

Vital

CKD

KEEPING KIDNEYS HEALTHY

*Your essential reference
for the diagnosis and management of
Chronic Kidney Disease*

Dr Rob Higgins

*Consultant Nephrologist, University Hospitals,
Coventry and Warwickshire NHS Trust*



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in primary care*

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Introduction

Dear Colleagues

Welcome to Vital Chronic Kidney Disease

For many years kidney disease was thought to be rare, and was the preserve of those incredibly clever nephrologists who followed up all their patients for life in specialist clinics. Now it's apparent that up to 10% of the population may have some type of chronic kidney disease. Importantly, this book explores the debate surrounding the question of whether all these people really do have a 'disease'. In any case, their care is not especially difficult. All that is required in the majority of cases are occasional blood and urine tests, and careful treatment of blood pressure. Most do not need to see a nephrologist.

The book is divided into nine chapters with topics clearly presented. The detailed **contents list** will help you find your way around with ease. At the end of each topic you will find one or more **vital points** to give you essential information in just a few words. Most chapters also contain sections on **patient and carer information** that can be photocopied and enlarged for your patients.

You will also find useful **appendices** and other information at the end of the book, including a glossary, useful addresses, websites and contacts, and references and further reading. We would welcome your comments or suggestions for improvements.

This book aims to remove any remaining mystique around kidney disease and its treatment. Practitioners in primary care should be able to care for patients with chronic kidney disease confidently, make appropriate referrals to secondary care, and understand better what secondary care had in mind when they sent the patient back for shared care or follow-up.

Rob Higgins

1

Kidney basics

- The two primary functions of the kidneys are:
 - ◆ To maintain the body's salt and water balance, and to keep the blood levels of various minerals stable
 - ◆ To excrete waste products
- About 25% of the cardiac output at rest goes through the kidneys. There are about 1 million filters, called glomeruli, in two normal kidneys
- Each glomerulus is about the size of a pinhead and contains a network of delicate blood vessels and supporting cells
- The glomeruli filter about 100 ml of plasma per minute in a normal person – about 140 litres in 24 hours
- The tubules in the kidneys then reabsorb about 138 litres of this filtrate, so that the remaining 2 litres is excreted as urine
- In order to perform these functions, the kidney has to be able to respond very quickly to changes in blood pressure and the amount of salt and water in the body
- The kidneys also have three other functions, which are reflected in the problems that can occur if someone has chronic kidney disease (CKD). These functions are:
 - ◆ Control of the blood pressure through salt and water balance, and renin production
 - ◆ Control of the haemoglobin level by sensing oxygen delivery and secreting erythropoietin (EPO)
 - ◆ Maintenance of calcium balance, by producing activated vitamin D
- The kidneys affect the blood pressure, and high blood pressure affects the kidneys, so there can be a 'vicious circle' of cumulative damage

It will become apparent as you read through *Vital Chronic Kidney Disease* that the clinical importance of CKD is about circulatory disease, and not just the

development of kidney failure. The presence of CKD helps identify those people who are likely to benefit most from cardiovascular risk factor reduction, and is complementary to other well known risk factors such as blood pressure and cholesterol levels.

PATIENT AND CARER INFORMATION:

KIDNEY BASICS

- The kidneys produce urine. This is a very complex job. The body cannot tolerate even tiny changes in its chemical make-up and water content, yet people eat and drink quite different amounts of food and fluid every day. So the kidneys have to adjust to everything that comes their way
- Urine is produced in order to:
 - ☐ Regulate the amount of salt and water in the body
 - ☐ Maintain the levels of minerals in the blood to within very tight limits
 - ☐ Remove waste products from all the tissues of the body
- The kidneys do much more than produce urine:
 - ☐ Around the tubes in the kidney are cells that sense the oxygen level and send a chemical message to the bone marrow if it needs to produce red blood cells to carry more oxygen in the blood (see p. 61 for more details)
 - ☐ The kidney converts inactive vitamin D to active vitamin D, which is important in maintaining stable calcium levels in the blood and keeping the bones healthy (see p. 63)
 - ☐ The kidneys sense the level of blood pressure and try to maintain a stable blood pressure by controlling the level of salt and water in the body, and also by secreting a chemical messenger that can tighten or relax blood vessels

PATIENT AND CARER INFORMATION:

THE KIDNEYS AND THE CIRCULATION

- The kidneys are a vital part of the circulation, which also consists of the heart and the blood vessels, running to every part of the body
- Problems with the kidneys can affect the circulation in all parts of the body, mainly by increasing the level of blood pressure. Heart attack, heart failure and stroke are possible consequences
- Because the kidneys can damage the circulation and the circulation can damage the kidneys, a 'vicious circle' of increasing damage in both areas may develop
- The risk of developing circulation problems is affected by the blood pressure, cholesterol level and kidney function. The importance of blood pressure was first recognised in the 1950s, and cholesterol soon after. Further research since the 1990s has added CKD as an important additional marker of risk
- One in three people will develop a serious problem in their circulation during their lives
- The good news is that by measuring blood pressure and cholesterol levels, and checking for CKD, it is increasingly possible to identify people at risk. These people are now able to benefit from increasingly effective preventative treatments

WHAT IS CKD AND IS IT IMPORTANT?

CKD is the abbreviation for chronic kidney disease. Each of these three words will be examined in turn. Some nephrologists are unhappy with the term CKD as 'chronic' is often misunderstood by patients. It also is debatable whether all CKD patients actually have a disease. But it looks as though we will have to use this term for the time being.

Chronic

- Chronic means the abnormality is sustained for at least 3 months
- Isolated urinary tract infection does not mean someone has CKD
- Acute renal failure, or decompensation of kidney function during an episode of heart failure or dehydration, does not constitute CKD, although the patient may have CKD if their 'baseline' or usual kidney function is abnormal

Kidney

- In CKD there has to be some abnormality attributable to the kidneys, either reduced kidney function, a structural abnormality, haematuria or proteinuria
- Bladder disease is not CKD unless there is ascending infection or ureteric obstruction that causes problems in the kidneys themselves
- Haematuria can come from the bladder or the kidneys, so it is technically possible that someone could be classified as having CKD on the basis of haematuria coming from the bladder. However, this is not too important in clinical practice, as it is proteinuria that is a much more important trigger to enhanced monitoring and investigation

Disease

- One definition of disease is 'illness or sickness often characterised by typical patient problems (symptoms) and physical findings (signs)'
- Many people with CKD do not have symptoms. The only physical finding may be an abnormal urine test or an abnormal blood test result
- CKD is very common in older people. It is uncertain whether older people with CKD stage 3 have a 'disease' or whether they have 'normal ageing'
- 'Normal ageing' is a concept that is hard to define. It is unfashionable in an age when many variations in the human condition are 'medicalised' by being given diagnostic labels for which new pharmaceutical markets are then developed (see p. 25)

HOW IS CKD DIAGNOSED?

In order to diagnose and to classify CKD into stages only a few pieces of information are required. They are:

- Renal function, measured by estimated glomerular filtration rate (eGFR)
- Proteinuria, measured by urine dipstick and urine protein to creatinine ratio (PCR)
- Haematuria, measured by dipstick and/or urine microscopy
- Kidney size and structure, measured by ultrasound (not required in everyone)

Unfortunately each of these variables is not quite so simple to measure accurately as may appear at first sight. Complications and uncertainties in testing and in the interpretation of data will be examined later (see rest of chapter).

VITAL POINTS

- * It is not necessary to screen the entire population for CKD*
- * Testing for CKD should be performed in patients with high blood pressure, diabetes, any known circulatory disease (eg stroke, heart attack or heart failure), family history of kidney disease, emergency admission to hospital or blood tests being performed for any other reason*
 - * The primary test for CKD is measurement of blood creatinine level as this will identify those in CKD stages 3–5*
 - * Much of CKD management is about developing the treatment pathways in people who are already having blood tests rather than going out and checking for kidney disease in new population groups*

eGFR

- eGFR stands for 'estimated glomerular filtration rate', the rate at which plasma is filtered by glomeruli in the kidneys
- There are several methods for measuring renal function. The gold standards are elimination methods, for example a compound labelled with a radio-isotope is injected into the blood and a series of blood samples are then taken to measure its clearance. This is called an 'isotope GFR' and is seldom used clinically
- Measurement of creatinine clearance by a 24-hour urine collection is inaccurate and is now seldom performed
- The blood urea level can effectively be ignored as a measurement of renal function as it is affected by fluid status
- The prescribing of many drugs should be adjusted if the GFR is markedly reduced. However, eGFR calculated from the Modification of Diet in Renal Disease (MDRD) equation normalises renal function to body surface area (ie ml/min per 1.73 m^2), whereas prescribing information for most drugs is based on the GFR as an absolute value (ie ml/min). Therefore, if prescribing depends critically on the GFR value, either the eGFR should be converted to ml/min using the patient's body surface area or another method used, such as creatinine clearance estimation by the Cockcroft–Gault equation
- The blood level of creatinine may vary in an individual by 10–20% depending on the state of hydration and whether a meal with meat has recently been eaten (muscle, ie meat, contains creatinine). It is slightly more accurate for eGFR to be estimated on a fasting morning blood sample, but this is not a routine recommendation

VITAL POINTS

- * *eGFR is an estimation of renal function obtained from a measurement of the blood creatinine level, and the patient's age, sex and ethnicity*
- * *The normal eGFR is about 75–125 ml/min per 1.73 m^2 in young adults, and falls by about 1 ml/min per 1.73 m^2 per year*

VITAL POINTS (cont'd)

*** The normal eGFR in people aged 80 years is therefore about 25–85 ml/min per 1.73 m². It is not clear whether older people with eGFR of 25–50 ml/min per 1.73 m² are ‘normal’ or not (see p. 25)**

*** It is not just the level of eGFR that is important, it is also the rate of change. So an eGFR that falls from 40 to 35 ml/min per 1.73 m² over 5 years is less of a concern than an eGFR that falls from 50 to 45 ml/min per 1.73 m² over 2 years**

The table shows examples of eGFR and blood creatinine levels. These are real estimations of eGFR and creatinine levels, but note that there are differences between laboratories in the methods for measuring creatinine that can affect the derived eGFR slightly. The examples in the table have been chosen to illustrate the large differences in eGFR between individuals of different age, sex and ethnicity even when their respective creatinine levels are the same.

