey in the UK (of a predominantly Caucasian population) using chemical pathology central records and a serum creatinine of >180µmol/l for men and 135µmol/l for women to define CKD, found a prevalence of 5554 PMP (or 0.55% of the population) for CKD.
- Only 15% of these were already known to renal services. This should have changed with the introduction of new payments for GPs in the UK incentivizing the early detection and treatment of kidney disease (amongst others)
- Prevalence increased hugely with age, from 78 PMP in those <40years to 58913 PMP in those >80years.
- A similar survey in Northern Ireland found 1.3% of the population (having a blood test) had a creatinine >150µmol/l, rising to 10.5% of patients with diabetes.
- Nephrologists cannot see all patients with CKD as defined above! Guidelines have been drawn up to try and identify those patients who need referral, those that need ongoing care by nephrologists, and those that can be managed in the community.

**When patients should be referred to a nephrologist:**

Suspected acute kidney injury

Estimated glomerular filtration rate (eGFR)  $<30\text{ml}/\text{min}/1.73\text{m}^2$

eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$  and falling  $>3\text{--}4\text{ ml}/\text{min}/\text{year}$

Proteinuria: protein:creatinine ratio  $>100\text{mg}/\text{mmol}$

Microscopic haematuria

Fall in GFR on starting angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB)  $>15\%$

Possible systemic illness

Haemoglobin (Hb)  $<11\text{g}/\text{dl}$

Electrolyte, Ca or phosphate disturbance

Refractory hypertension

## Causes of end-stage kidney disease

The most informative renal dialysis and transplant registries are:

- The USRDS (collects data on >90% of all patients undergoing dialysis in the USA).
- The European Dialysis and Transplant Association (EDTA; data voluntarily supplied from units in 40 countries across Europe; 70% of the patients live in France, Germany, Italy, Spain or the UK).
- The Australia and New Zealand Dialysis and Transplant Registry (ANZDATA; contains data on all patients in Australia and New Zealand who have received dialysis or a transplant since 1980).
- The UK Renal Registry: collects data on almost all patients on dialysis in the UK.

Causes of ESKD across the world (most recent data usually 2005/6).  
Percentage of all patients in each registry with each diagnosis

Primary renal disease	ANZDATA	UK	USRDS
Glomerulonephritis (GN)	23	15	18
Diabetes	32	13	37
Hypertension/renovascular	15	9	24
Infective or obstructive nephropathies (inc. reflux)	4	12	3
Cystic or congenital disease	6	7	7
Miscellaneous	15	18	7
Unknown	5	26	4

## Causes of end-stage kidney disease: details

### Arteriopathic renal diseases

Include hypertension, malignant hypertension, renal artery stenosis or occlusion. Hypertensive diseases represent 25% of all primary diagnoses in the USRDS, but <10% in Europe.

### Glomerulonephritis

The most common cause of renal failure in Australia and New Zealand (23% of all patients) and common in Europe (up to 25%), but only the third major cause in the USA (18%). Only two-thirds of these have a defined histological diagnosis. In some registries, patients can be labelled as likely GN (not biopsy proven)

### Diabetes

The most common cause of renal failure in the USA and many other countries (Mexico for example). In the USA, ~40% of new patients starting dialysis had diabetes. The proportion of patients with diabetes has doubled over the last 20 years. Surprisingly low prevalence in the UK ESKD population. Over the last couple of years the relative increase in diabetic patients reaching ESKD seems to have slowed.

### Infective and obstructive nephropathy

Includes reflux, pyelonephritis, chronic interstitial nephritis, urolithiasis, and congenital and acquired obstructive nephropathies. Common cause of RRT in Europe and UK, but rare in other registries.

### Familial disease

Predominantly adult (autosomal dominant) polycystic kidney disease but also includes oxalosis, Fabry's disease, cystinosis, Alport's, and tuberosc sclerosis.

### Miscellaneous

Analgesic and gouty nephropathy, cortical necrosis, tuberculosis (TB), human immunodeficiency virus (HIV) nephropathy, sickle cell disease, radiation nephritis, sarcoidosis, and traumatic renal loss. Specific toxins such as lead, cadmium, lithium, and ciclosporin are more regionally confined. Also includes acute interstitial nephritis. Neoplasms are a rare cause of ESKD, but include myeloma, amyloidosis, light chain deposition disease, and renal tract tumours.

## Causes of acute kidney injury

The most common causes of AKI occurring in hospitals are pre-renal disease (volume depletion, dehydration, cardiac failure or sepsis) and acute tubular necrosis (ATN; ischaemia or nephrotoxins). The distinction between pre-renal, intrinsic renal and post-renal causes for AKI is useful in excluding possible causes of acutely impaired renal function.

### Causes of hospital-acquired AKI (but huge variations between individual hospitals)

ATN	45%
Pre-renal	21%
Acute on chronic renal failure (usually ATN)	13%
Urinary tract obstruction	10%
GN or vasculitis	4%
Acute interstitial nephritis	2%
Atheroembolic disease	1%

Many of these are treatable, with excellent recovery of renal function.

- ATN, rhabdomyolysis, and toxic nephropathy usually recover over a period of days to a few weeks.
- Obstruction can be relieved surgically or percutaneously, and renal function returns often within a couple of days.
- Most causes of rapidly progressive GN (RPGN) can be successfully treated with immunosuppression. Almost all patients with antineutrophil cytoplasmic antibody (ANCA)-associated disease will recover renal function, even with severe renal failure, while those with moderate renal failure caused by anti-glomerular basement membrane (GBM) disease will also recover.
- Acute interstitial nephritis, acute pyelonephritis, and accelerated hypertension also have a good prognosis (at least in the short term).
- Myeloma cast nephropathy, haemolytic uraemic syndrome (HUS), and atheroembolism have poorer outcomes, with significant numbers of patients failing to recover renal function.

### ICUAKI

In intensive care units, 10–30% of patients develop AKI, with high mortality rates (30–70%). Many of these patients have multiorgan failure, rather than isolated renal failure, and a significant number of survivors require long-term RRT. Prognosis is usually dependent on the co-morbid conditions and number of organs failing, rather than the presence of renal failure *per se*.

## Modality of renal replacement therapy worldwide

In the USA, 91% of patients with ESKD receive in-centre haemodialysis (HD), 0.6% home HD, and 8% peritoneal dialysis (PD), with marked geographic variation. The number of new patients starting PD per year has fallen in the USA from a peak of 9407 in 1995 to 6875 in 2005, representing a fall from 15 to 7% of new patients starting dialysis.

Home HD remains common in New Zealand (14%), Australia (11%), and France (6%), but elsewhere (including the UK) comprises <2% of the dialysis population. PD is most widely used in Hong Kong (79% of ESKD patients), New Zealand (48%), Canada, Australia, and Denmark. Renal transplantation remains the most successful form of RRT. Rates vary from 67 PMP in Spain, 59 PMP in the USA, 50 PMP in Norway, 32 PMP in Germany and Canada, 30 PMP in Italy, 28 PMP in the UK, 22 PMP in New Zealand, and 5 PMP in Malaysia.

	In-centre HD	Home HD	PD
USA	91	0.6	8
UK	80	2	18
Australia	69	9	22
Canada	79	3	18
Chile	94	0	6
Denmark	73	3	24
Finland	74	3	23
Germany	94	1	5
Italy	86	1	13
Japan	96	0	4
New Zealand	42	14	44
Norway	83	1	16
Russia	93	0	7
Taiwan	93	0	7
Turkey	88	0	12

### Cost of ESKD

In the USA, the total direct medical payment for ESKD exceeds US\$21 billion. This is expected to double by 2020. Figures from other countries are difficult to obtain. A dialysis patient costs US\$34 000 as an outpatient per year, or US\$77 000 per year, including hospital admissions. In the UK, total costs for elderly dialysis patients are ~£30 000/year, mostly for dialysis itself and transport (to and from the dialysis unit).

## Patient survival with ESKD

Survival rates of patients starting RRT continue to improve year on year. In the UK, 87% of patients survive 1 year (after the first 90 days). 6% of patients die within the first 90 days. 5-year survival ranges from 87% for those aged 18–34, 67% for those aged 45–54, and 29% for those aged 65–74.

USRDS data exclude the first 90 days of care and exclude patients who die within this time. Over the last decade, the overall 1st year death rate for patients has not changed significantly and is ~23 deaths per 100 patient years. 1-year survival is ~80% overall. 5-year survival, however, continues to rise and is 35% overall for all dialysis modalities.

In the USA, patients starting dialysis aged 15–19 have an estimated 17 remaining years of life compared with 61 years for the general population; for those aged 30–34 years these figures are 11 and 47 years, respectively; for those aged 50–54 years, 6 and 27 years, respectively; and for those aged 60–65 years, 4.5 and 21 years, respectively. Survival is increased in American black people and worse in diabetics. Dialysis does not prolong life!

### Co-morbidity

Increasingly common in new patients with ESKD; overall 55% of patients in the UK were reported to have one or more co-morbidities: 29% diabetes, 24% ischaemic heart disease, 17% angina, 13% peripheral vascular disease, 10% cerebrovascular disease or previous cerebrovascular accident, 7% chronic obstructive pulmonary disease (COPD), and 12% cancer. Diabetes is reported in 25% of ESKD patients in Australia, 36% in Germany, and 44% in the USA.

### Cause of death in ESKD

Overall, cardiac arrest, acute myocardial infarction (MI), and other cardiac causes account for half of the reported deaths in ESKD patients. Infection is the next major cause (25%) and cerebrovascular disease is the third largest cause of death (6%). One in five dialysis patients withdraws from dialysis before death in the USA because of failure to thrive or medical complications. Withdrawal is more common in older, Caucasian dialysis patients. Withdrawal rates in the USA are higher than in most other countries, possibly because of the initial acceptance of patients with marginal benefit from dialysis. In the UK, 35% patients die from cardiac disease, 20% from infection, 13% from stopping dialysis, 9% from malignancies, and 7% from cerebrovascular disease.