Blood creatinine (μmol/l)	Sex	Age (years)	Ethnicity	eGFR (ml/min per 1.73 m ²)	CKD stage*
120	Male	18	Black	103	1
	Male	55	White	68	2
	Female	92	White	46	3A
175	Female	27	South Asian	33	3B
	Male	40	White	41	3B
	Female	77	White	27	4
340	Male	20	Black	23	4
	Male	65	Black	14	5
	Female	95	White	12	5

*Note that CKD stages 1 and 2 also require other evidence of kidney disease.

Proteinuria

- Twenty-four-hour urine collections for protein are no longer necessary as they are notoriously inaccurate. If protein is filtered through the glomerulus, it will be lost at a rate equivalent to the filtration of creatinine, whatever the eventual urine volume. The albumin to creatinine ratio (ACR) is now preferred – this adjusts the protein level for the volume and concentration of urine

- The PCR (protein to creatinine ratio) is measured on a small single urine sample – 10 to 20 ml in a plain container is enough. It should be measured when the dipstick test is + or more
- A PCR of >45 mg/mmol is abnormal (the reference range may vary slightly between laboratories)
- The PCR is about 1/100th of the 24-hour urinary protein excretion in grams. So a PCR of 100 mg/mmol is roughly equivalent to proteinuria of 1 g/24 hours, and 45 mg/mmol is equivalent to about 0.5 g/24 hours
- Some people have small amounts of protein in their urine when active during the day that are not present first thing in the morning. A morning specimen is therefore more helpful in excluding low levels of proteinuria
- The routine urine test performed when screening people with diabetes is the ACR. This is confusing and rather inconvenient, as the PCR measures proteins additional to albumin in the urine, and the result is usually higher than the ACR
- Urine ACR >30 mg/mmol should be considered positive for proteinuria (roughly equivalent to a PCR of 45 mg/mmol)

VITAL POINTS

- * *Dipstick analysis for protein is indicated as part of the initial assessment of patients with newly discovered eGFR <60 ml/min per 1.73 m², haematuria, hypertension, oedema, heart failure and suspected multi-system disease (eg systemic lupus erythematosus (SLE), see p. 55)*
- * *Dipstick analysis for protein is also indicated as part of annual monitoring of patients with previous evidence of proteinuria, and in patients with diabetes*
- * *Urine protein should be quantified by the ACR if the dipstick urine protein test is positive (1+ or greater)*
- * *Urine ACR >30 mg/mmol should be considered as positive for proteinuria*

VITAL POINTS

- * Microalbuminuria is used to screen people with diabetes for early signs of diabetic nephropathy and is not a screening test for CKD*
- * Urine albumin should be measured using a laboratory method, preferably on an early morning urine sample. If dipsticks are used to detect urinary albumin, positive tests should be followed by laboratory confirmation*
- * Patients should not be tested for microalbuminuria during an inter-current illness*
- * ACR >2.5 mg/mmol in a man or >3.5 mg/mmol in a woman is consistent with microalbuminuria*
- * Active urine infections can cause proteinuria, as well as CKD*
- * It is not necessary to send a mid-stream urine (MSU) sample for culture every time there is a positive test for proteinuria: reviewing previous results will determine whether urine should be sent for culture*

Haematuria

The National Institute for Health and Clinical Excellence (NICE) guidance published in 2002 states that referral to a urology haematuria clinic should be made for anyone with macroscopic haematuria or anyone with microscopic haematuria aged over 50 years. This guidance was refined by a joint statement on the initial management of haematuria from the Renal Association (RA) and the British Association of Urological Surgeons (BAUS) in 2008. The joint RA/BAUS guideline states that:

- Haematuria may be 'visible' (macroscopic) or 'invisible' (microscopic), and if invisible may be symptomatic or asymptomatic
- Significant invisible haematuria may be diagnosed by dipstick test (one if symptomatic, two out of three if asymptomatic). 1+ is positive and trace can be regarded as negative. Routine microscopy to diagnose haematuria is not necessary
- Haematuria due to exercise or menstruation should be excluded
- Initial investigations for haematuria include exclusion of urine infection and measurement of eGFR, proteinuria and blood pressure

- Urological referral is warranted for all patients with visible haematuria or symptomatic in visible haematuria, and all patients with invisible haematuria aged over 40 years
- Nephrological referral may be indicated for:
 - ◆ Evidence of declining eGFR (by >10 ml/min at any stage within the previous 5 years or by >5 ml/min within the last 1 year)
 - ◆ Stage 4 or 5 CKD
 - ◆ Significant proteinuria (ACR ≥ 30 mg/mmol or PCR ≥ 50 mg/mmol)
 - ◆ Isolated haematuria (ie in the absence of significant proteinuria) with hypertension in those aged <40 years
 - ◆ Visible haematuria coinciding with intercurrent (usually upper respiratory tract) infection
- Patients not meeting criteria for referral to urology or nephrology, or who have had negative urological or nephrological investigations, need long-term monitoring because of the uncertainty of the underlying diagnosis. Patients should be monitored for the development of:
 - ◆ Symptoms when passing urine
 - ◆ Visible haematuria
 - ◆ Significant or increasing proteinuria
 - ◆ Progressive renal impairment (falling eGFR)
 - ◆ Hypertension (noting that the development of hypertension in older people may have no relation to the haematuria and therefore not increase the likelihood of underlying glomerular disease)

It is important that you are aware of the local guidelines for urology referral in haematuria. These should have been reconciled with your local guidance for CKD management, NICE guidance and the RA/BAUS statement.

Screening for haematuria

- Screening of unselected populations for haematuria by dipstick is not recommended
- Screening is indicated as part of the initial assessment in anyone who has:
 - ◆ Newly detected eGFR <60 ml/min per 1.73 m^2
 - ◆ Newly discovered proteinuria or
 - ◆ Suspected multi-system disease with possible renal involvement (see particularly rapidly progressive glomerulonephritis, p. 50)

- The laboratory will usually report the level of red blood cells in a urine sample as the number $\times 10^6/l$. Less than $25 \times 10^6/l$ is not normally of consequence, and may be regarded as normal. This value is equivalent to three to five red blood cells per high power field on microscopy, a way of reporting haematuria that has now been superseded

VITAL POINTS

- * *Haematuria is blood in the urine, and may be visible or invisible to the naked eye*
- * *The local urological pathway for the care of patients with macroscopic haematuria should be followed (see p. 16)*
- * *Screening of unselected populations for haematuria by dipstick is not recommended*
- * *Screening is indicated as part of the initial assessment in anyone who has newly detected $eGFR < 60 \text{ ml/min per } 1.73 \text{ m}^2$, newly discovered proteinuria or suspected multi-system disease with possible renal involvement (see particularly rapidly progressive glomerulonephritis, p. 50)*
- * *The laboratory will usually report the level of red blood cells in a urine sample as the number $\times 10^6/l$ (less than $25 \times 10^6/l$ may be regarded as normal)*

IMAGING

Ultrasound

The results of ultrasound scans usually fall into one of several distinct categories:

- Two normal sized kidneys (they should be $>10 \text{ cm}$ lone or $>9 \text{ cm}$ in a very small person)
 - ◆ This is obviously the best result to have, but does not exclude acute renal disease, nephrotic syndrome, CKD stages 1–3 with minor kidney damage (there could be ongoing haematuria and proteinuria). CKD stages 4–5 caused by diabetic nephropathy is often associated with normal sized kidneys. Amyloid or other infiltrative kidney diseases (eg lymphoma) may also be associated with normal sized kidneys

- Two small kidneys (both <9 cm , except in a very small person)
 - ◆ This suggests long-standing kidney disease with damage to the kidneys. The kidney disease may be of any type, for example hypertension or chronic glomerulonephritis. Renal dysplasia or reflux nephropathy are causes of bilateral small kidneys, especially in younger people
- Unequal sized kidneys (>1.5 cm difference in size)
 - ◆ There are three main causes for this appearance. First, dysplasia affecting primarily one kidney – obviously this will be apparent from childhood onwards. Second, reflux nephropathy, the ultrasound appearances may be apparent from an early age (see p. 45). Third, renal artery stenosis, which is most often due to atheromatous disease and is seen in older people who are known to have vascular disease elsewhere, or as smokers (see p. 48)
- Dilated upper tract
 - ◆ If the collecting system of one or both kidneys is dilated, further investigation is needed. Common causes include bladder outflow obstruction due to prostatic hypertrophy and reflux nephropathy without obstruction to the urinary tract. Unilateral dilatation can also be due to a pelvi–ureteric junction (PUJ) obstruction. During pregnancy it is normal to have mild bilateral hydronephrosis. This does not require further investigation unless there are other features (eg recurrent urine infections, proteinuria that is not pregnancy-related)

VITAL POINTS

- * *Not everyone with CKD needs imaging of their kidneys*
- * *The kidneys should be at least 10 cm long, with right and left having no major difference in size*
- * *Renal ultrasound is the first test to request if imaging is indicated*
- * *The indications for ultrasound are: CKD stages 4 or 5, or CKD 1–3 with declining renal function; CKD with proteinuria, PCR >100 mg/mmol; recurrent urine infection, loin pain, suspicion of stone disease (consider whether a bladder ultrasound should be requested as well); family history of reflux nephropathy or polycystic kidney disease*

Other types of imaging

Other imaging of the urinary tract may be performed. These tests are usually requested in secondary care.

- The intravenous pyelogram (IVP), or intravenous urogram (IVU), used to be the primary investigation to image kidneys but is seldom performed in patients with CKD, although it still has a role in the diagnosis of acute stone disease. IVU may sometimes be performed using a CT scanner rather than plain x-rays. This may give useful additional information about the structure of the urinary tract
- CT scans of the urinary tract can provide information about structural lesions and can also be used to image the renal arteries. A diagnostic angiogram (injecting radiographic contrast into the renal artery from a catheter passed up the femoral artery) has been superseded by CT or MR angiograms. Angiography should only be needed when other imaging shows renal artery stenosis and angioplasty is being planned
- Magnetic resonance angiography (MRA) is used to image the renal arteries. Either CT or MR scans may be used to image the renal arteries. The choice depends partly on local availability of equipment and also on any risk of the intravenous contrast used for CT scanning
- There are several different types of isotope imaging that can be used in CKD. These will be requested in secondary care
 - ◆ Isotopic measurement of GFR is used when it is really important to quantify renal function more precisely than by eGFR
 - ◆ Functional studies of the kidneys can be obtained with diethylene triamine penta-acetic acid (DTPA) scans, where the gamma camera can measure the rates of excretion of isotope by each kidney and confirm functional obstruction
 - ◆ A dimercaptosuccinic acid (DMSA) scan can show functional renal tissue in detail and may be useful in confirming the presence of scars in the renal cortex that may occur in reflux nephropathy

3

Classification of CKD

The table shows the original classification of CKD proposed by the National Kidney Foundation of America, and adopted in the Royal College of General Practitioners (RCGP)/RA guidelines for CKD (www.renal.org/CKDguide/ckd.html)

CKD stage	eGFR	Other features (ml/min per 1.73 m ²)
No CKD	>60	No features kidney disease
1	>90	Evidence of kidney abnormality
2	60–89	Evidence of kidney abnormality
3	30–59	Defined by eGFR alone
4	15–29	Defined by eGFR alone
5	<15	Defined by eGFR alone

- When this classification of CKD was first proposed it was noted that the importance of reduced eGFR was uncertain in certain groups of people, such as the very young, the very old and vegetarians (as they have a reduced creatinine intake). These uncertainties are not fully resolved. The CKD classification is not generally used in children, and it remains unclear whether some elderly people with CKD have ‘normal ageing’ of their kidneys (see p. 25).
- Further sub-classification of CKD has been suggested, and some modifications were endorsed by a UK national consensus meeting in Edinburgh in February 2007. Time will tell whether they are universally adopted
- The first proposed modification was an extra subdivision according to eGFR, so that there would be CKD stage 3A (eGFR 45–59 ml/min per 1.73 m²) and CKD stage 3B (eGFR 30–44 ml/min per 1.73 m²). This change is supported by those who point out that there is a large group of elderly people in CKD stage 3A that does not seem to have a major increase in mortality rate
- The second proposed modification is the addition of a ‘P’ suffix to the CKD stage if someone has significant proteinuria, such as a PCR >100 mg/mmol. So someone with eGFR 28 ml/min per 1.73 m² and

PCR 120 mg/mmol would be CKD stage 4P. This proposal is supported by those who say that the presence of proteinuria is a powerful marker of significant kidney disease and represents an additional risk over and above their eGFR level

VITAL POINTS

- * The diagnosis of CKD stages 1 and 2 requires additional evidence of kidney abnormality, as well as demonstrating an eGFR of 60–99 ml/min per 1.73 m²*
- * This abnormality may be proteinuria, haematuria or abnormal structure of the kidney on imaging (eg an ultrasound scan)*
- * CKD stages 3–5 (eGFR <60 ml/min per 1.73 m²) are defined on the basis of eGFR alone, regardless of whether there is evidence of other kidney abnormality*

EXAMPLES OF CLASSIFICATION OF CKD

- Check you are aware of some common misconceptions in CKD classification! Answers follow

- Case 1** A 65-year-old man with heart failure is unwell with mild pulmonary oedema and a chest infection. His serum creatinine is 155 µmol/l, giving him an eGFR of 44.7 ml/min per 1.73 m². What CKD stage does he have?
- Case 2** A 95-year-old lady has a routine check-up and has a creatinine of 174 µmol/l. What do you think her eGFR is likely to be at this level of creatinine, and how will this affect her?
- Case 3** A 25-year-old man has a blood creatinine level of 85 µmol/l, giving an eGFR of 144 ml/min per 1.73 m². A renal ultrasound was performed because of a family history of polycystic kidneys. This scan confirms polycystic kidneys. Does he have CKD?

Answers

- 1 Although an eGFR of 44.7 ml/min per 1.73 m² puts him in the middle of CKD stage 3, there is only one estimation of renal function,

taken when there is an acute illness. So the renal function might be temporarily worse than usual, and he should have another blood test when at his best, and 3 months later, to establish the level of any chronic kidney disease.

- 2** Her eGFR is 26 ml/min per 1.73 m², putting her into CKD stage 4. However, this is within the 'normal range' for her age, at least the normal range as defined by mean minus two standard deviations (see p. 26). The effect on her life expectancy may be minimal, but she should be assessed in light of other known comorbidities and risk factors.
- 3** He has CKD stage 1. Even with this excellent eGFR, the structural abnormalities in the kidneys are enough for him to be defined as having CKD.

4

Epidemiology of CKD

- The table shows the percentages of the adult population who had CKD in Coventry (Raymond *et al.*, 2007) using blood samples taken between 2000 and 2003 (CKD stage 3A, eGFR 45–59 ml/min per 1.73m²; CKD stage 3B = eGFR 30–44 ml/min per 1.73 m²). These results are similar to those obtained in other epidemiological studies, and show that CKD is twice as common in diabetic patients
- It can be seen from the table that marked CKD (ie which may go to require dialysis, and used to be called chronic renal failure, is still quite rare)

CKD stage	Total (%) (N=106,366)	Diabetic (%) (n=10,286)
No CKD		
and stages 1+2	88	75
3A	6	12
3B	3	7
4	2	4
5	0.7	2

VITAL POINTS

- * *Studies in Europe and the USA have consistently shown that CKD increases in frequency and severity with age, diabetes and non-white ethnicity*
- * *A high proportion of very elderly people have CKD according to their eGFR but are not at a survival disadvantage solely by virtue of CKD, so it is questionable whether they have kidney disease*

- Figure 4.1 shows the percentages of the adult population who had CKD in using blood samples taken between 2000 and 2003 (CKD stage 3A, eGFR 45–59 ml/min per 1.73 m²; CKD stage 3B, eGFR 30–44 ml/min per 1.73 m²)
- CKD becomes more frequent with age, so that 50% of people over the age of 85 years had at least CKD stage 3 in this study
- It is questionable whether 50% of very elderly people really do have kidney disease, especially when they are not at a survival disadvantage (see Figure 4.3)

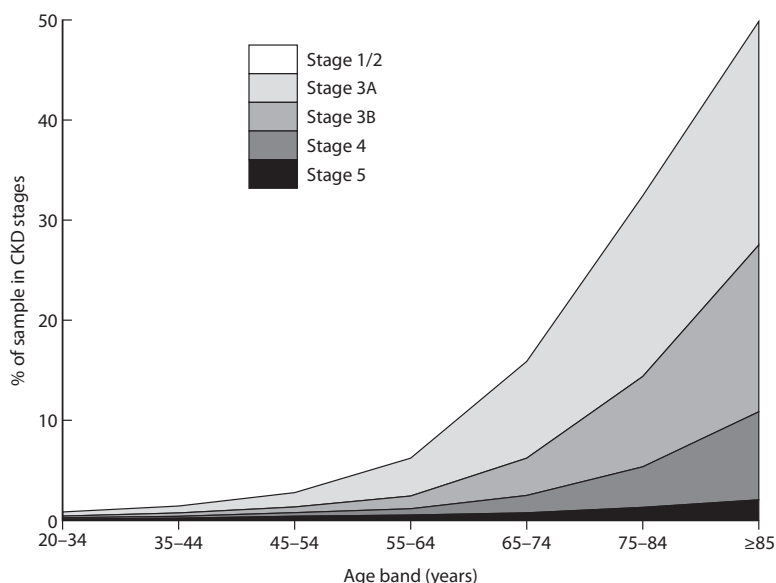


Fig 4.1 The percentages of the adult population who had CKD in using blood samples taken between 2000 and 2003 (CKD stage 3A, eGFR 45–59 ml/min per 1.73 m²; CKD stage 3B, eGFR 30–44 ml/min per 1.73 m²) (adapted from Raymond *et al.*, 2007, with kind permission)

- Figure 4.2 shows the same data for population eGFR as in Figure 4.1, but for each age group the mean eGFR is shown (the upper sloping line), together with one and two standard deviations below this
- At age >85 years, in this study, the lower limit of ‘normal’ (mean value minus two standard deviations) was about 20 ml/min per 1.73m², ie CKD stage 4

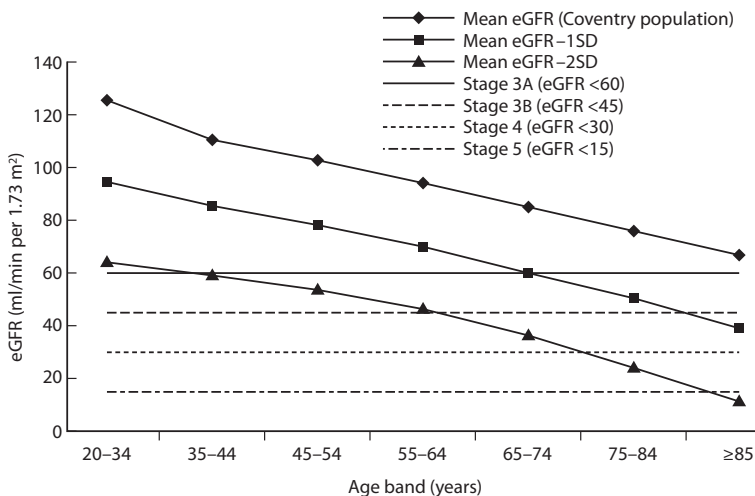


Fig 4.2 The same data for population eGFR as in Figure 4.1, but for each age group the mean eGFR is shown (the upper sloping line) together with one and two standard deviations below (adapted from Raymond *et al.*, 2007, with kind permission)

- These data are similar to those obtained in other studies, and question the validity of the CKD classification in the very elderly. However, the mortality rate for the very elderly in CKD stage 4 is increased compared with those in CKD stages 1–3, so the CKD classification probably has some relevance. However, in elderly people, CKD stage 3 is not associated with a major increase in mortality rate

MORTALITY RATE

- Figure 4.3 shows the mortality rate in the adult population in Coventry using blood samples taken between 2000 and 2003 (CKD stage 3A, eGFR 45–59 ml/min per 1.73 m²; CKD stage 3B, eGFR 30–44 ml/min per 1.73 m²)
- Figure 4.3 separates the effects of age and CKD stage on mortality rate. Although the elderly were much more likely to die than the young, the effect of CKD was less marked with only a modest effect, if any, on mortality for CKD stage 3A. Younger people, by contrast, were less likely to die than older people, but CKD stages 3A and 3B did have a significant effect on mortality rate