## Presentation of renal disease

Patients with renal failure present with the relatively non-specific symptoms of renal impairment (see below), with symptoms attributable to an underlying systemic disease, e.g. vasculitis, systemic lupus erythematosus (SLE), myeloma, hypertension, or because a doctor has found an elevated urea or creatinine, or performed urinalysis. The key task of the nephrologist is to identify the underlying disease, and to distinguish possibly recoverable AKI from ESKD. Other roles of the nephrologist include:

- establishing the precise degree of renal impairment;
  - detecting and correcting reversible factors;
  - correcting and minimizing the complications of renal failure;
  - detecting and treating coincidental and co-morbid diseases;
  - assessing social circumstances;
  - assessing the patient's understanding of the disease and its prognosis;
  - planning follow-up, management, and potential future dialysis and transplantation needs;
  - providing a clear explanation to the patient and family.
- Reversible causes of AKI must be promptly diagnosed and treated:
- ureteric or bladder outflow obstruction;
  - anti-GBM disease or vasculitis (especially ANCA associated);
  - other causes of RPGN (SLE, crescentic primary GN);
  - acute interstitial nephritis;
  - accelerated hypertension;
  - renal vascular disease;
  - acute pyelonephritis (especially in diabetics, transplant recipients);
  - drug-induced renal failure;
  - ATN;
  - rhabdomyolysis;
  - myeloma cast nephropathy.

## Presenting clinical features of ESKD

In approximate order of frequency:

- anorexia
- nausea and vomiting
- fatigue and weakness
- pruritus
- lethargy
- peripheral oedema
- dyspnoea
- insomnia
- bleeding tendency
- pulmonary oedema
- apathy
- muscle cramps
- feeling cold
- Raynaud's phenomenon
- metabolic flap
- nocturia, polyuria
- headache
- pericarditis
- fever
- cough
- diarrhoea
- constipation
- seizures
- hiccough
- restless legs
- growth retardation is very common in children.

Sexual dysfunction (loss of libido, impotence, and infertility) is rarely volunteered spontaneously, but is extremely common (in men and women). It may be caused by the renal failure itself or a variety of prescribed drugs.

Neuropathy, cognitive impairment, confusion, coma and proximal myopathy are now very rare features of ESKD.

### Additional features in AKI

- Macroscopic haematuria
- Loin pain
- Haemoptysis
- Rash
- Neuropathy
- Infections
- Predisposing factors, e.g. hypotension, drug use, hypovolaemia.

## Examination findings in ESKD

Often depend on the length of history of CKD, and time of referral to nephrologist. Early referral can often prevent these signs developing by appropriate and timely interventions [e.g. erythropoietin (EPO) therapy, control of Ca and PO<sub>4</sub> balance, blood pressure (BP) control].

- Skin pigmentation or excoriation
- Anaemia
- Hypertension
- Postural hypotension
- Oedema
- Left ventricular hypertrophy (LVH)
- Peripheral vascular disease
- Arterial bruits
- Respiratory crackles
- Pleural effusions
- Palpable kidneys (polycystic) or liver
- Abdominal scars
- Peripheral neuropathy
- Proximal myopathy
- Corneal calcification
- Retinal fundal examination (hypertension or diabetes).

Urine may show a variety of changes depending on the cause of renal failure (haematuria, proteinuria, casts).

## Investigations for patients with ESKD

### Baseline investigations in patients with ESKD

Sodium	Usually normal, but may be low with water overload
Potassium	Raised—often with precipitant, e.g. diet, ACEIs, transfusion, surgery, gastrointestinal (GI) bleed, potassium-sparing diuretics
Bicarbonate	Low
Chloride	Normal in renal tubular acidosis
Urea	Affected by protein intake, hydration, liver disease
Creatinine	Affected by muscle mass and increasing tubular secretion with advancing renal impairment
Albumin	Reflects urinary losses, protein intake and hepatic synthesis. Low levels (<40) at start of RRT strongly associated with poor prognosis
Calcium	May be normal, low or high depending on parathyroid activity
Phosphate	Rises late in CKD. Ca-P product predictor of metastatic calcification
Alkaline phosphatase	Raised in hyperparathyroidism or osteomalacia (bone isoenzyme)
Aspartate aminotransferase and bilirubin	Normal unless liver disease
Glucose	Undiagnosed diabetes (type II) common, especially in Asian populations
Parathyroid hormone (PTH)	Raised progressively in renal impairment
Cholesterol and triglycerides	Both may be raised—cardiovascular disease major cause of morbidity and mortality
Hb	Usually low (less commonly in polycystic disease). Exclude other haematinic deficiency or haemoglobinopathy as necessary.
Ferritin, iron, transferrin saturation	Large iron stores required for effective use of EPO. Relative iron deficiency nearly universal
White cells	Usually normal unless SLE, drugs, etc.
Platelets	Usually normal unless drugs, hypersplenism, aplasia
Clotting	Usually normal except prolonged bleeding time
Blood grouping	For cross-matching as necessary, and for transplant purposes
HLA tissue typing	As pre-transplant investigation
Cytotoxic antibodies	Especially in women and those who have received blood transfusions

Hepatitis serology	Define baseline hepatitis B virus (HBV) and hepatitis C virus (HCV) status. Vaccinate non-immune patients (HBV). Hepatitis B serum antigen (HBsAg)-positive patients should have eAg and eAb status defined
Cytomegalovirus (CMV) serology	Pre-transplant assessment
HIV	All patients should be counselled and screened pre-transplant, and in some units pre-dialysis
ECG	For LVH and ischaemia
Echocardiography	If indicated for ventricular function, hypertrophy, ischaemia, chamber dilatation
CXR	Cardiomegaly
Bone X-rays (hands, spine)	If evidence of hyperparathyroidism
Renal ultrasound	To confirm diagnosis or exclude treatable acute on chronic cause
Other tests as necessary, e.g. complements, antinuclear antibody (ANA), lupus anticoagulant, ANCA, anti-GBM antibodies, thyroid function, cryoglobulins, protein electrophoresis.	

## Assessment of kidney function at/near end stage: serum biochemistry

### Serum creatinine

Serum creatinine is an unreliable marker of renal function in ESKD.

- Produced from the breakdown of creatine phosphate in muscle at a constant rate (♂ 15–25mg/kg body weight/day, ♀ 10–20mg/kg per day).
- Excreted predominantly by filtration without reabsorption.
- Tubular secretion also plays a part in creatinine excretion.
- For most patients serial plasma creatinine measurements can be used to monitor change in renal function (deterioration or improvement). However, early in the development of renal impairment, plasma creatinine may not increase as GFR declines because of increased tubular secretion of creatinine. This process becomes saturated at a plasma creatinine of ~140–170µmol/l. Thereafter, a further decline in GFR will manifest as a rise in serum creatinine.
- Near ESKD, increasing uraemia will often be associated with a decline in dietary intake, and further rises in serum creatinine will not occur as GFR falls. In fact low serum creatinine is associated with higher mortality.
- Finally, creatinine generation rates decline with advancing renal failure.

Other factors affecting serum creatinine include:

- dietary meat intake;
- drugs inhibiting tubular creatinine secretion (cimetidine and trimethoprim can increase serum creatinine by up to 50µmol/l);
- interference with colorimetric creatinine assays (especially ketones, cefoxitin, and flucytosine) increases the reported value by up to 40µmol/l;
- women, children, the elderly, and those with reduced muscle bulk also have reduced creatinine generation rates, and hence will have a lower serum creatinine for a given GFR.
- Protein and creatinine supplements.

### Blood urea

A less useful measure of renal function because:

- Rate of production is not constant (increasing with high protein diets, tissue breakdown, steroids, and haemorrhage, and low in liver disease and low protein diets).
- 40–50% of filtered urea is reabsorbed in the proximal tubule.
- Volume depletion will enhance urea reabsorption together with salt and water retention in the proximal tubule [under the action of arginine vasopressin (AVP)].

Urea clearance can be a useful measure, but underestimates GFR.



## Assessment of renal function at/near end stage: creatinine clearance

Can be determined from a timed urine collection (usually 24h) and contemporaneous plasma sample:

$$\text{Creatinine clearance (ml/min)} = \frac{\text{Urine volume} \times \text{Urine [creatinine]}}{\text{Plasma [creatinine]} \times 1440}$$

- Errors arise from tubular secretion of creatinine (overestimates GFR by 10–15%), from variability in the assay for creatinine (10–15%), and particularly from the timing and completeness of urine collection.
- Incomplete urine collection is the most common cause for error, and can be estimated from the total creatinine present in the sample. Men usually excrete 175–220  $\mu\text{mol/kg}$  lean body mass/day, and women 130–175  $\mu\text{mol/kg}$  per day.
- Changes in diet and body mass will affect serum and excreted creatinine concentrations.
- Tubular creatinine secretion increases in progressive renal failure (acute or chronic) as the GFR falls, and can increase by >50%. This can lead to a gross overestimation of GFR by creatinine clearance ( $C_{\text{crea}}$ ) measures. A single dose of oral cimetidine can completely inhibit tubular secretion of creatinine and allow a more accurate measure of GFR from  $C_{\text{crea}}$ .
- If the errors are all minimized and the patient carefully instructed, then 24h urine collections can provide a reasonably accurate estimate of GFR, but this rarely happens in practice.

Urea clearance can be measured simultaneously, and averaging creatinine and urea clearance produces the best approximation for GFR. This can be done automatically in laboratories to provide more accurate estimates of GFR.



## Assessment of renal function at/near end stage: eGFR and calculated creatinine clearance

Estimating GFR by calculation from serum creatinine has become the most common method for measuring renal function (eGFR) and, although there are concerns about the accuracy of this in some circumstances, overall eGFR represents a major benefit in identifying reduced GFR.

### MDRD (modification of diet in renal disease) formula

For patients with known renal disease the MDRD formula is more accurate, estimates GFR rather than  $C_{\text{crea}}$ , and includes factors for race and serum albumin. It is corrected for body surface area (BSA). It is less accurate in patients with either very poor levels of renal function or near normal function.

In SI units:

$$\text{GFR}/1.73\text{m}^2 = 170 \times \text{PCr} (\mu\text{mol/l}) \times 0.0113)^{-0.999} \times \text{Age}^{-0.176} \times (\text{Urea}(\text{mmol/l}) \times 2.8)^{-0.17} \times \text{Albumin}^{0.318} \times [0.762 \text{ if female}] \times [1.18 \text{ if black}]$$

In conventional units:

$$\text{GFR}/1.73\text{m}^2 = 170 \times \text{PCr}(\text{mg/dl})^{-0.999} \times \text{age}^{-0.176} \times \text{Serum Urea Nitrogen} (\text{mg/dl})^{-0.17} \times \text{Albumin}^{0.318} \times [0.762 \text{ if female}] \times [1.18 \text{ if black}].$$

A simply variant using only serum creatinine, age, and sex is almost as accurate:

$$\text{GFR}/1.73\text{m}^2 = 186.3 \times (\text{SCr} (\mu\text{mol/l}) \times 0.0113)^{-1.154} \times (\text{age})^{-0.203} \times 0.742 \text{ (if female)}.$$

These formulae will overestimate  $C_{\text{crea}}$  in patients on low protein (or low meat) diets, but are otherwise reasonably accurate. They are not of value in patients with rapidly changing renal function. Calculated  $C_{\text{crea}}$  is often more reliable than 24h urine collections due to the inaccuracies in the urine collection itself. The calculation is still based on serum creatinine and will thus be inaccurate in patients with low muscle bulk, and has not been fully validated in children, pregnancy, and the very elderly. It is not accurate in normal renal function and cannot be used to estimate true GFR accurately in this setting.

The formula are available through many web sites, e.g. [www.renal.org](http://www.renal.org), [www.nephron.com](http://www.nephron.com), [www.hdcn.com](http://www.hdcn.com)

**Cockcroft–Gault formula**

This was developed to calculate  $C_{\text{crea}}$  based on plasma creatinine. It has all the potential problems for all formulae based on serum creatinine. In conventional units:

$$CCr \text{ (ml/min)} = \frac{(140 - \text{Age (years)}) \times \text{weight (kg)}}{72 \times PCr \text{ (mg/dl)}}$$

For women multiply by 85 (not 72).

In SI units:

$$CCr \text{ (ml/min)} = \frac{1.23 \times (140 - \text{Age (years)}) \times \text{weight (kg)}}{PCr \text{ (}\mu\text{mol/l)}}$$

For women multiply by 1.04 rather than 1.23.

This method is reasonably reliable in mild renal impairment but overestimates GFR by up to 100% as GFR falls to 10ml/min. The eGFR calculated from the MDRD equation is a better alternative. The only exception may be in drug dosing since the eGFR is normalized for BSA while conventionally the Cockcroft–Gault calculation is not, and includes patient body weight which might be relevant in drug distribution.

## Assessment of renal function at/near end stage: other methods

### Pre-dialysis Kt/V

Kinetic methods may be a more reliable measure of renal function in patients close to dialysis, but are not familiar to non-nephrologists. Mean normalized urea clearance (daily Kt/V) can be calculated using a 24h urine collection for measurement of urea clearance (multiply  $\times 7 = Kt$  for a weekly figure), and estimating V from the patients' height and weight. Alternatively, Kt/V can be calculated using the same computerized models as in dialysis patients on the basis of a 24h urine urea quantitation and plasma urea. Using conventional criteria for institution of dialysis, many patients have a daily pre-dialysis Kt/V of  $\sim 0.15$  when dialysis is begun, which would be considered underdialysis in a patient established on HD (daily Kt/V  $\sim 0.5$ ). Using Kt/V as the measure of renal function in patients with CKD will generally prompt earlier initiation of dialysis and also provides a better measure of nutritional status by the simultaneous calculation of normalized protein catabolic rate (nPCR). Dialysis should be considered when the weekly Kt/V  $< 2.0$  or nPCR  $< 0.8$ .

### Isotopic measures

More accurate measures of GFR use [ $^{51}\text{Cr}$ ]EDTA, [ $^{99\text{m}}\text{Tc}$ ]DTPA, or [ $^{125}\text{I}$ ]iothalamate clearance, and overestimate GFR by only a few ml/min (very little secretion). They require IV injection of radiolabelled compound, and subsequent blood sampling to measure rate of loss of isotope from blood. DTPA clearance can be determined by external gamma camera counting over the kidneys to estimate the proportion of the isotope taken up by the kidneys after a given time. In severe renal failure, isotopic methods are more reliable measures of renal function than serum creatinine or  $C_{\text{crea}}$ . Non-isotopic indicator decay methods include iohexol clearance.

### Cystatin C

An endogenous cysteine protease inhibitor produced by almost all nucleated cells at a constant rate, regardless of volume status, inflammation, or drug interactions. Measurement reflects GFR more accurately than serum creatinine. Routine assays may become available soon.



## Complications of renal failure: symptomatic

Complications of renal failure include immediate symptomatic problems and more long-term effects on rate of deterioration of renal function or future morbidity and mortality.

### Symptomatic complications

#### Cardiovascular disease

This is the major complication of renal disease; many more patients will die from a cardiovascular event than develop ESKD.

- Long-term follow-up studies of general health in the USA [National Health and Nutrition Examination Survey (NHANES) II] have shown that cardiovascular mortality is almost doubled in people with GFR <70 ml/min, i.e. even with very moderate renal impairment.
- Presence of microalbuminuria (in diabetics and non-diabetics) doubles cardiovascular mortality.
- Overt proteinuria (>300mg/24h) trebles or quadruples risk of cardiovascular events and death.
- There is an increased mortality in patients known to have cardiovascular disease if renal impairment also present.
- Large epidemiological studies have shown that risk of cardiovascular events increases as GFR falls below 60 ml/min, with risk increased 2- to 4-fold for stages 4 and 5 CKD. One study has shown that the risk of a cardiac event is increased 100-fold for a 40-year-old man on dialysis compared with what is expected if renal function is normal.

#### Risk factors for cardiovascular disease in renal patients

Many are the same as in the general population, although some may be more common in patients with renal disease, e.g. hypertension, lipid abnormalities, diabetes, male sex, and LVH.

#### Anaemia

Contributes towards the tiredness experienced by patients with renal failure. Also predisposes to LVH (an independent cardiovascular risk factor). Data from several national registries show that patients starting dialysis with a higher Hb survive longer.

- Hb can start to fall when GFR declines to 30–40ml/min.
- Failure of EPO production is the major cause of renal anaemia, although it is essential to check other haematinics (iron, plasma vitamin B12, and red cell folate levels). Haemoglobinopathies, such as thalassaemia, should also be considered.
- Many patients will respond to oral iron treatment.
- Recent trials of early use of EPO in pre-dialysis patients have suggested an increased mortality in patients with Hb >13g/dl.
- UK National Institute for Health and Clinical Excellence (NICE) guidelines state a Hb target of 10.5–12.5g/dl,
- US K/DOQI guidelines state a Hb target of 11–12g/dl and no greater than 13g/dl,
- Use of IV iron and EPO to achieve these targets is discussed later.

**Major complications of renal failure**

A. Symptomatic:	Cardiovascular disease
	Anaemia
	Renal bone disease
	Malnutrition
	Growth retardation in children
	Fluid overload
	Pericarditis
B. Metabolic and/or risk factor for future event:	Hypertension
	Lipid abnormalities
	LVH
	Vascular calcification and stiffness
	Hyperkalaemia
	Acidosis
	Secondary hyperparathyroidism
	Hyperphosphataemia
	Inflammatory state

## Complications of renal failure: renal bone disease

Caused mainly by hyperparathyroidism and osteomalacia. Develops at a relatively early stage of renal failure when the GFR starts to fall below 30–40ml/min. The underlying cause is decreased production of 1,25 dihydroxy vitamin D by the failing kidney. This results in decreased intestinal calcium absorption and hypocalcaemia. Low plasma calcium and 1,25 vitamin D levels both cause increased secretion of PTH. Retention of phosphate also stimulates PTH secretion. Early manifestations of hyperparathyroidism are biochemical: hyperphosphataemia, hypocalcaemia, and raised plasma PTH levels. Symptoms develop later and consist of bone and joint pains, and pruritus. Closely linked with the development of cardiovascular disease. See later for management.

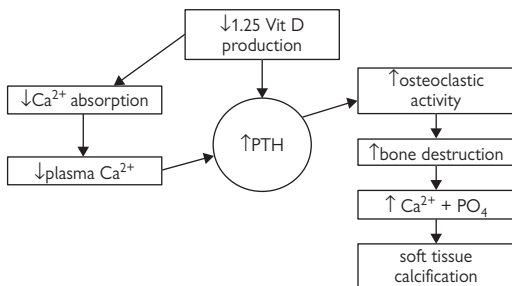


Fig. 1.3 Mechanisms underlying renal bone disease.

## Complications of renal failure: malnutrition

### Poor nutrition

This is a predictor of poor outcome at the start of dialysis. It develops as patients become anorectic. Patients spontaneously reduce their protein intake as well as their overall calorie intake, and some become severely cachectic. There are various biochemical markers of nutrition, but the most easily measured is plasma albumin. Low albumin may also reflect ongoing inflammation rather than nutritional status. Restrictive diets, persistent heavy proteinuria, co-existing disease, and increasing age are all risk factors for malnutrition.

### Growth retardation

This is a major complication of renal failure in children; the younger the child when renal failure develops, the more severe the growth retardation. At early ages, reduced growth rate is predominantly due to poor nutrition; around puberty, retardation is due to insensitivity to the action of growth hormone.

## Complications of renal failure: fluid overload

This is both a complication and a mode of presentation of severe renal failure.

- Clinical features are ankle oedema, pulmonary oedema, pleural effusions, and ascites.
- Clinical examination findings will depend on the degree of fluid retention:
  - if mild—ankle oedema alone;
  - in more severe fluid overload—more extensive oedema and pulmonary oedema;
  - high BP (can differentiate from fluid overload of heart failure).
- Patients with co-existing cardiac disease will be at increased risk of developing pulmonary oedema with fluid overload.
- The simplest way to monitor changes in fluid control is by body weight. An increase in weight by 1kg equates to retention of 1litre of fluid. This is only true over short periods of time, or if the body weight is constant. If the patient is anorectic and losing flesh weight, he/she could become fluid overloaded with little change in total body weight.

### Clinical features of fluid overload

Symptoms:

Shortness of breath  
Paroxysmal nocturnal dyspnoea  
Ankle swelling

Signs:

Raised jugular venous pressure (JVP)  
Basal crepitations  
Generalized oedema  
Increasing weight  
Rise in BP



## Complications of renal failure: metabolic

### Lipid abnormalities

Occur in all patients with heavy proteinuria. The main abnormality is a raised plasma cholesterol level, which occurs as hepatic synthesis is increased. Lipoprotein (a) levels start to rise as soon as microalbuminuria appears as the first manifestation of renal disease in diabetics. The hyperlipidaemia of renal disease contributes to the high incidence of cardiovascular disease and may play a role in the progression of renal damage. Patients without proteinuria may have relatively increased serum triglycerides, and dysregulation of normal apolipoprotein metabolism.

### Hyperkalaemia

A potentially fatal complication of renal failure. As potassium is predominantly an intracellular ion, a small shift of potassium from the intracellular to extracellular space will cause a rise in plasma potassium.

### Acidosis

Invariably occurs with severe renal failure but is found at an earlier stage in tubulointerstitial renal diseases. Unless severe (when hyperventilation occurs), acidosis itself will not cause symptoms. Bone disease, muscle catabolism (leading to negative nitrogen balance), poor nutrition, and growth retardation in children are all exacerbated by acidosis. Acidosis also predisposes to hyperkalaemia, and is associated with a faster decline in renal function.