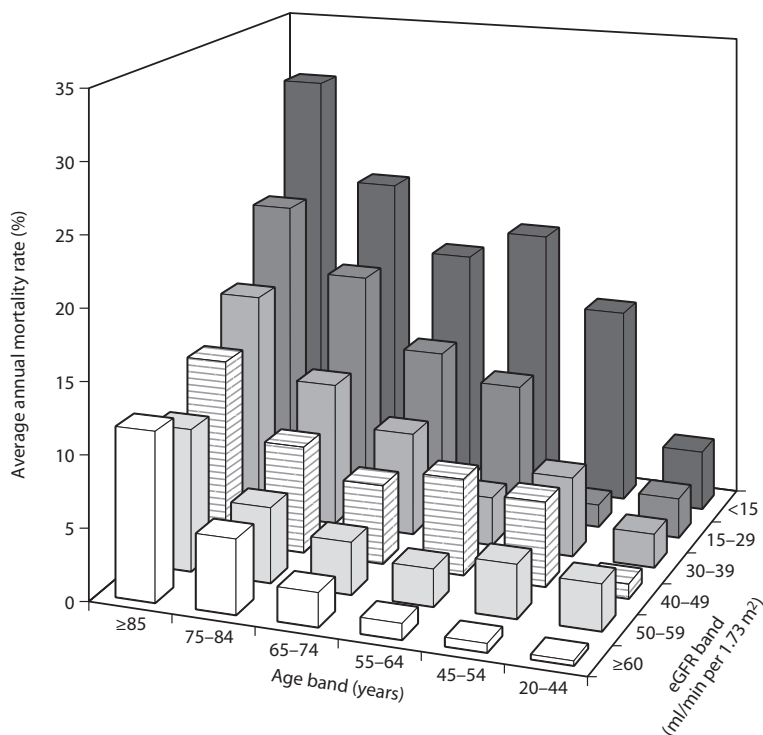


Fig 4.3 The mortality rate in the adult population in Coventry using blood samples taken between 2000 and 2003 (CKD stage 3A, eGFR 45–59 ml/min per 1.73 m²; CKD stage 3B, eGFR 30–44 ml/min per 1.73 m²) (adapted from Raymond *et al.*, 2007, with kind permission)

ETHNICITY

- Studies in Europe and the USA have consistently shown that CKD is more frequent in black people and those of south and east Asian origin
- In the UK, CKD stage 5 is approximately three times more frequent in people of south Asian ethnicity than in those of white ethnicity, because of an increased incidence of diabetes and also to an increased incidence of renal dysplasia and almost all types of glomerular disease. Whether this is due to the incidence of these diseases regardless of severity, or whether this is due to increased rate of progression to clinically apparent disease is not clear. There is good evidence that once

diabetic nephropathy has developed, it will progress faster in those of south Asian ethnicity

- In those of black ethnicity, CKD stage 5 is again about three times more frequent than in those of white ethnicity. This is explained by an increased risk of diabetes, hypertension and some glomerular diseases
- On a worldwide basis, many ethnic groups have an increased rate of CKD compared with those of white ethnicity; indeed, it has been speculated that the atypical ethnicity is white, where CKD is less frequent than in other population groups
- Some studies show that once on dialysis, people of south Asian and black ethnicities have better survival rates than those of white ethnicity, increasing further the tendency of the dialysis population and transplant list to have a high prevalence of non-white ethnicities

DEPRIVATION

- A recent study from the Renal Registry in the UK (Caskey *et al.*, 2006) has suggested that though progression to CKD stage 5 was not directly associated with social deprivation, there was an association with worse outcomes because increased comorbidities were associated with social deprivation

REFERENCES

- Caskey FJ, Roderick P, Steenkamp R *et al.* (2006) Social deprivation and survival on renal replacement therapy in England and Wales. *Kidney International* 70: 2134–40
- Raymond NT, Zehnder D, Smith SCH *et al.* (2007) Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. *Nephrology Dialysis Transplantation* 22: 3214–20

5

Management of CKD

- The principles for the management of CKD are well established in the RCGP/RA guidelines, but the operational details may vary from place to place around the UK. The information given here is not intended to replace or conflict with local guidelines, which should be followed
- Most local CKD guidelines have been reduced to brief flow sheets. The information here and elsewhere in *Vital Chronic Kidney Disease* will add background to your local guidelines

VITAL POINTS

- * *Pay attention to diet and lifestyle (see p. 68)*
- * *Manage blood pressure and cholesterol (see pp. 33 and 38)*
- * *Consider aspirin if there is >20% risk of cardiovascular disease in the next 10 years, so long as blood pressure <150/90 mmHg*
- * *Give vaccination against flu each year, and give a single vaccination against pneumonia caused by the pneumococcus bug*
- * *Treat anaemia if present (p. 60)*

MANAGEMENT OF STAGES 1–3

- CKD stages 1–3 are normally managed in the GP surgery, and most people do not need to see a kidney specialist or have scans of their kidneys
- The eGFR should be measured each year together with the PCR or ACR if the initial level is high
- Most people in this category will not develop serious kidney disease

during their lifetime, and information to the patient about CKD should concentrate on the context of cardiovascular risk factor reduction

- Referral to a kidney specialist may be triggered if the eGFR falls over time, or if there is some other factor such as uncontrollable blood pressure or repeated kidney infections (see p. 56)

MANAGEMENT OF STAGES 4–5

- People with CKD stages 4 or 5 may go on to develop symptomatic kidney failure, and are at a higher risk of developing acute kidney failure than those with CKD stages 1–3
- These people will therefore need to know more about their kidney disease than those in CKD stages 1–3. Information might include an understanding of the risks of developing established renal failure and how to reduce the risks of acute renal failure (for example, avoiding volume depletion and getting prompt treatment for intercurrent infections)
- CKD stages 4 and 5 require more careful review of the medication someone is taking as side effects from treatment are more likely at this lower level of kidney function
- The RCGP/RA guidelines state that all people with CKD stage 4 or 5 should have their cases discussed by a kidney specialist or be referred to one. This would include many apparently healthy people aged >85 years, where the lower limit of ‘normal’ eGFR is within CKD stage 4. It is not clear from evidence pertaining to this specific age group how many patients will benefit from this guidance for mandatory referral/discussion with a nephrologist
- Note that if someone has a deterioration in eGFR during an acute illness, this does not change their CKD classification, which depends on the sustained, chronic, level of eGFR. So if someone’s usual eGFR is 35 ml/min per 1.73 m², and this falls to 22 ml/min per 1.73 m² during a chest infection and then recovers to 32 ml/min per 1.73 m², that patient has CKD stage 3. They do not have CKD stage 4 and did not temporarily have CKD stage 4 during the acute illness
- If there is a progressive loss of kidney function there may be a risk that someone will develop established renal failure – stage 5 CKD. A decision will need to be taken whether to proceed to dialysis, and if so, which type of dialysis. If someone is suitable for a kidney transplant, they will

need an assessment by a specialist. If someone in the family wishes to give a kidney transplant they will be carefully assessed. All these choices are dealt with in greater detail in the resources listed on p. 90

REFERRAL TO A SPECIALIST

Not everyone with CKD needs to see a kidney specialist. The basic principles are that:

- CKD stages 1–3 can be managed in primary care, so long as they are uncomplicated
- CKD stages 4–5 should be referred or discussed with a nephrologist (but do not all need to be referred, see previous page)

Immediate referral to a nephrologist (same day)

- Suspected acute renal failure, which may be superimposed on existing CKD
- Newly detected CKD stage 5, unless known to be stable
- Accelerated or malignant phase hypertension with suspicion of kidney disease (see p. 35)
- Hyperkalaemia ($K^+ > 7.0$ mmol/l)

Urgent referral to a nephrologist (within a week)

- Nephrotic syndrome (p. 52)
- Newly detected CKD stage 4, if appropriate to refer in view of comorbidities
- Multi-system disease (eg SLE) with evidence of kidney disease
- Hyperkalaemia ($K^+ 6.0$ – 7.0 mmol/l) after exclusion of artefactual and treatable causes

Urgent referral to a urologist

- Urology referral may be appropriate in the first instance if there is haematuria and a bladder or kidney cancer is suspected (see p. 32), or if there are problems such as kidney stone or incontinence
- In some people with microscopic haematuria or recurrent urinary tract

infections, it is not always easy to decide to whom to refer in the first instance. Referral to a nephrologist is more likely to be indicated if there is significant proteinuria, or if the eGFR is reduced

Referral to a haematuria clinic

- Urology referral is indicated for:
 - ◆ All patients with visible haematuria (any age)
 - ◆ All patients with symptomatic visible haematuria (any age)
 - ◆ All patients with asymptomatic invisible haematuria aged ≥ 40 years

Other indications for referral (within a month)

- Stages 1–2
 - ◆ Structural renal disease that might require a long-term management plan or advice about family screening, such as polycystic kidney disease (see p. 45) or reflux nephropathy (see p. 58)
 - ◆ Some patients with recurrent urinary tract infection (though urology referral may be more appropriate in many patients)
 - ◆ Symptoms that might be related to the kidneys, eg loin pain
 - ◆ Heavy proteinuria (PCR > 100 mg/mmol) or urgently in nephrotic syndrome (PCR usually > 300 mg/mmol with fluid retention; see p. 45)
 - ◆ Uncontrolled moderate/severe hypertension with evidence of kidney disease
- Stage 3
 - ◆ In addition to the indications for CKD 1–2
 - ◆ Decline in eGFR > 5 ml/min per 1.73 m^2 per year
- Stages 4–5
 - ◆ Many people with CKD stage 4 have significant comorbidity, for example heart failure (see p. 60). This does not mean that they should not be referred and seen at least once
 - ◆ Some people who are approaching end-of-life care for non-renal conditions may also develop CKD stages 4–5. It may not be appropriate for them to see a nephrologist, but if renal function is deteriorating rapidly it may be worth considering the possibility of treating problems such as ureteric obstruction – relief from this can give some prolongation of life with reasonable quality in some people

- ◆ Patients with intrinsic renal disease who are not going to benefit from dialysis may still benefit from seeing a nephrologist for treatment of anaemia (see p. 60) and help with other palliation of symptoms of renal failure

Information to include with the referral to a nephrologist

- A list of known previous measurements of blood creatinine level. This is especially important if there have been abnormalities for many years, even if the elevation in creatinine was only slight
- Medical history and list of prescribed drugs
- Blood pressure, ideally with some representative levels over the whole period of treatment if there is high blood pressure
- Results of urine dipstick and PCR if performed
- Other relevant investigations, including previous imaging of the renal tract. It may not be necessary to obtain up-to-date renal imaging if this is provided in a one-stop nephrology clinic – refer to local guidelines

MANAGEMENT OF HYPERTENSION

- Blood pressure should be measured at least annually in anyone with CKD and managed according to current British Hypertension Society and NICE guidelines
- The current British Hypertension Society definition of high blood pressure is greater than 140/90 mmHg, with a target level on treatment of <130/80 mmHg
- Treatment should be initiated at a level of more than 130/80 mmHg for those with PCR >100 mg/mmol, with a target level of <125/75 mmHg
- Home blood pressure monitoring machines may be a useful adjunct to monitoring, but need not be routinely advised to all patients
- Management of hypertension should include offering lifestyle advice, maintaining a normal body weight, taking aerobic exercise, reducing dietary sodium intake to <100 mmol/day (see p. 68 for examples), limiting alcohol intake to less than three units a day in men and two units a day in women
- Drug treatment will often involve using several agents from different classes

PATIENT AND CARER INFORMATION:

MANAGEMENT OF CKD

Everyone with CKD should have:

- A healthy diet and lifestyle
- Their blood pressure and cholesterol managed (see pp. 37 and 39)
- Aspirin to thin the blood if they already have had a heart attack or stroke, or are at particular risk of circulatory disease
- Vaccination against flu each year
- Assessment for treatment for anaemia

CKD stages 1–3:

- CKD stages 1–3 are normally managed in the GP surgery, and most people do not need to see a kidney specialist or have scans of their kidneys
- Blood should be taken to measure the kidney function (eGFR) each year, together with a urine sample to measure the protein level (PCR) if the initial level was high
- Referral to a kidney specialist may be triggered if the eGFR falls over time, or if there is some other factor such as uncontrollable blood pressure or repeated kidney infections

CKD stages 4–5:

- CKD stages 4 and 5 require more careful review of the medication someone is taking, as side effects from treatment are more likely at this lower level of kidney function
- Referral to a kidney specialist should be considered, though not everyone needs to see a specialist
- If there is a progressive loss of kidney function, there may be a risk that someone will develop established renal failure – stage 5 CKD. A decision would then need to be taken whether to proceed to dialysis, and if so, which type of dialysis. Some people with other health problems may decide not to have dialysis. If someone is suitable for a kidney transplant, they will need an assessment by a specialist

- Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) are particularly beneficial, especially if someone has proteinuria (PCR >100 mg/mmol), diabetes with microalbuminuria or heart failure (see p. 36 for prescribing these agents in CKD)
- For people of black ethnicity, calcium blockers may be more effective than ACE inhibitors or ARBs in the first instance
- Patients with refractory hypertension, ie BP >150/90 mmHg on three types of antihypertensive drug, should be referred for specialist evaluation

VITAL POINT

Treatment of hypertension is arguably the most useful medical intervention that the medical team can make in someone with CKD

Malignant hypertension

- Hypertension in the malignant phase should be referred to hospital immediately
- Malignant phase hypertension is defined by end-organ damage, specifically loss of cerebral autoregulation with papilloedema and eventually fits. There could also be acute renal failure or heart failure
- There is not an exact level of blood pressure at which hypertension becomes malignant. Most people with malignant hypertension have a diastolic blood pressure in excess of 130 mmHg, but someone who is accustomed to a normal blood pressure can develop malignant phase if the blood pressure rises acutely
- One common cause of accelerated hypertension is someone stopping their medication for treatment of hypertension. This is one of the reasons why it is important for people to understand what hypertension is, understand why they have been prescribed medication and to be motivated to take it regularly

The safe use of ACEI/ARB

- Agents in these classes provide extra protection to the kidneys in CKD patients with increased blood pressure, especially if there is proteinuria. The reason for this is probably an effect on intra-renal blood flow over and above the effect on systemic blood pressure, further reducing the strain on glomeruli
- However, they may also cause a fall in eGFR/rise in blood creatinine level or hyperkalaemia
- The level of eGFR by itself is not a contraindication to the initiation of ACEI/ARB therapy. Known or suspected renal artery stenosis (eg if the patient is a known arteriopath and smoker) is a contraindication to the initiation of these agents, though some patients with renal artery stenosis may tolerate the agents and nephrologists will sometimes continue them in selected patients. This should not be attempted in general practice
- A blood potassium level above the upper limit of normal is a contraindication to the initiation of ACEI/ARB. It is sometimes possible to control the potassium level (eg lower it to <4 mmol/l with a loop diuretic) then add an ACEI or ARB
- The potassium and creatinine levels should be checked approximately 2 weeks after starting ACEI/ARB and also after any dose change, and thereafter at least twice a year
- An increase in creatinine level of up to 20% or fall in eGFR of up to 15% consequent on the drug is acceptable, although if the fall in eGFR/rise in creatinine is 10–15%, another blood test after further 2 weeks is advisable
- If the eGFR does fall by $>15\%$, the drug should be stopped and the eGFR re-checked. A nephrologist should advise on whether renal artery stenosis should be excluded
- If the potassium level is greater than 6.0 mmol/l, the ACEI/ARB should be stopped and attention given to other potassium-retaining drugs, eg spironolactone, amiloride, triamterene
- If someone taking ACEI/ARB has an acute illness and goes into hospital, these drugs are often stopped. Problems such as the vasodilation during a septic illness, or reduced cardiac output during an episode of heart failure, are likely to add to the effects of the ACEI/ARB on the renal circulation and cause a marked rise in creatinine level/fall

in eGFR. In many cases, these drugs can be restarted after discharge from hospital when the patient is back to their usual condition

PATIENT AND CARER INFORMATION:

HIGH BLOOD PRESSURE

What is high blood pressure?

- The current definition of high blood pressure agreed by the British Hypertension Society (hypertension is the medical term for high blood pressure) is blood pressure greater than 140/90 mmHg
- The first number (140) is the highest pressure after a heartbeat, and is called the systolic blood pressure. The second number (90) is the lowest pressure in-between heartbeats, and is called the diastolic blood pressure
- The pressure is measured by the height in millimetres (mm) it can push a column of mercury (Hg is the chemical symbol for mercury)
- Most people with high blood pressure feel completely well. Very severe high blood pressure can cause headaches and affect the vision, but this is rare. Some people get headaches with moderately high blood pressure, but they are in the minority

How should blood pressure be measured?

- The blood pressure varies from minute to minute, according to the body's need for oxygen
- The blood pressure should be measured after someone has been sitting quietly for 5 minutes
- It should be measured by the same person, on the same machine, at the same time of day and on the same arm
- Even if they do not feel stressed, the blood pressure may be higher in hospitals or clinics than in normal day-to-day life. This may be overcome by measurement of the blood pressure at home, which can be performed easily using a small machine

PATIENT AND CARER INFORMATION:

HIGH BLOOD PRESSURE (cont'd)

How should high blood pressure be treated?

- Drugs to treat high blood pressure are generally used if the blood pressure is 140/90 mmHg or more despite losing excess weight and taking lifestyle measures (see p. 68). The aim is to get the blood pressure down to 130/80, or 120/75 if someone has diabetes or a lot of protein in the urine
- For most people with kidney disease, taking either ACE inhibitor drugs or ARB drugs is particularly beneficial. ACE inhibitors have names that end in -opril (for example captopril) and ARBs have names that end in -sartan (for example losartan). There are several similar agents in each class, and doctors will choose whichever one suits someone best or is recommended for use in their locality
- For people of black ethnicity, a class of drug called calcium blockers may be more effective than ACE inhibitors or ARBs in the first instance
- Once someone has started on blood pressure drugs, they usually need to be taken regularly for life. Many people with CKD require a combination of several blood pressure drugs to get the desired effect

MANAGEMENT OF CHOLESTEROL

AND BLOOD LIPIDS

- Patients with established atherosclerotic disease should receive treatment for hyperlipidaemia according to the Joint British Societies Guidelines, ie a total cholesterol <4.0 mmol/l and LDL-cholesterol <2.0 mmol/l
- For those without known atherosclerotic disease, the target blood cholesterol in people with CKD is uncertain, and there has not been enough research with lipid-lowering therapy in CKD patients to

establish exactly who should be considered for statin therapy. Some large trials are under way to address this question

- The Renal Association has recommended that people with CKD who have an estimated 10-year risk of cardiovascular disease of >20% should have a total cholesterol level <5.0 mmol/l, and there is a more recent European recommendation of <4.5 mmol/l
- Standard risk calculators that estimate the future risk of developing cardiovascular disease have not been developed specifically for CKD patients. However, as CKD is so common in the elderly, large numbers of people with CKD stage 3 were probably included in the original research used to develop these calculators
- If statin therapy is to be administered, this can be done according to local guidelines as in someone without CKD. However, the risk of adverse effects from statins is probably higher in people with CKD. This applies especially to the risk of muscle inflammation in CKD stages 4–5

PATIENT AND CARER INFORMATION:

CHOLESTEROL

What is cholesterol?

- Cholesterol is a fatty substance, one of several different types of fat found in the body
- If blood vessels are damaged, cholesterol can be deposited, eventually causing narrowing. This is more likely to occur if the blood level of cholesterol is high
- A tendency to high cholesterol may run in families. A diet high in fat and cholesterol may lead to a high cholesterol level

The ideal cholesterol level

- The Renal Association (the UK national association of kidney specialists) has recommended that people with CKD who are at risk of disease in their circulation should have a total cholesterol level <5.0 mmol/l, and there is a more recent European recommendation of <4.5 mmol/l

PATIENT AND CARER INFORMATION:

CHOLESTEROL (cont'd)

The ideal cholesterol level (cont'd)

- Research in people without CKD has suggested that someone who is known to have disease in their circulation should have a total cholesterol <4.0 mmol/l

Diet for reducing cholesterol

- Foods that are high in cholesterol include dairy products, eggs, and the fatty parts of red meat. Many processed foods can contain a lot of cholesterol and the information on the labels should be checked
- The type of fats that increase blood cholesterol levels are often called 'saturated fats', while 'unsaturated fats' (which include olive oil) may be less harmful
- The aim with diet is to reduce the intake of harmful fats, and to maintain a balanced diet with the right amounts of protein, carbohydrate, and fresh fruits and vegetables

Drugs to reduce cholesterol

- If diet and losing weight do not bring the blood cholesterol down to acceptable levels, drugs may be used. The type of drug most often used reduces production of cholesterol in the liver, called 'statins'
- Statin drugs may have side effects. Some people feel generally unwell with nausea or sickness, and may have to stop the drug if this persists. Statins can cause aches and pains in the muscles – this is a serious side effect and should be reported to a doctor immediately