### Inflammation

Is part of the MIA syndrome (malnutrition, inflammation, atherosclerosis), which is a feature of the normal ageing process, but is exacerbated by renal failure. Markers of inflammation [C-reactive protein (CRP), interleukin-6] increase with age and decreasing GFR, and are associated with vascular disease and malnutrition.

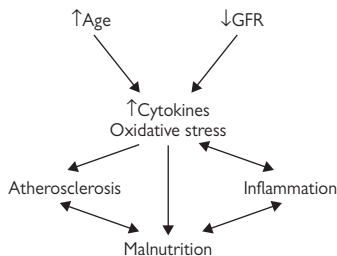


Fig. 1.4

**Causes of hyperkalaemia in renal failure**

Increased potassium intake

Dietary intake  
 Potassium supplements  
 (oral or IV)  
 Absorption from blood  
 (haematoma or GI bleed)

Shift of potassium from cells

Acidosis  
 Muscle breakdown  
 Released from red blood cells  
 after transfusion

Decreased renal excretion

Worsening renal failure  
 Potassium-sparing diuretics

Decreased secretion in collecting  
 duct (i.e. ↓ aldosterone action)

Spirolactone  
 ACEIs  
 ARBs  
 Ciclosporin  
 Tacrolimus

## **Complications of renal failure: cardiovascular**

### **Pericarditis**

Occurs only in severe renal failure. Chest pain is not invariable and the diagnosis is made by detecting a pericardial rub. The pericardial effusion is usually haemorrhagic and may be large enough to cause tamponade. Pericarditis is now a rare complication as dialysis is commenced earlier.

### **Hypertension**

Almost invariable in renal disease, even when there is minimal deterioration in renal function. Detection of hypertension is often the initial presentation of renal disease. Control of hypertension is vital to minimize cardiovascular risk and LVH. Hypertension control is the most effective method of slowing the rate of progression of most types of renal disease.

### **Left ventricular hypertrophy**

Develops because of hypertension and anaemia. LVH is an independent risk factor for cardiovascular disease and poor survival on dialysis.

### **Vascular calcification**

More common in ESKD than in patients with other causes for vascular disease, and includes the heart valves. Associated with stiffening of arteries. Multiple predisposing factors, including hyperparathyroidism, inflammation, hyperphosphataemia, calcium loading in the form of calcium-containing phosphate binders, and use of vitamin D metabolites.

## Management of renal failure: aims

The aims of management of renal disease are:

- diagnosis and treatment of reversible causes;
- slow rate of progression of renal damage;
- minimize cardiovascular risk;
- BP control slows the rate of progression of renal damage and minimizes cardiovascular risk;
- control dyslipidaemia—minimizes cardiovascular risk and may slow down rate of progression of renal damage;
- identify and treat complications—particularly anaemia and hyperparathyroidism (can occur even in stage 3 CKD when GFR is in the 30–40ml/min range);
- prevention of symptoms—mainly those due to fluid overload or uraemia;
- start planning and education for dialysis or conservative care;
- start planning and education for transplantation if appropriate.

## Management of renal failure: blood pressure control

This is the cornerstone of management of CKD. Factors to consider are:

- What level is control?
- Which drugs to use?
- Achievement of control.

### What level of BP is control?

Most guidelines for BP control have targets that are often difficult to achieve in practice.

British Hypertension Society guidelines for BP control (2004)

BP	Measured in clinic		Mean daytime ABPM	
	Diabetes	No diabetes	Diabetes	No diabetes
Optimal	<130/80	<140/85	<120/75	<130/80
Minimum level of control	<140/80	<150/90	<130/75	<140/85

ABPM = ambulatory blood pressure monitoring.

### Guidelines for BP control in CKD

Renal Association (2007)  
K/DOQI (2004)

BP <130/80  
BP <130/80

## Management of renal failure: which drugs for BP?

### Which antihypertensive drugs should be used?

Some drugs may have an additional renoprotective effect in addition to lowering BP.

- ACEIs or ARBs minimize the effect of angiotensin II on the kidney, reduce proteinuria, and cause dilatation of the efferent arteriole with increased blood flow. They also reduce the growth factor activity of angiotensin II in the kidney.
- Both ACEIs and ARBs have been shown to reduce proteinuria more than any other class of drugs.
- There is evidence in diabetic and non-diabetic renal disease that the addition of an ACEI for BP control results in a slower rate of deterioration in renal function, particularly when proteinuria is present.
- ARBs have also been shown to reduce the rate of decline of renal function in diabetic nephropathy [in type II diabetes mellitus (DM)].
- ACEIs and ARBs are increasingly used in combination to provide maximal suppression of the renin–angiotensin system (RAS) and maximal reduction in proteinuria, and to achieve better BP control.
- Both ACEIs and ARBs are contraindicated for patients with known renovascular disease (RVD) and should be used with caution in patients at risk of having RVD. They both block efferent arteriolar constriction caused by angiotensin II, and the resultant efferent arteriolar dilatation leads to a drop in glomerular perfusion and hence a decrease in GFR.
- Hyperkalaemia can be a complication of either drug, particularly if they are used in combination.
- Calcium antagonists cause afferent arteriolar dilatation with increased blood flow through the kidney. They also inhibit the action of many growth factors in the kidney. Their effect on proteinuria is variable and not as marked as with ACEIs.
- Calcium antagonists have not been shown to have a direct renoprotective effect, but remain a very important group of drugs to achieve BP control.
- Use of diuretics enhance actions of ACEI and ARBs on BP lowering and reduction of proteinuria, but may cause deterioration in renal function. May also worsen metabolic control of glucose, lipids, and uric acid.
- Spironolactone may be a useful additional drug at higher levels of renal function, but has to be used with caution as renal function deteriorates because of risk of hyperkalaemia—best avoided if patient also on an ACEI and an ARB.
- Aliskerin is a new direct renin inhibitor which may have a useful role. BP lowering effects are comparable with those of other agents blocking the RAS, and there is evidence for benefit in kidney disease, diabetics, and in slowing progression of renal disease.

## Management of renal failure: how to achieve blood pressure control

This involves careful monitoring of the patient and selection of appropriate drugs. Compliance is a major problem, so drugs chosen should have minimal side effects and preferably need to be taken only once a day, with long duration of action to achieve full 24h BP control (but reduce dose if renally excreted when renal function declines). The following are useful guidelines for controlling BP in renal disease:

- In diabetics, and non-diabetics with proteinuria  $>1\text{g}/24\text{h}$ , use an ACEI or ARB unless the patient is at risk of having RVD. Use an ARB if the patient develops a cough on an ACEI.
- Dose of ACEI or ARB should be increased to full dose (if tolerated) to provide maximal reduction of proteinuria (independent of BP lowering).
- If BP not controlled, the logical next choice is to use a drug raising renin levels as this will enhance the action of the ACEI or ARB.
  - note: thiazides are not effective in patients with low GFR;
  - loop diuretics (bumetanide, furosemide) should be used with caution, as GFR will decrease further if patient becomes volume depleted; a modest rise in plasma creatinine, however, may have to be accepted if this is the only means of achieving BP control;
  - calcium antagonists are well tolerated in patients with renal failure; as well as causing vasodilatation, they enhance renin release.
- $\alpha$ -Blockers, e.g. doxazosin, are useful as third-line drugs to achieve control.
- $\beta$ -Blockers are sometimes needed and are particularly useful if the patient also has angina. They should be used with caution in diabetic patients requiring insulin and in patients with peripheral vascular disease.
- If significant proteinuria persists, consider a combination of ACEI and ARB.
- Frequent monitoring of BP is essential:
  - ambulatory BP monitoring (ABPM) and home monitoring of BP by the patient often give a more accurate measure of BP control than clinic BP readings;
  - this is particularly important in trying to achieve the low levels of BP required in renal disease, as there is a risk of overtreatment and symptomatic hypotension;
  - upper arm cuff monitors are reasonably accurate for home monitoring and are relatively cheap.
- Encouraging patients to monitor their own BP often improves control, as the patient is more involved with their treatment. Once a week checks are sufficient, but it is sensible to do these at different times of the day.
- Home BP readings have been shown to correlate better with decline in renal function than clinic readings

**NICE/British Hypertension Society Recommendations 2007**

These guidelines have recently been revised as a result of head-to-head trials showing that  $\beta$ -blockers were usually less effective than the comparator drug at reducing major cardiovascular events, in particular stroke.

**Use of  $\beta$ -blockers**

Evidence from recent trials have resulted in recommendations that  $\beta$ -blockers are not a preferred initial therapy for hypertension. They may, however, be considered in younger people, particularly:

- those with an intolerance or contraindication to ACEI or ARBs
- women of childbearing potential (use of ACEIs and ARBs is contraindicated if a woman is trying to conceive)
- patients with evidence of increased sympathetic drive
- If a second drug is then required, add a calcium channel blocker rather than a thiazide-type diuretic to reduce patient's risk of developing diabetes
- If BP is well controlled with regimen which includes a  $\beta$ -blocker, there is no absolute need to replace it with another agent

**Algorithm for treatment of hypertension**

	<55 yrs *	≥55 yrs, or black patient
Step 1	A	C or D
Step 2	A + C or A + D	
Step 3	A + C + D	
Step 4	Add: further diuretic therapy or alpha-blocker or beta-blocker	

A=ACEI or A2RB; C=calcium-channel blocker;

D=thiazide-type diuretic

\* For patients with CKD, includes patients with proteinuria >1g/24h or diabetes, though this is not addressed in these guidelines

## Management of renal failure: slowing the rate of decline

Other means of slowing the rate of deterioration of renal function are:

- **Blood glucose control in diabetics:** there is evidence in both insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) that tight control of blood glucose has a beneficial effect on the rate of deterioration of renal function. In NIDDM, this can be achieved with both oral agents and insulin. Metformin should be used with care and at reduced dose in patients with renal impairment (eGFR <60ml/min), but the benefits (cardiovascular and metabolic) probably outweigh the risk until eGFR is <30ml/min. Metformin should be stopped once eGFR is <30ml/min (risk of lactic acidosis).
- **Lipid control:** there is evidence from animal studies, and some evidence in patients, that lowering plasma cholesterol and the use of low fat diets slow the rate of decline of renal function.
- **Optimizing fluid balance:** fluid depletion affects renal function adversely as it causes hypotension and poor renal perfusion.
- **Low protein diet:** whether protein restriction slows the rate of progression of renal failure remains controversial. Compliance is difficult, particularly if patients are also restricting fat intake, and in diabetics. There is also a major concern over protein malnutrition, particularly if the renal disease is very slowly progressive (long-term use of diet).
- **Correcting acidosis:** there is recent randomized controlled trial (RCT) evidence that oral sodium bicarbonate slows rate of decline of renal function.
- **Use of EPO:** some data that rate of decline of renal function may be slower in patients using EPO, though this needs to be confirmed in a sufficiently powered RCT.

## Management of renal failure: lipids and fluid balance

### Lipid control

The increased risk of cardiovascular disease in renal failure is partly due to the increased frequency of hyperlipidaemia. Other risk factors include raised lipoprotein (a) and homocysteine. Although there are no clinical studies demonstrating the benefits of lipid control in renal disease, general recommendations are to minimize risk factors and aim for plasma cholesterol  $<5.0\text{mmol/l}$ . This is achieved by:

- diet—all patients with renal disease should be given advice about 'healthy eating';
- drug therapy—particularly statins (dose depends on renal function because of risk of myositis); fibrates are contraindicated in advanced renal disease;
- ezetimibe can safely be added to a statin to enhance cholesterol lowering
- folate supplementation may reduce homocysteine levels, but trials fail to show any effect on cardiovascular outcomes

### Optimizing fluid balance

#### *Fluid overload*

All patients should be assessed for fluid overload whenever seen. This can be corrected by the use of diuretics, and salt and fluid restriction. Larger doses of diuretics are needed as renal function worsens, but renal function can deteriorate during diuresis because of the reduction in blood volume and hence renal perfusion. Patients with advanced renal failure can be precipitated on to dialysis when treated with diuretics. Patients with cardiac failure can often only maintain adequate renal perfusion when oedema, with some degree of pulmonary oedema.

#### *Fluid depletion*

Worsens renal function because of reduced renal perfusion. Any patient with renal impairment, normal BP (not on hypotensive drugs), and no oedema is probably fluid depleted. If necessary this can be managed with oral sodium supplements (slow sodium or sodium bicarbonate). IV saline is indicated in the presence of postural hypotension.

## Management of renal failure: treatment of anaemia

Anaemia causes significant morbidity in patients with renal failure.

- Detection of anaemia and its treatment is one of the principal goals of good pre-dialysis management.
- Anaemia may be considered a result of uraemia if GFR <30ml/min (<45ml/min in diabetics) and no other cause is identified.
- If Hb <12g/dl in men and postmenopausal women, or <11g/dl in premenopausal women, check ferritin, transferrin saturation, B12, and red cell folate.
- Aim for serum ferritin  $\geq 200\mu\text{g/l}$ .
- Iron replacement: should initially be with oral iron, but if ferritin remains below target, or if more rapid response needed (Hb <10g/dl) arrange for IV iron.
- Once serum ferritin  $\geq 200\mu\text{g/l}$  for at least a month, EPO, darbepoetin alfa, or an erythropoietin-stimulating agent (ESA) should be commenced if:
  - Hb <10.5g/dl;
  - Hb 10.5-11.5/dl *and*
    - symptomatic angina or claudication;
    - exertion significantly limited by shortness of breath;
    - patient does job dependent on manual labour or exertion.
- Target Hb for pre-dialysis patient on EPO is 10.5–12.5g/dl and <13g/dl, i.e. same as for patients on dialysis.

Once EPO or darbepoetin alfa or an ESA is started, management is the same as for patients on dialysis.

## Management of renal failure: calcium and phosphate

### Hyperparathyroidism

The principles are the same as for patients on dialysis. It is important to avoid hypercalcaemia, which can cause acute deterioration in renal function because of fluid depletion and calcium precipitation in the kidney.

### Hyperphosphataemia

This is caused by phosphate retention and hyperparathyroidism. Management involves:

- dietary phosphate restriction;
- use of phosphate binders: calcium carbonate, calcium acetate (less calcium absorbed so lower risk of hypercalcaemia), sevelamer and lanthanum carbonate—for more details, see p. 466.

## Management of renal failure: metabolic complications

### Hyperkalaemia

Plasma potassium needs to be monitored regularly. Hyperkalaemia does not cause warning symptoms before fatal arrhythmia occurs. Management consists of:

- Monitoring of drug treatment—avoid potassium supplements and potassium-sparing diuretics (amiloride, triamterene, spironolactone); careful use of ACEIs and ARBs, especially in combination
- Low potassium diet.
- Oral ion-exchange resins (e.g. Resonium A<sup>®</sup>, which exchanges sodium for potassium, or Calcium Resonium<sup>®</sup>, which exchanges calcium for potassium). Resonium A<sup>®</sup> should not be used in patients with fluid overload. Expensive if used long term, not very palatable, and can cause constipation. Can be dissolved in lactulose to avoid constipation.
- Fludrocortisone may help lower serum potassium by increasing colonic potassium excretion.
- IV insulin and dextrose if plasma potassium is  $>6.5$  mmol/l, given as a bolus of 50 ml of 50% dextrose with 10–12 units of short-acting insulin. Blood glucose must be monitored carefully for several hours afterwards. Plasma potassium should be repeated 1 h later—if still high, an insulin and dextrose infusion may be needed (same concentration, run at 5 ml/min).
- Oral or IV sodium bicarbonate if the patient is acidotic but not fluid overloaded.
- $\beta$ -Agonists such as salbutamol given by inhaler or nebulizer can lower serum potassium by 0.6–1 mmol/l, but can worsen tachycardias.
- HD if plasma potassium remains high despite these methods—very unusual except with advanced renal failure.

### Acidosis

- Plasma bicarbonate should be maintained in the normal range with oral sodium bicarbonate to prevent exacerbation of bone disease and increased muscle catabolism
- Start at dose of sodium bicarbonate 500 mg bd and titrate upwards until plasma bicarbonate is in normal range
  - 1 g sodium bicarbonate provides 10 mmol sodium
- Correction of acidosis will lower plasma potassium
- Use of oral sodium bicarbonate often limited by the increased sodium intake which makes control of fluid overload and BP more difficult.

### Poor nutrition

Appropriate nutritional advice should be given to all patients with renal failure as low plasma albumin and malnutrition are poor prognostic factors for long-term survival on dialysis. There is an increasing awareness that starting dialysis early (i.e. GFR  $<10$  ml/min, rather than when the patient is very symptomatic with GFR  $<5$  ml/min) avoids the anorexia and poor nutrition associated with severe renal failure.

## Management of renal failure: prevention of symptoms

The level of GFR at which symptoms develop varies from individual to individual. Generally, symptoms are less pronounced when renal failure progresses slowly over several years. Most patients remain asymptomatic until GFR is  $<20\text{ml/min}$ . Older patients and diabetics tend to develop symptoms at relatively higher GFRs. Initial symptoms include increasing tiredness and exhaustion on exertion, and patients later become overtly anorectic. Family or friends may notice changes before the patient.

Management should prevent and treat these symptoms and enable patients to maintain their usual lifestyle and employment. This can be achieved by:

- correction of anaemia by the use of an erythropoietic agent;
- counselling and education—depressive symptoms are very similar to those of uraemia, and patients can become anxious or depressed by the thought of dialysis;
- protein restriction—prevents the accumulation of nitrogenous waste products and makes the patient feel better (less uraemic); however, protein intake usually falls spontaneously in advancing renal failure because of anorexia, and additional protein restriction may worsen malnutrition;
- control fluid balance—fluid overload causes shortness of breath, and fluid depletion causes hypotension, both of which will exacerbate tiredness;
- starting dialysis early when symptoms restrict the patient's lifestyle, even if GFR is still  $\sim 10\text{ml/min}$ . American (K/DOQI) guidelines are to start dialysis when GFR is  $15\text{ml/min}$ , but this is not the practice in the UK or most of Europe, and is probably not acceptable to many patients; there is no evidence that a very early start to dialysis leads to better survival.

## Assessment of patients for dialysis: early referral

Patients who require dialysis within 3 months of referral to a nephrologist are at increased risk of morbidity and mortality compared with those under long-term specialist care. Up to 40% of patients begin RRT <6 months after referral to a nephrologist; this is particularly true for older patients. Advantages of early referral include:

- ability to slow rate of progression of renal deterioration;
- control of BP and lipids minimizes cardiovascular risk thereby reducing 'co-morbidity load' when patient eventually starts dialysis;
- use of ACEIs and statins, both of which may have beneficial effects over and above BP lowering and cholesterol control;
- timely treatment of anaemia and use of EPO;
- prevention of bone disease by proper management of serum phosphate and calcium, and PTH;
- early dietary interventions including 'healthy lifestyle' advice to minimize cardiovascular morbidity;
- hepatitis B vaccination can be carried out pre-dialysis when the immune response is greater;
- patient can be educated about dialysis;
- most appropriate modality of dialysis can be chosen;
- psycho-educational interventions can delay time until dialysis needed;
- access for dialysis can be planned in advance—emergency access for HD and PD has more complications;
- protection of forearm veins;
- increases compliance with treatment;
- enables pre-emptive transplantation (mostly from living donors);
- dialysis can be commenced 'early' before become symptomatic; patients are fitter and long-term outcome may be improved;
- higher quality of life and better physical functioning.

Late referral to a nephrologist also represents a loss of chance for the patient and loss of money for society.

## Assessment of patients for dialysis: when to start

Patients can be placed on the UK deceased donor transplant list once their GFR is  $<20\text{ml/min}$ . Ideally, information about the various dialysis options should be introduced within a year of the projected need to start dialysis. Some patients are content just to 'know' that they will need dialysis some time in the future, but do not want any more details until closer to the time. Some do not want to know the details because they are frightened. Such patients may come to false conclusions, e.g. they can no longer go on holiday for fear they may be caught abroad needing urgent dialysis. Some patients will have to make major career decisions, e.g. whether to accept a post abroad. There are also patients who are 'in denial', i.e. know that they will need dialysis, but think it will never actually happen to them, so deny all symptoms and end up starting dialysis when they are really sick. Finally, a few patients will decide that dialysis is not for them—time will be needed to counsel them and their families or friends appropriately.

## Assessment of patients for dialysis: factors to be assessed

The assessment period helps to determine which modality of RRT is best suited for the patient, assuming that there is no resource limitation affecting dialysis supply.

### Treatment modalities for ESKD

- HD
  - centre
  - satellite
  - home
- PD
  - continuous ambulatory PD (CAPD)
  - automated PD (APD)
- Transplantation
  - cadaver
  - living related donor
  - living unrelated donor (emotionally related)
- Conservative management
  - best supportive care.