MANAGEMENT OF MEDICINES

- Spironolactone may cause life-threatening hyperkalaemia, and should not be used when the blood creatinine level is $>200 \mu\text{mol/l}$ or $\text{eGFR} <30 \text{ ml/min per } 1.73 \text{ m}^2$. In anyone with $\text{eGFR} <60 \text{ ml/min per } 1.73 \text{ m}^2$, the potassium level should be monitored carefully, especially if the patient is also on ACEI/ARBs, and spironolactone discontinued if there is hyperkalaemia (for more information on hyperkalaemia see p. 64)
- Diuretics may be used if there is salt and water retention with oedema. Loop diuretics can be used as in patients with no CKD, but it is best to combine their use with advice on salt restriction ($<100 \text{ mmol/24 hours}$), and fluid restriction depending on the circumstances (see p. 68)
- Non-steroidal anti-inflammatory drugs (NSAIDs) reduce renal blood flow and may be harmful to renal function in the long term. Therefore, they are best avoided in CKD stages 3–5. If someone does have ongoing pain without NSAID, it may be possible to use a milder agent or get specialist advice on other ways to control the pain. If NSAIDs are used, they should only be taken as little as possible, and avoided if someone is volume depleted or has a severe inter-current infection
- Paracetamol is safe in CKD in the standard doses. Opiates can be used, but especially in CKD stages 4–5, their half-life is increased and there is a risk of accumulation with drowsiness. Gabapentin, if indicated, can be used but the dose should be adjusted according to renal function – check the British National Formulary (BNF) (www.bnf.org/bnf/)
- For all other drugs, check the prescribing information. Further details of drugs with cautions for prescribing in renal impairment are given in appendix 3 of the BNF

VITAL POINT

*** *The medications administered to patients with CKD need to be reviewed carefully in light of the need to reduce dosage if renal function reduced, drugs that may be harmful to the kidneys in patients with CKD, drugs that may be especially beneficial in patients with CKD and potential interactions between drugs***

VITAL POINTS

- * It is even more important than usual that patients understand the rationale for taking their prescribed medications, report any problems, look after the medications properly and make sure they do not run out of drugs*
- * An email to a friendly local nephrologist can be a way of getting advice on prescribing in a stable patient*

Many prescribing issues are dealt with in other sections of *Vital Chronic Kidney Disease*:

- Hypertension (p. 33)
- ACEI and ARBs (p. 36)
- Hyperlipidaemia (p. 38)
- Aspirin (p. 29)
- eGFR (p. 13) is only a guide to the level of renal function when prescribing, and clearance estimation should be used if an accurate measurement of renal function is needed for safe prescribing

Over-the-counter medications and alternative therapies

- Caution needs to be used with the use of some drugs available over-the-counter, and alternative therapies
- Ibuprofen: see section on NSAIDs (p. 41). Topical NSAIDs may be absorbed through the skin and have systemic effects similar to systemic NSAIDs
- Omeprazole and ranitidine: there are no additional cautions in CKD, although interactions between omeprazole, warfarin and ciclosporin should be remembered
- St John's wort: this may interact with other prescribed medications and so its use should be carefully reviewed
- Homeopathic medicines: these seem unlikely to have adverse effects and can probably be used by patients with CKD without restriction
- Herbal and similar remedies: many nephrologists advise caution with herbal remedies, especially in CKD stages 4 and 5. This is because these

remedies may contain agents that could accumulate with reduced renal function and have adverse effects. However, details of the risks of particular agents are not fully documented. Many nephrologists take the view that it is the responsibility of those who market these agents to establish their safety

6

Kidney diseases

It is not possible or desirable to produce a full textbook of kidney disease, but some information has been given that will help those sharing the care of CKD patients with a specialist renal unit

The information given here should also help in answering questions from patients about their condition. However, this section does not contain full information for patients, which can be obtained from various sources (see p. 60)

HYPERTENSIVE NEPHROSCLEROSIS

- Long-standing high blood pressure may damage the kidneys by causing changes in small arteries in the kidneys, and also by damaging glomeruli, leading to hypertensive nephrosclerosis
- There may also be low-grade embolisation of cholesterol crystals for atherosclerotic lesions proximal to the kidneys
- CKD in patients with long-standing hypertension who have slightly small kidneys on ultrasound, no haematuria and modest proteinuria is often attributed to hypertensive nephrosclerosis
- Hypertension is regarded as one of the commoner causes of established renal failure in those starting dialysis, and may be a very common cause of CKD stage 3. However, it is hard to identify those people in the CKD population who have a minor kidney disease leading to hypertension and those who have hypertension leading to minor kidney disease. Fortunately the treatment for both groups is to treat the hypertension

DIABETES

- Diabetic kidney disease occurs in up to one-third of people with long-standing diabetes, both type 1 and type 2 diabetes

- Diabetic nephropathy is part of systemic microvascular disease of diabetes, so that someone with diabetic nephropathy would normally have evidence of diabetic retinopathy
- The first sign of diabetic nephropathy is microalbuminuria, which presents when the eGFR is still normal. This is why NICE recommends that people with established diabetes should have an annual urine test
- If diabetic nephropathy does develop, because the nephropathy is part of a systemic microvascular (and often macrovascular) disease process, the diabetic patient is more likely to develop severe cardiac disease, stroke or peripheral vascular disease than they are to progress to established renal failure requiring dialysis
- Thus the development of microalbuminuria should trigger an enhanced management of the blood sugar level, blood pressure and lipids, but by itself need not trigger nephrology referral
- Nephrology referral is indicated when there is doubt about the diagnosis, eg if there is proteinuria but no eye disease, or if there is haematuria as well as proteinuria, or when the proteinuria is of rapid onset. Other problems such as uncontrolled hypertension or recurrent urine infections may also trigger nephrology referral. A nephrologist should see someone with diabetic nephropathy who has CKD stage 3 and falling eGFR, so that a management plan can be made in advance for the eventuality of established renal failure

PATIENT AND CARER INFORMATION:

DIABETES

- Diabetes is a condition where the body does not control the sugar (glucose) levels in the blood properly – the levels can go too high after meals and too low if someone misses a meal
- Diabetic kidney disease occurs in up to one-third of people with long-standing diabetes. A kidney affected by diabetes looks abnormal under the microscope with scarring and swelling in the filters, and protein leaks into the urine
- People with established diabetes should have annual urine test

PATIENT AND CARER INFORMATION:

DIABETES (*cont'd*)

- If protein does appear in the urine, careful control of the blood pressure, cholesterol and blood sugar levels will reduce the rate of progression of CKD, and also problems in other parts of the circulation
- Controlling blood pressure is very important, both in terms of preventing heart attacks and strokes, and in delaying the progression of CKD (and thus delaying or preventing the onset of dialysis)
- However, some people with diabetic kidney disease will have progressive kidney failure despite these measures

REFLUX NEPHROPATHY

- Reflux of urine from the bladder back up the ureters may lead to CKD by causing bacterial kidney infections in childhood, with renal scarring and subsequently proteinuria and hypertension
- The condition used to be called 'chronic pyelonephritis', but this term is no longer used as it suggests ongoing infection in the kidneys, which is rarely the case
- The severity of CKD due to reflux nephropathy varies from asymptomatic scars in the kidneys, to renal failure requiring dialysis or transplantation
- Although some people do get urinary tract infections, these are less common as people get older, and any progressive kidney damage is associated with high blood pressure and proteinuria. Thus treatment of hypertension is an important part of management
- Although once performed regularly, surgical re-implantation of the ureters is rare nowadays
- Reflux nephropathy is an inherited condition, with each first-degree relative of someone with reflux having a one in three chance of also

having reflux. Screening for reflux may be particularly useful in children of affected parents as reducing the numbers of infections in the first 3 years of life is thought to reduce renal scarring and improve long-term outcomes

RENAL CYSTS AND POLYCYSTIC KIDNEYS

- A cyst is a dilated renal tubule, and may be up to 3 cm diameter (the size of a table tennis ball). Normal kidneys may contain several cysts, up to three in each kidney in an adult
- There are several kidney diseases characterised by multiple cysts in the kidneys, some of which may be associated with kidney failure (polycystic kidney disease, medullary cystic disease), and some of which may not (medullary sponge kidney)
- Adult polycystic kidney disease (APCKD) is the most important cystic disease of the kidneys. It is an inherited condition. Adults have multiple cysts in both kidneys and sometimes in the liver
- Very small cysts are present at birth and they gradually enlarge. With the imaging available 25 years ago, it was said that there was no value in scanning children at risk of APCKD. However, modern imaging may detect some small cysts in the kidneys of children, or even in utero, meaning that the diagnosis can be made much earlier
- APCKD classically has an autosomal dominant inheritance. In other words, each child of an affected parent has a one in two chance of having APCKD, and there are no hidden carriers. New mutations also occur
- APCKD classically causes established renal failure in middle age, leading to dialysis or transplantation
- APCKD is also associated with problems elsewhere in the body, such as cerebral aneurysms (leading to subarachnoid haemorrhage), diverticular disease and mitral valve prolapse
- There are a number of clinical trials under way examining novel therapies that may reduce the rate of progression of APCKD. It is hoped that these will eventually lead to an improvement in prognosis
- A form of polycystic kidney disease may also be seen in children, where the inheritance is recessive, and renal failure may develop during childhood

- Some adults who are found to have polycystic kidneys on ultrasound have no family history of APCKD, and do not seem to develop kidney failure as they grow older. Although it is not yet possible to classify polycystic kidney disease according to the genetic profile, it is possible that some types of APCKD do not cause kidney failure. However, everyone with polycystic kidney disease should be carefully monitored in the long term

RENAL ARTERY STENOSIS

- Dysplasia of the renal artery, with webbing and narrowing, may be found in younger people, and causes severe hypertension. Angioplasty may be an effective treatment. This condition is rare
- Atherosclerotic renal artery stenosis (ARAS), on the other hand, is very common
- ARAS may be present, to some extent or other, in about one in three people with significant atherosclerotic disease of the coronary arteries or peripheral arteries. It often causes <50% stenosis of the renal artery, but does not cause CKD
- In other cases, however, ARAS may cause hypertension and renal impairment. The renal function may deteriorate acutely if ACEI/ARB are given, though this is not invariable
- Another feature of ARAS may be recurrent acute pulmonary oedema (sometimes called ‘flash pulmonary oedema’) in the absence of acute cardiac disease. This may be caused partly by salt and water retention (the kidney having a reduced blood flow will try and retain salt and water in the body)
- ARAS may be unilateral or bilateral, but it often affects one kidney more than the other, and is suspected if the kidney sizes are unequal on ultrasound scanning
- The presence of ARAS can be confirmed by CT or MR scanning; diagnostic catheter angiography is no longer required
- If ARAS is present, the usual measures used to treat CKD should be instituted, especially control of hypertension and hyperlipidaemia. In addition, a nephrologist will assess a patient for suitability for angioplasty/stenting of the artery. At present, it is uncertain who will benefit most from these procedures – a large randomised trial of renal artery stenting is being performed in the UK