### Factors that need to be assessed

- **Age:** not a barrier to dialysis—both PD and HD can be used successfully in the elderly. The elderly are at greater risk from co-morbid illnesses, physical disabilities, and social isolation; all need to be taken into account when determining the optimum modality of dialysis.
- **Eyesight:** although there are aids enabling poorly sighted individuals to carry out PD, these are only suitable for very motivated patients with social support.
- **Mobility:** if hospital transport is needed for HD, hours spent away from home are greatly extended. PD, however, is not suitable for patients with poor mobility unless there is appropriate social support to help with exchanges or carry out APD.
- **Manual dexterity:** poor dexterity makes PD difficult unless family members can help.
- **Housing:** PD is only possible if there is room to store supplies, and a clean area close to running water (for hand washing), where exchanges can be performed. If assessment is made early, it may be possible to change or alter accommodation to suit PD requirements.
- **Family or social support:** dialysis is stressful, whichever modality is used. Many PD patients benefit from support at home particularly if they are disabled or have other medical problems. Family support is also important for enabling compliance with dietary restrictions, and for transport to hospital for clinic visits and HD sessions.
- **Attitude to chronic illness:** very variable both between individuals and between different cultural and ethnic groups. Some patients are determined to live as normal a life as possible on dialysis, while others take on the sick role and depend on family support, without much objective evidence of their need to do so.

- **Work:** all attempts should be made to enable dialysis patients to remain in work. Many patients in full-time employment opt for PD (particularly APD) or HD at home or overnight in hospital. Depending on the flexibility of their employer, some patients on HD dialyse during the day, usually in a late afternoon or early evening shift. The increase in satellite units means that HD can be organized nearer to the patient's home or place of work, thereby decreasing travelling time.
- **Diabetes:** many patients with diabetes have co-existent vascular disease. Patients with active retinopathy are at risk of vitreous haemorrhage, and should be warned of the increased risk with the use of heparin on HD. There is no good evidence that HD or PD is more suited to the diabetic patient.
- **Co-existent vascular disease:** patients with ischaemic heart disease are at risk of angina or MI during hypotensive episodes that can occur on HD. Hypotension is more frequent on HD in patients with poor left ventricular function. Vascular access can be difficult to establish in patients with arterial disease.
- **Respiratory disease:** there is no evidence that the presence of intra-abdominal fluid in PD causes deterioration in pulmonary function in lung disease. Such patients tend to tolerate excess fluid less well and can become short of breath when only mildly fluid overloaded.
- **Abdominal examination:** a prerequisite to proceeding with PD. PD is contraindicated if likelihood of adhesions from previous surgery, particularly in the pelvis. Presence of colostomy, ileostomy, or ileal conduit contraindicate PD, but a feeding gastrostomy does not. Hernias should be repaired before catheter insertion. An inoperable hernia may be a contraindication to CAPD, but reduced volume overnight APD or intermittent PD (IPD) may be possible if HD is not an option. Retroperitoneal surgery, e.g. nephrectomy, aortic surgery, should not be a contraindication to PD, as subsequent adhesions are unlikely. PD should be delayed until 3months after aortic aneurysm repair to ensure that fibrous tissue has grown over the graft.
- **Compliance:** patients known to be poor compliers tend to do badly with a home-based treatment such as PD, unless they become motivated by the fear of changing to a modality of dialysis they do not want. Often such patients choose PD as they want to retain their independence and would cope equally poorly with the routine of HD.
- **Use of immunosuppressive drugs:** patients taking immunosuppressive drugs at the start of dialysis (e.g. for SLE, vasculitis, or a failing transplant) have an increased risk of infections related to central venous catheters (CVCs) or peritonitis, and infections are more severe. Steroids in particular delay wound healing, hence a longer time should be allowed for planning dialysis access whether for PD or HD.
- **Hepatitis B status:** hepatitis B-positive patients must be isolated if on HD. This has resource implications, and some patients may feel isolated if dialysed separately from the main unit. These difficulties are not encountered on PD.

## **Assessment of patients for dialysis: when not to dialyse**

Apart from patient choice, there are no hard and fast rules. Some practitioners would argue that all patients should be treated unless they explicitly refuse. This is not a universal view. Predictors of poor outcome are:

- dementia, unless there are family members who are dedicated to helping with treatment and care;
- severe peripheral arterial disease;
- hypotensive heart failure;
- severe mental illness, so the patient has no awareness of the treatment and is unable to comply;
- malignant disease with poor prognosis.

However, any experienced dialysis doctor or nurse will have treated patients doing better or worse than expected. If the patient is being assessed some time before needing dialysis, the option of not dialysing should be discussed if the prognosis is thought to be very poor. 'Not dialysing' does not mean 'no care', but rather full conservative and supportive management. However, it can be difficult to identify such patients, and a trial of dialysis for 1–2 months should be considered to establish whether the overall condition of the patient improves. Decisions not to dialyse must be taken after full discussion with the entire care team, the family, and almost always the patient, unless mentally incompetent. If a patient decides not to undertake dialysis, family members need to be informed. All discussions and decisions should be recorded in the notes, so that dialysis is not commenced should the patient come to hospital terminally ill due to renal failure.

Patients who present with severe renal failure needing immediate dialysis are the most difficult to assess. Severely uraemic patients can be confused and very ill. Increasing dementia in an elderly patient may be due to progressively severe renal failure. The decision not to dialyse can therefore only be made if it becomes obvious that the physical or mental state of the patient is not improving after some time on dialysis.

## Supportive care in ESKD

With increasing awareness of the poor outcome on dialysis for older patients with multiple co-morbidities, the option of no dialysis is increasingly becoming a standard component of pre-dialysis education. Around 8% of the pre-dialysis patients in London select conservative management after careful discussion with pre-dialysis kidney teams.

Patients who opt for conservative or supportive management (rather than dialysis) continue to need regular follow-up from the renal team. Symptoms can be treated and quality of life enhanced, although death is clearly inevitable at some point. For elderly patients with significant co-morbidities, however, length of life may not be increased by dialysis, and quality of life may suffer (high incidence of sepsis, hospital admissions, repeated interventions for vascular access, greater likelihood of dying in hospital rather than at home).

- Optimal management of BP will minimize rate of further deterioration of renal function, and reduce the risk of a cardiovascular event such as MI or stroke.
- Treatment of anaemia with IV iron and erythropoietic agents will greatly enhance quality of life.
- Correction of hypocalcaemia to prevent fits.
- Symptom control:
  - **tiredness:** treatment of anaemia;
  - **nausea:** low protein diet and use of antiemetics such as metoclopramide;
  - **shortness of breath and oedema:** cautious use of diuretics; if patient becomes volume depleted, renal function will deteriorate further, thereby exacerbating uraemic symptoms;
  - **pain:** mostly due to co-morbidities such as peripheral vascular disease or arthritis; non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided, and codeine-containing drugs should be used with caution.
- Death is inevitable, so the patient's and family wishes should be established:
  - patient should be referred early to the local palliative care team for appropriate inpatient and community management;
  - primary care and community palliative care services should be utilized so that patient can die at home if he/she/family wishes.
- Often patients will die from their co-morbid disease, e.g. cardiac or vascular disease, malignancy, etc.

## **Assessment of patients for dialysis: role of pre-dialysis nurses**

Specialist nurses have taken on a major role in most units for the pre-dialysis assessment and education of patients with severe CKD, and often other tasks.

- As part of the multidisciplinary care for patients with CKD.
- Patient education.
- Home visits combined with education, assessment, and family involvement.
- Family education.
- Management of renal anaemia, iron, EPO dosing and titration.
- Contribution to control and management of hypertension.
- Control and management of calcium and phosphate (with dieticians).
- Prevention of renal bone disease.
- Avoiding malnutrition (with dieticians).
- Dialysis access planning.
- Transplant planning
- Social and psychosocial support.
- Formal counselling.
- Patients' information evenings.
- Liaison with employers, educational institutions.

## Checklist for assessing patients in a low clearance clinic

### Dialysis plans

- Assess medical suitability (PD/HD/either).
- Refer to dialysis education nurse.
- Refer to renal social worker.
- HD: book arteriovenous fistula (AVF) surgery 3–6 months pre-ESKD
- PD: book catheter insertion before patient too symptomatic—allows patient to be maintained on residual renal function rather than having temporary HD if there are catheter-related problems
- Check HBsAg, anti-HBsAg antibodies, anti-HCV antibodies.
- Consent and test for HIV if potential transplant candidate.
- Immunize against HBV.
- Check antibody response 7–8 months post-vaccination.

### Biochemistry

- Deteriorating biochemistry may indicate need to start dialysis.
- Refer to dietician early (especially if  $K > 5 \text{ mmol/l}$ ,  $\text{PO}_4 > 1.6 \text{ mmol/l}$ , hyperlipidaemia, obese, or losing weight).
- Calcium carbonate/acetate to achieve  $\text{PO}_4$  1.3–1.8 mmol/l (consider sevelamer if calcium high).
- Alfacalcidol/calcitriol to achieve  $\text{Ca}$  2.2–2.6 mmol/l and PTH 2–3 times normal.
- Calcimimetics (Cinacalcet) may play an important role in controlling PTH,  $\text{Ca}$ , and  $\text{PO}_4$  when routinely available.
- Oral sodium bicarbonate if bicarbonate  $< 24 \text{ mmol/l}$  (watch BP, oedema).

### Anaemia

- IV iron to achieve ferritin  $> 200 \text{ mg/l}$ —most patients do not tolerate or absorb oral iron, which is therefore not particularly efficacious
- Check B12 and folate, add folic acid and B12 vitamin supplements as needed
- Consider erythropoietic agent if  $\text{Hb} < 10 \text{ g/dl}$  or symptomatic (and BP controlled, iron replete, no other cause for anaemia).

### Transplantation

- Consider in all patients once  $\text{GFR} < 20 \text{ ml/min}$
- Co-morbidity and not age is factor limiting transplantation
- Assess cardiac and respiratory fitness (CXR, ECG, consider pulmonary function tests, stress test, echocardiogram, and coronary angiography).
- Assess urinary tract, peripheral vasculature, obesity.
- Assess patient desire, understanding, and psychological state.
- Discuss pros and cons of transplantation.
- Refer to transplant education nurses.
- Discuss possibility of living related or unrelated transplant donors.
- Blood group, tissue type, serum for cytotoxic antibodies, CMV status.

## Haemodialysis vs peritoneal dialysis

The relative advantages and disadvantages of HD and PD are related to the inherent differences between the two modes of dialysis

	HD	PD
Dialysis characteristics	Intermittent	Continuous
Dialysis procedure	3 × 4h on machine, usually in hospital	Daily: 4 exchanges/day or cycling machine at night
Transport time	Mostly dependent on nurses and technicians	Carried out by patient in own home
	Session times dependent on availability in unit; can be at antisocial hours	Dialysis can be fitted round patient's lifestyle
Travel/holiday	Independent of patient's ability to learn or carry out technique	Dependent on patient or family member performing dialysis
	Extends time needed for dialysis sessions If hospital transport needed, transport time greatly increased	Treatment done at home
Dialysis adequacy	Arrangements need to be made with a local HD unit prior to travel—payment often needed	Transport to hospital only needed for clinic or emergency visits
	Patient has to dialyse at times offered by unit Some units will not accept patient if hepatitis B, hepatitis C or HIV +ve	PD fluid can be delivered to most parts of world with prior notice—cost usually included in contract with company providing dialysate
Dialysis adequacy	Dependent on blood flow, dialysate flow and membrane characteristics	Dependent on peritoneal membrane permeability and exchange number and volume
	Adequacy easily increased by increasing hours on dialysis or size of membrane	Residual renal function plays important role Increased adequacy achieved by increasing exchange volume and number; often with aid of APD

	HD	PD
Ultrafiltration (UF)	Reasonably predictable	Less predictable—poor UF can be cause for conversion to HD
	Regulated by degree of negative pressure in dialysate compartment	Regulated by increasing concentration of dextrose in dialysate or by use of glucose polymer solution
	Pre-set at beginning of dialysis on the machine	Dependent on membrane permeability—poor UF with high permeability
	Amount that can be removed limited by cardiac status; greater risk of hypotension with poor cardiac function	UF often declines with time on dialysis
Access for dialysis	Need to allow 2–3months for fistula to develop before useable	Access easy to establish. PD catheter can be used immediately, but advisable to allow to heal for 2weeks
	Fistulae can be difficult to create in diabetics or patients with arterial disease	
	Acute access with CVCs have high complication rate: infection, thrombosis, venous stenosis	
Infectious complications	Septicaemia associated with catheter infections can be life threatening. Complications of catheter infections often dangerous, e.g. SBE, septic arthritis, epidural abscess	Catheter exit site infection—rarely serious. Peritonitis—if serious, usually resolves after catheter removal; rarely fatal
Cardiovascular complications	Risk of hypotension with fluid removal—increased if poor cardiac function Arrhythmias can occur as plasma potassium falls during dialysis Angina, MI, and stroke can be precipitated by hypotensive episode. Fluid overload can occur if poor UF	Safer for patients with poor cardiac function, severe ischaemic heart disease,, or cerebrovascular disease

Table Continued

	HD	PD
Anaemia	Frequent—caused by reduced EPO levels and increased GI blood losses related to use of heparin  70–80% require EPO	Less severe—prolonged red cell survival and less GI blood loss  30–50% require EPO
Psychosocial	Not suitable for patients with needle phobia. Body image problems with fistula, particularly young women  As dialysis carried out by others, not dependent on patient's physical or mental ability  Can be inconvenient for family or social support as patient may have to dialyse at antisocial hours and require help with transport	Hb usually rises spontaneously for first few months on PD. Body image problems with PD catheter—may prevent patient from accepting PD  Dependent on patient or family member being able to learn and comply with technique. 'Burnout'—occurs after long period of time on PD  Care of dependent family member can be easier if dialysis carried out at home and life not disrupted by 3 times per week hospital visits
Contraindications	Inability to achieve vascular access. Severe ischaemic heart disease. Severe heart failure	Presence of colostomy, ileostomy, or ileal conduit. Intra-abdominal adhesions. Inoperable hernia
Survival	Survival on PD and HD similar for first 3–4years  High technique survival—low drop out to PD (because of lack of vascular access)  Experience with long-term patient survival for 20years plus	Survival on PD and HD similar for first 3–4years  Relatively high drop out rate (to HD) because of peritonitis, poor UF, or inadequate dialysis when residual renal function lost  Little experience of long-term survival. Risk of encapsulating peritoneal sclerosis with long term (>5 years) PD.

## Choosing which dialysis modality

Ideally, selection of dialysis modality should be driven by patient choice, unless there is a medical or social contraindication to a particular modality. Unfortunately, resource availability (limited HD facilities or lack of HD nurses) often limits patient choice (very variable across the world). There is also prejudice against PD driven either by local medical or nursing misinformation, or by a healthcare reimbursement system that favours HD (in some countries).

Contraindications to HD or PD	
	Dialysis modality contraindicated
<b>Absolute contraindications</b>	
Colostomy, ileostomy, ileal conduit	PD
Intra-abdominal adhesions	PD
Very poor housing	PD
No spare space in home	PD
Poor personal hygiene	PD
Morbid obesity	PD
Thrombosed central veins	HD
Severe angina	HD
Hypotensive heart failure	HD
<b>Relative contraindications</b>	
Frailty/dementia	PD (unless assistance from family member or carer)
Long distance from HD unit	HD
Severe vascular disease	HD
Active diabetic retinopathy	HD

## Concept of integrated care

Rather than thinking of one modality of treatment vs another, it is best to think of the patient's life span on renal replacement treatment. A single patient may well utilize all modalities so it is sensible to use each to its optimal benefit.

Modality	Strength	Weakness
PD	Increased patient freedom	Risk of underdialysis when patient becomes anuric
	Arm vessels not used for vascular access	Increase in membrane permeability and loss of UF with time on PD
	Longer preservation of residual renal function	
HD	Long-term technique survival	Limited by availability of vascular access
	Suitable for patients unable to perform own dialysis	Availability dependent on local resources
Transplantation	Longer patient survival than on dialysis	Limited by lack of kidneys Depends on patient's age and co-morbidities.

Thinking of the patient pathway through the various treatment modalities:

- optimal time to use PD is when there is residual renal function, i.e. when starting dialysis or when transferring back to dialysis after transplantation;
- use of PD at onset of dialysis delays need for vascular access, which is preserved for later on when PD is no longer suitable.

## Education for dialysis

Should be commenced once GFR approaches 20ml/min and/or within the year preceding need. It is a time-consuming process so is best done away from a busy clinic, by a dedicated nurse or counsellor. Home visits by an educator often extremely useful. It requires:

- involvement of family members and social support network, as appropriate;
- information about kidney function;
- knowledge about symptoms to expect as kidney failure gets worse;
- information about pros and cons of HD and PD;
- information about pros and cons of pre-emptive transplantation, transplantation after dialysis starts, use of living donors, and how the deceased waiting list works;
- developing an understanding of how each modality would impact on the patient's lifestyle, particularly with regard to work needs, hours of work, and need for travel, both for holiday and for work;
- an assessment as to whether a patient's home is suitable for PD or home HD (especially storage area);
- an assessment of the support the patient can reasonably expect from family and social networks;
- providing opportunities for the patient to visit PD and HD units;
- providing opportunities for the patient to talk to other PD or HD patients (if necessary);
- developing an understanding that RRT is not usually restricted to just one modality, but follows different pathways involving several modes of treatment;
- developing an understanding that outcomes of RRT treatment are mostly related to associated co-morbidities and that lifespan is reduced;
- enabling a patient to make a decision not to have a dialysis by giving realistic information about likely benefits of dialysis and how dialysis procedure will affect quality of life;
- providing information to a patient about end of life and how it can be managed if the patient is opting for or interested in conservative care.

## **Choice of dialysis modality: case histories**

### **Case 1**

G.F. is a 42-year-old man with immunoglobulin A (IgA) nephropathy. He had been an erratic attender at the renal clinic though aware his renal function was deteriorating. He presented with increasing tiredness and some nausea. Blood tests confirmed he had reached ESKD. Several family members were keen to offer him a kidney. After discussion, G.F. selected PD as this could be fitted round the shift patterns of his job as a bus driver. Six months later he had a successful transplant from his brother.

### **Case 2**

A.G. is an 83-year-old woman who lives on her own. Her only living relative is a niece who lives 200miles away; most of her friends have died. When told that she had ESKD, her initial reaction was to say that she did not want dialysis. However, she was frightened of dying and was pleased to think that she could feel less tired. She therefore agreed to a trial of dialysis. She had no social support, and was very anxious. It was therefore felt that she would do better on HD. Dialysis was started using a Tesio line as access. Unfortunately, this became infected and two further catheters did not function well. During this time she developed angina at rest. She was not fit for an anaesthetic to create a fistula, and HD became increasingly difficult because of angina. The option of stopping dialysis was again discussed, but she decided to try assisted APD with a healthcare assistant visiting her at home.

### **Case 3**

D.W. is a 47-year-old man with severe learning problems needing institutionalized care. He initially presented as an emergency with undiagnosed renal failure. Fortunately, there was some improvement in renal function, allowing time for many discussions with him and his carers. It was clear that the care home would not be able to carry out PD. By the time he needed dialysis, he had some understanding of what was involved. He has now been on HD for several years. Initially, he needed to be brought to hospital with a carer, but was then able to come on hospital transport on his own.

## When to start dialysis in ESKD

When dialysis was first available, it was only offered to patients who were uraemic and at risk of imminent death. Since then, the threshold at which dialysis is started has steadily fallen. The current K/DOQI (USA) and European guidelines are to start dialysis when the GFR is  $<15\text{ml/min}$ , and taking into account whether patients have any symptoms from ESKD, but definitively before  $\text{GFR} = 6\text{ml/min}$ . The UK Renal Association guidelines are to start dialysis when the GFR is  $<10\text{ml/min}$ . The potential advantages of starting dialysis early are:

- improved rehabilitation—patient usually still able to work;
- fewer complications starting dialysis as patient is fitter;
- patient does not become ill if there are delays in starting dialysis (e.g. poorly draining PD catheter, poorly functioning vascular access);
- avoids poor nutritional state associated with more severe renal failure—a low plasma albumin when starting dialysis is a poor prognostic factor;
- avoids emergency need for dialysis—decline of renal function is very variable so that patients who appear to be quite stable can suddenly present as an emergency.

Trials however have not shown any survival advantage of earlier starts to dialysis.

Dialysis is started in some patients to enable specific treatments or interventions which would carry high risk with severe renal failure. Examples are:

- coronary interventions pre-transplantation
- major surgery, e.g. abdominal surgery for malignancy
- parenteral nutrition because of fluid volume and risk of fluid overload.