GLOMERULAR DISEASE

- Glomerulonephritis is a condition where the primary abnormality in the kidney is in the glomerulus. It is diagnosed by renal biopsy, and abnormalities are seen in the mesangium (supporting structure), the basement membrane (that filters the blood), or both. However, many patients suspected of having a glomerular disease do not require renal biopsy, but can be monitored and treated according to their CKD stage
- Patients with glomerulonephritis will have haematuria and/or proteinuria, almost without exception (occasionally in remission some patients will have clear urine). Thus someone who consistently has no haematuria or proteinuria will not have glomerulonephritis. But there are other causes of haematuria and proteinuria
- Outside a specialist renal unit, there is very little knowledge about glomerulonephritis that is vital – certainly there is no need to understand the differences between all the different types of glomerulonephritis
- The treatment for glomerulonephritis is essentially the same as for other causes of CKD, with particular attention to blood pressure and lipid control. Nephrologists will advise immunosuppression in selected patients
- It is important to be able to recognise the patients who have a potentially rapidly progressive glomerulonephritis, so they can be referred to a specialist unit immediately
- It is important to be able to make a diagnosis of nephrotic syndrome, and to recognise relapses of nephritic syndrome when patients are established on longer term treatment

VITAL POINTS

- * *There are many different types of glomerulonephritis, but the non-specialist does need to understand the detailed differences between them*
- * *The non-specialist should be able to recognise patients who may have rapidly progressive glomerulonephritis or nephrotic syndrome*

Rapidly progressive glomerulonephritis

- Rapidly progressive glomerulonephritis is a syndrome in which renal failure may develop over a period of a few days. Early detection of the syndrome is important, as it may be treatable in the early stages, and may be fatal if unrecognised
- The incidence of new cases is about 40 per million persons per year – in other words, in a population of 10,000, one new case every other year would be expected. It is more frequent in older people, and also in the spring and autumn
- Several renal diseases can cause rapidly progressive glomerulonephritis. The commonest group is systemic vasculitis (sub-types include microscopic polyarteritis and Wegener's granulomatosis). These people may have positive anti-neutrophil cytoplasmic antibody (ANCA). Anti-glomerular basement membrane disease (Goodpasture's syndrome) and SLE are other causes
- Henoch–Schönlein purpura is a more common form of vasculitis that only occasionally causes the syndrome of rapidly progressive glomerulonephritis. The urine of anyone with Henoch–Schönlein purpura should be tested for blood and protein by dipstick, and the renal function measured urgently if these are abnormal
- Many patients experience non-specific symptoms, with malaise, sickness and breathlessness. Some people get a purpuric rash, most often on the legs, and some may develop pulmonary haemorrhage with haemoptysis. Nosebleeds or ear problems can be early signs of Wegener's granulomatosis
- Rapidly progressive glomerulonephritis should be suspected in someone of new onset renal impairment who has blood and protein on urine dipstick, and constitutional symptoms or typical rash. Referral should be made immediately by telephone to whoever is on call for emergencies at the local renal unit

IgA nephropathy

- This is one of the commonest forms of glomerulonephritis disease worldwide
- IgA is deposited in the mesangium (supporting structure) of the glomerulus
- Clinical presentation is variable. Many people have microscopic

haematuria, perhaps with some proteinuria. Sometimes there are episodes of macroscopic haematuria, perhaps triggered by viral infections

- Most people with this condition will remain well for many years, but progressive loss of renal function will occur in some. Proteinuria and hypertension are markers of worse prognosis. Scarring on renal biopsy and a raised creatinine/reduced eGFR on presentation are also poor prognostic markers

Membranous nephropathy

- Immune complexes (small masses of protein and immunoglobulin) are deposited in the glomerular membrane, the membrane across which plasma is filtered (hence the name 'membranous')
- This causes proteinuria, normally without any haematuria, and there may be nephrotic syndrome
- The outcome of the condition is variable. About one-third of patients will develop spontaneous remission, one-third will have chronic nephritic syndrome and one-third will develop progressive loss of renal function
- Selected patients with declining renal function may be treated with immunosuppressive drugs by nephrologists, otherwise the usual treatment measures in CKD will be taken. If there is nephrotic syndrome particular attention will be paid to the cholesterol level
- Sometimes membranous nephropathy occurs in patients with SLE. It is occasionally associated with a solid tumour, and the patient should have a chest x-ray. If there are any new onset symptoms suggestive of a gastrointestinal tract tumour, this should be investigated

Focal and segmental glomerulosclerosis

- In this condition there is contraction and scarring in segments ('segmental') of some ('focal') glomeruli (hence the name focal and segmental glomerulosclerosis, FSGS)
- FSGS may present with nephrotic syndrome, or may be found on renal biopsy in patients with impaired renal function and some proteinuria
- There is no single known cause for the condition. Indeed, scarring in the glomeruli may be very non-specific, and could be the end point of several different processes

- Nephrotic syndrome will be treated with ACEI/ARB, fluid balance control and management of hyperlipidaemia in the first instance, but steroids and other immunosuppressive drugs may be given to selected patients by nephrologists. The response to immunosuppressive therapy is variable, and may be disappointing in some cases
- It can recur in hours following a renal transplant, although not necessarily leading to kidney disease

Mesangiocapillary glomerulonephritis

- Mesangiocapillary glomerulonephritis (MCGN) is also known as membranoproliferative glomerulonephritis
- In this condition immune complexes are deposited in both the mesangium (hence 'mesangio-') and the filtering membrane capillaries (hence '-capillary') inside the glomerulus
- There may be nephrotic syndrome, or reduced renal function with proteinuria. Some patients have MCGN alone, in other cases it is associated with SLE, or chronic infections, or cryoglobulinaemia and hepatitis C
- Rather like other glomerular disease, first-line treatment consists of general measures to treat CKD and nephrotic syndrome, and nephrologists may treat selected patients with immunosuppression, though the response to this is variable and may be disappointing

NEPHROTIC SYNDROME

- Nephrotic syndrome is a combination of heavy proteinuria (>3 g/24 hours or PCR >300 mg/mmol), low serum albumin level and fluid retention. There is often a high blood cholesterol level
- Minimal change nephropathy is a common cause of nephritic syndrome. This is an important condition because the serum albumin level can become very low, and the patient can develop complications such as infection or venous thrombosis. On the other hand, it usually responds well to treatment with steroids
- Other causes of nephrotic syndrome include various types of glomerulonephritis (see p. 49), diabetes, amyloid and glomerulonephritis in SLE

- Nephrotic syndrome should be suspected in anyone with new onset fluid retention, and a urine dipstick for protein will immediately tell whether the diagnosis is possible. Nephrotic syndrome is associated with at least ++ of dipstick protein. Blood may or may not be present, depending on the cause of nephrotic syndrome
- If the urine dipstick is positive for protein, urine for PCR and bloods for creatinine level, serum albumin and serum cholesterol should be sent. If nephrotic syndrome is confirmed, urgent referral should be made to the local renal unit
- The renal unit will consider whether to perform a renal biopsy, and will advise on treatment. If minimal change disease is found on biopsy (or in some cases, especially children, is suspected without a biopsy being performed), steroids will be started. General measures such as blood pressure control, ideally with an ACEI or ARB, and cholesterol control will also normally be advised. Fluid retention will be treated by salt and water restriction; in some cases a diuretic will be used
- Venous thrombosis is a complication of nephritic syndrome, and should be suspected if there are symptoms of deep vein thrombosis (DVT) or pulmonary embolus. Prophylactic warfarin will be given to some patients, especially if the serum albumin level is <20 g/l

Minimal change nephropathy

- In minimal change nephropathy the serum albumin level can fall to very low levels with marked fluid overload. The patient can develop infection or venous thrombosis. The condition usually responds well to treatment
- It is by the far the commonest cause of nephrotic syndrome in children, who normally receive steroid treatment without renal biopsy, this being kept in reserve for non-responders. In adults, minimal change remains an important cause of nephrotic syndrome, but renal biopsy is usually performed because other conditions that are steroid non-responsive often occur
- Minimal change describes the appearances on renal biopsy. The kidney usually looks normal by light microscopy and minor changes in the glomerulus (foot process fusion) are seen on electron microscopy
- Patients treated with steroids and who have a good response will have their steroid dose reduced over time. About one-third of such patients will experience relapse, and may test for this at home with urine

dipsticks. If a relapse does occur, steroids usually need to be started immediately. It is helpful if primary care either have a treatment plan for relapse in advance, or telephone the responsible renal physician for advice as soon as a relapse is detected

- Long-term treatment of nephrotic syndrome will include optimal blood pressure and cholesterol control, and a plan for steroids and immunosuppressive drugs in individual patients. Patients who relapse on treatment may have repeated courses of steroids, long-term steroids, or drugs such as ciclosporin or cyclophosphamide. A less toxic alternative occasionally used is levamisole
- Minimal change nephropathy does not cause CKD stages 3–5. It can cause acute renal failure if there is severe haemodynamic imbalance during the acute phase, or if there is renal vein thrombosis or serious infection. If CKD stages 3–5 develops in someone with minimal change disease, either the original disease was not minimal change (it could have been FSGS, see p. 51) or a second renal disease has developed

MYELOMA

- Myeloma can cause renal disease in a variety of ways – student textbooks of medicine will contain long lists of the possible causes
- Myeloma can cause acute renal failure, and a renal unit will screen all cases of acute renal failure (ARF) for myeloma. Myeloma will be suspected especially if the ARF is associated with hypercalcaemia, new onset back pain or disproportionate anaemia. In the acute setting, such patients are almost always very volume depleted. Rapid rehydration will help improve and preserve renal function
- Myeloma can cause CKD if the myeloma protein (fragments of the monoclonal antibody produced by the plasma cell clone) is filtered through the glomerulus, precipitating as Bence–Jones proteins in the tubules, as the filtrate is concentrated into urine –this damages the tubule. In this case, the patient should keep themselves well-hydrated, and treatment of the underlying myeloma will be a priority for the nephrology and haematology teams