## **How to persuade the patient to start dialysis**

This can be surprisingly difficult. Patients, understandably, do not want to start dialysis and many would rather put it off as long as possible. Even intelligent patients given detailed education can remain in a state of denial. This is most frustrating for the medical team who want to shield the patient from developing an acute and potentially life-threatening complication such as pulmonary oedema or hyperkalaemia. The patient should be encouraged to continue attending the renal clinic so that he/she can be monitored regularly, and can eventually be persuaded to start dialysis.

It is sometimes useful to use expressions such as 'You are in the grey area—dialysis will make you feel better; you have the advantage of being able to start at a time which is convenient for you. You do not want to wait until the black area where dialysis is needed as an emergency and therefore with many more complications'.

There are some patients who fail to attend any clinic and eventually present as an emergency.

## Clinical indications for starting dialysis in ESKD

### Plasma creatinine

No absolute figure can be given as this depends as much on muscle mass as on renal function. An elderly woman may have to start dialysis with a plasma creatinine of  $<300\mu\text{mol/l}$ , while a 25-year-old man may not start until his plasma creatinine is  $800\mu\text{mol/l}$ . Ethnicity is also important; Asians tend to have low muscle mass while Afro-Caribbeans have a high muscle mass. Low creatinine can be associated with poor outcome since it reflects malnutrition and low muscle mass.

### GFR

Difficult to measure at low levels of renal function.  $C_{\text{crea}}$  tends to overestimate GFR because of tubular secretion. Radioisotope measurements such as  $^{51}\text{Cr}$ EDTA are more accurate, but expensive and often not routinely available. Calculated GFR using the MDRD formula is now widely used and is reasonably accurate at low levels. The problem with using eGFR or plasma creatinine is that renal function can remain stable for long periods, therefore it is important to consider the rate of decline and patient symptoms additionally.

### Symptoms

Tiredness and anorexia develop once the GFR is  $<10\text{ml/min}$ . However, tolerance of renal impairment is very variable, with some patients (especially the elderly or diabetics) becoming markedly symptomatic with GFRs of  $\geq 10\text{ml/min}$ , while others remain well with GFRs as low as  $5\text{ml/min}$ . Patients may also be in a state of denial, and only present as an emergency.

### Weight loss

Any evidence of weight loss indicates the need to start dialysis, as poor nutrition is such a poor prognostic factor.

### Fluid overload

Only a relative indication. Initial management should be with diuretics (with caution to avoid a decline in renal function). If function worsens, or the patient remains fluid overloaded despite high dose diuretics, dialysis ought to be commenced.

### Hyperkalaemia

Another relative indication as it can usually be managed medically.

### Pericarditis

A very late complication of renal failure and rarely seen today. It remains an absolute indication for starting dialysis.

## The acutely presenting patient or ‘crashlander’

Around 30–40% of patients start dialysis in an unplanned manner. Many studies and registry data show that such patients have a worse outcome in terms of both morbidity and mortality. To improve outcomes, it is therefore important to consider why patients with ESKD should present ‘acutely’, how this can be avoided or minimized, and how management of these patients may be improved to avoid complications.

### Reasons for ‘crashlanding’

- Acute deterioration in renal function in a patient with CKD; this can occur due to
  - fluid depletion of any cause; remember that trivial fluid losses, e.g. increased sweating in hot weather, can cause profound hypotension and drop in GFR if angiotensin system blocked
  - decreased cardiac function—coronary event, arrhythmias, heart failure
  - urinary obstruction, e.g. stone, tumour, blood clot
  - exposure to nephrotoxic agent, e.g. X-ray contrast, drugs such as NSAIDs, aminoglycosides
  - sepsis of any cause.
- CKD not recognized by other healthcare teams so patient not referred to nephrologist.
- Patient not known to medical teams—more common with older patients who explain non-specific symptoms as ‘getting old’. Not unknown for younger patients to tolerate symptoms without seeking medical help.
- Foreign patients who present acutely ill—some know that they have CKD and hence this is the reason for leaving their own country, but some are genuinely unaware of diagnosis.
- Patients in denial of diagnosis or of need for dialysis so do not attend clinic or refuse to start dialysis until crisis occurs, e.g. pulmonary oedema, vomiting, etc.
- Delays in forming access for dialysis so no available fistula or PD catheter when symptoms or biochemistry dictate that dialysis should be started.

### Avoiding acute starts

- Use of eGFR and guidelines for when to refer to renal clinics should improve detection of CKD in the community—though at the risk of overloading nephrology services with stable mild CKD.
- Avoidance of nephrotoxic agents and drugs in patients known to have CKD.
- Advising patients on ACEIs and ARBs to drink more in hot weather.
- Appropriate fluid replacement in patients when fluid depleted.
- Pre-dialysis education and counselling to help patients come to terms with and choose the treatment modality that suits their lifestyle.
- Adequate resources for timely placement of vascular and peritoneal access.

### Reasons for poor outcome

- Patients often ill with multiple co-morbidities, septic, etc.
- Use of CVCs for access to start HD often out of hours—increased complication rate as staff may be inexperienced.
- High risk of line sepsis when using temporary catheters, particularly femoral catheters.
- Risk of femoral vein thrombosis or occluded central neck veins.
- Often fluid and electrolyte problems could have been managed medically and without need of acute dialysis with its attendant risks.

### Long-term outcome for 'crashlanders'

- Higher mortality than patients starting dialysis in a planned manner.
- Patients tend not to have same quality of education as those in pre-dialysis clinics—or given no education.
- They therefore tend to remain on HD and are not given option of transferring to or starting on PD.

### Use of PD

- PD can be safely used and may well be optimal mode of dialysis if poor cardiac function with risk of hypotension on HD.
- Avoids use of temporary venous access with all its complications.
- PD catheter can be used immediately if incisions are kept small—APD regimen with small volume exchanges should be used.
- Most patients who present acutely do not actually need urgent dialysis—though there is a tendency to do so. This gives time to discuss option of PD with patient and family.

## **Psychosocial effects of starting dialysis in ESKD**

Initial reactions to a diagnosis of ESKD include shock, grief (loss, helplessness, and despair), denial, and finally acceptance. Patients also become aware (though often not initially) that dialysis is not curative.

Psychosocial factors, especially depression and social support, may be associated with mortality in dialysis patients, poor adequacy of dialysis, low serum albumin, and low Hb. They may also interfere with a patient's access to medical care, their compliance with dialysis and drug treatments, their nutritional status and eating habits, and with hypothalamic-pituitary and immune functions. Conversely, psychosocial adaptation is crucial for long-term survival.

Assessing psychosocial morbidity in ESKD is problematic, and most instruments are confounded by medical co-morbidity common in these patients, the case mix and the effects of a physical intervention (dialysis) on patient responses.

Common effects include:

- depression
- anxiety
- behavioural changes
- short temper
- poor concentration
- lack of motivation
- anger
- denial.

## Psychosocial effects of starting dialysis in ESKD: depression and anxiety

### Depression

Incidence varies from 5 to 60%. True clinical depression is much less common than 'feeling sad'. Depression is related to loss of: kidney function, physical and cognitive abilities, sexual function, and of their role in family, work, and community life, and is initially triggered by the severe medical illness the patient has suffered. Symptoms include:

- depressed mood
- loss of interest
- change in appetite (increased or decreased)
- sleep disturbance
- fatigue
- aches and pains
- difficulty concentrating
- loss of libido
- suicidal ideation
- feelings of worthlessness or guilt
- psychomotor agitation or retardation.

Some of these can of course be a consequence of uraemia. Depression scores are reduced with higher dialysis adequacy. Daily dialysis provides excellent psychological rehabilitation. Post-dialysis fatigue is also associated with depression.

Treatment involves awareness, early assessment, counselling, and drug treatment as appropriate:

- Tricyclic antidepressants can worsen hypotension, and have significant anticholinergic side effects, and can cause cardiac conduction disturbances.
- Selective serotonin reuptake inhibitors can cause GI disturbance, tremor, headache, and nervousness, but are generally better tolerated than tricyclics. Although cleared by the liver, the dose is generally reduced. Fluoxetine has been most widely used in ESKD, but also paroxetine and citalopram
- Selective norepinephrine reuptake inhibitors such as venlafaxine should probably be avoided as they are renally excreted, with active metabolites also potentially renally excreted, which can cause fits.
- Monoamine oxidase inhibitors are best avoided in ESKD.

### Anxiety

Reported in 50–70% of ESKD patients, and is related to social status, work, long-term health, early mortality, financial circumstances, and dialysis access. Usually managed by counselling, cognitive or behavioural therapy, and stress reduction techniques.

Dementia is an increasing problem in the ESKD population and can present as depression or anxiety.

## **Psychosocial effects of starting dialysis in ESKD: others**

### **Body image**

Is closely associated with self-esteem and easily perturbed in ESKD. Can result in a variety of emotional reactions. Often viewed very differently by staff (a 'good' fistula may be disfiguring to the patient).

### **Social support**

Has been strongly related to survival in most chronic illnesses. Family problems are common in ESKD. Lack of social support is an important factor in failure of CAPD and transfer to HD. May be viewed negatively in the form of dependency and lack of independence.

### **Sexual dysfunction**

Very common in ESKD. Up to 65% of patients never have intercourse, and half of these would like to do so. Associated with anxiety and depression, and also with hyperprolactinaemia, hyperparathyroidism, vascular disease, neuropathy, antihypertensive drugs, diabetes, and possibly zinc deficiency. For young patients the issue of fertility often arises.

### **Non-compliance**

Found in 2–50% of patients. Often due to differing beliefs (of the patient) in the effectiveness of the treatment, lack of knowledge and education, or unpleasant side effects. Associated with increased risk of death. Can often be overcome by improved communication and patient education. Also related to the relationship between the patient and staff (patients who don't like their nurses are less compliant). Increasingly referred to as concordance.

### **Quality of life measurement**

Essentially subjective. Scoring systems need to be disease-targeted, with appropriate control populations. Quantitated using KDQOL (kidney disease quality of life) primarily. Other measures include Karnofsky index, Beck depression inventory, Illness Effects Questionnaire, Sickness Impact Profiles, and SF-36 health survey. Elderly patients generally have the same outcome measures as younger patients. Quality of life improves when patients have the freedom of choice of modality of dialysis.

### **Others**

ESKD affects patients' ability to travel, have holidays, obtain life insurance, loans, and mortgages. These issues are often not raised with medical staff, but may be of great concern to the patient. Dialysis units should be able to help patients with these issues rapidly, and without giving conflicting advice. The effects of ESKD on the patient's family are also important, both for their own physical and mental health, and for that of the patient.

Mental and physical well-being of dialysis staff can also affect, and be affected by, that of the patients.