AMYLOIDOSIS

- Amyloid is protein deposited in tissues in a particular fashion ('beta-pleated sheets'). The amyloid sits in tissues and interferes with organ function
- In the kidney, amyloid can cause severe nephrotic syndrome and/or kidney failure, and is diagnosed on renal biopsy
- The commonest cause of amyloid is a monoclonal gammopathy. As well as the usual measures for CKD management, a nephrologist will advise on the management together with a haematologist
- Other causes include familial amyloid and amyloid associated with chronic inflammation, eg rheumatoid arthritis

SYSTEMIC LUPUS ERYTHEMATOSUS

- SLE is a multi-system autoimmune disease characterised by antibodies against double-stranded DNA. It is seen most frequently in young women, and is more common in those of Asian and black ethnicity
- SLE can affect all parts of the body, including the kidneys. Everyone with SLE should have a dipstick test of their urine and measurement of eGFR. If there is proteinuria or reduced eGFR, a nephrologist should advise on whether a renal biopsy is indicated
- Renal biopsy appearances in lupus nephritis are varied. Some carry a good long-term prognosis, but some carry a significant risk of progression to kidney failure
- The care of someone with lupus nephritis is usually shared between a nephrologist and rheumatologist. If someone is taking immunosuppression medication, it should be clear who has the primary responsibility for monitoring the blood count and other indices, and then communicating with whoever is responsible for the prescribing of immunosuppressive therapy. Most immunosuppressive drugs have serious side effects and have to be handled carefully with clear shared guidelines if they are to be prescribed in primary care with secondary care supervision

URINE INFECTION

- Urine infections may occur in people who have no CKD. Even recurrent urine infections do not cause CKD unless there is a structural abnormality of the kidney, or proteinuria in between urine infections, or a reduced eGFR
- Although it is tempting to try and distinguish between upper and lower urinary tract infection on clinical grounds, this is very unreliable. The absence of loin pain does not mean there is not acute bacterial pyelonephritis
- Urine infections are more frequent in people who have any condition affecting emptying of the bladder, kidney stones or diabetes, or who have an indwelling bladder catheter
- To treat an infection, the first step is to increase the intake of fluid, and some patients will report that this will get rid of urine infection. If antibiotics are needed, they are usually given for 3–7 days, depending on the severity of the infection and whether there is underlying kidney disease or diabetes
- If someone has recurrent urinary tract infections and requires referral to a specialist, it is helpful to get a kidney and bladder ultrasound first. There is little value in sending someone who turns out to have kidney stones to a nephrologist
- Some patients, despite an effective course of antibiotics, may continue to have pain or frequency passing urine, or have ongoing microscopic haematuria. These features may trigger a secondary care referral, although often no particular treatable cause for these features is found
- The role of prophylactic antibiotics is uncertain, though some patients do seem to get relief from them. Evidence favouring prophylactic antibiotics for recurrent urine infection is based on at least a 6-month course of antibiotics (changing antibiotics every month for example). Rotating between different antibiotics should not be necessary, although some patients do report success with this when a single antibiotic has failed

PATIENT AND CARER INFORMATION:

URINE INFECTIONS

- Urine infections are caused by bacteria that cause inflammation or irritation in the lining of the bladder, causing pain and stinging when urine is passed, symptoms called 'cystitis'. A more severe infection may spread upwards to the kidneys with pain in the area of one or both kidneys, and a fever and sweating (pyelonephritis)
- Urine infections are much commoner in women than in men, and hardly ever cause CKD. However, urine infections are more frequent in people who have any condition affecting emptying of the bladder, kidney stones or diabetes, or who have a catheter in place to drain the urine
- To treat an infection, the first step is to increase the intake of fluid. At least 2 litres of fluid a day (five large glasses) should be taken. If antibiotics are needed, they are usually given for 3–7 days, depending on the severity of the infection and whether there is underlying kidney disease or diabetes

VITAL POINTS

- * *Symptoms of urine frequency and incontinence are essentially not features of CKD. In CKD stages 4 and 5, the kidneys may lose their ability to produce less urine at night, leading to nocturia*
- * *In most patients with urine frequency or incontinence there are local factors in the bladder that may require referral to a urologist or gynaecologist*
- * *CKD and problems with micturition are both common and can co-exist in the same patient (for example old men can have prostatism and CKD secondary to diabetes)*
- * *It is important that the patient does not confuse the two problems of CKD and problems with micturition, as the aims of treatment for CKD are quite different from the treatment of frequency or incontinence*

VITAL POINTS

- * Some people with dual problems may need dual referral to separate specialists*
- * If often confuses patients to have one kidney doctor (a urologist) for one problem, and another (a nephrologist) for another – the GP can help to explain this issue to patients*

HEART FAILURE

- Heart failure frequently co-exists with CKD (as age, diabetes and smoking can all cause ischaemic heart disease and renal artery stenosis), and is a particular management challenge
- Fluid balance needs to be managed especially carefully in some with CKD and heart failure. If the patient becomes volume-depleted, the heart may be all right, but the kidneys may be compromised and the eGFR may fall. On the other hand, the kidneys will not usually mind moderate fluid overload, but this may tip someone with heart failure into pulmonary oedema
- Management of fluid balance should include educating the patient so they understand the importance of controlling their fluid balance, and the consequences of both over- and under-hydration. They should maintain a steady level of water intake and restrict their salt intake
- It is appropriate for some patients to vary slightly the amount of fluid they drink in response to their hydration status. Some patients can learn to vary their diuretic dose to keep their condition stable
- ACEI or ARBs should not be withheld from patients with heart failure solely on the basis that they have a low eGFR (see p. 36)
- Spironolactone should not be given in CKD stages 4 or 5, and with great caution in CKD stage 3. This is because of the risk of hyperkalaemia
- If someone is prone to attacks of pulmonary oedema out of proportion to their known level of heart failure, renal artery stenosis should be considered (see p. 48)
- Care should be taken not to confuse fluid overload due to kidney disease with primary heart failure. This can be a particular catch if there is

nephrotic syndrome (see p. 52), and is the reason why urine dipstick for protein is indicated in all patients newly diagnosed with heart failure

- In CKD stages 4–5, fluid overload may occur as the kidneys fail, and this can be confused with heart failure, especially in patients with diabetes. Pulmonary oedema in this circumstance may be an indication for dialysis. Urgent assessment may need to be made by a nephrologist
- In someone with advanced heart failure, approaching ‘end-of-life’ care, it may be appropriate to ‘sacrifice’ renal function (ie carefully allow the creatinine to rise, and eGFR to fall) in order to stop them dying in pulmonary oedema. Palliative care referral may also help at this stage

PATIENT AND CARER INFORMATION:

HEART FAILURE

- Heart failure is a condition where the ability of the heart to pump blood around the body is reduced
- This can occur independently of CKD, but many people with heart failure also have CKD. When this occurs, it can be difficult to keep both the heart and the kidneys in a stable condition, as the heart generally prefers the amount of water in the body to be on the low side, while the kidneys prefer a fuller circulation
- Some of the drugs used to treat heart failure have to be used carefully, or even avoided, in someone with CKD
- Detailed advice from doctors on how to maintain steady levels of water in the body and to keep both the heart and the kidneys functioning well is needed

Probably the most important complication of CKD is hypertension. This is also a cause of CKD, so that uncontrolled hypertension will cause progressive kidney damage, more severe hypertension and hence a vicious circle of progressive renal disease

The management of hypertension has already been discussed (see p. 33)

ANAEMIA

- In someone with CKD the kidneys may be unable to produce enough erythropoietin (EPO), which stimulates the bone marrow to produce red blood cells. A relative lack of response of the bone marrow as eGFR declines also contributes in the anaemia of kidney disease
- If someone is anaemic, the blood levels of iron, vitamin B₁₂ and folic acid should be measured, and any deficiency treated. Symptoms suggestive of gastrointestinal blood loss should be investigated
- Although CKD can cause anaemia, this occurs most often in CKD stages 4 and 5. Anaemia in someone with CKD stage 3 should be considered to be due to other causes until these have been ruled out
- Drugs to stimulate the bone marrow may be used. These are called erythropoiesis-stimulating agents (ESA). They are essentially artificial versions of natural erythropoietin and are given by regular injection, together with monitoring of the haemoglobin level and the blood pressure (high blood pressure and fits are side effects of the drugs)
- NICE guidance say that EPO may be considered when the haemoglobin level is less than 11 g/dl, and should be used to keep the haemoglobin between 10.5 and 12.5 g/dl. Once started, the injections take a few weeks to raise the haemoglobin level, and injections usually need to be continued for as long as someone has CKD
- ESA may be an important part of the non-dialysis, palliative care of some people with CKD stage 5, and nephrologists will be happy to advise on treatment

- Arrangements for the prescribing and monitoring of ESA vary around the country, so primary care should be aware of the local arrangements

PATIENT AND CARER INFORMATION:

ANAEMIA

- Anaemia occurs when there are not enough red blood cells to carry oxygen from the lungs to the body. Anaemia can be caused by blood loss, blood destruction or, in someone with CKD the kidneys may be unable to produce enough of the chemical messenger (hormone) erythropoietin (EPO), which stimulates the bone marrow to produce red blood cells
- Common symptoms of anaemia are loss of energy and shortness of breath. Someone may also become irritable and frustrated at the difficulty experienced in doing daily tasks. There may be lethargy, mood fluctuations, disturbed sleep patterns and impaired sexual function
- Although some people have pale skin when they are anaemic, this is a very unreliable sign and a blood test is required to measure the haemoglobin level. The normal range is 13–17 g/dl for men and 12–15 g/dl for women
- Blood tests should be performed to measure the level of iron in the blood, and also two important vitamins (vitamin B₁₂ and folic acid). It is also important to detect any blood loss from the bowel. Any indigestion should be reported to the doctor, as well as any change in the stools, either with blood or blackening
- ESA may be given to stimulate the bone marrow. They are essentially artificial versions of natural EPO. EPO is given by regular injections, together with monitoring of the haemoglobin level and the blood pressure (high blood pressure can be a side effect of the drug). The injections can be easily self-administered at home or can be given at the local GP surgery
- National guidance says that EPO may be considered when the haemoglobin level is less than 11 g/dl, and be used to keep the haemoglobin between 11 and 12 g/dl. Once started, the injections take a few weeks to raise the haemoglobin level. Injections usually need to be continued for as long as someone has CKD

VITAL POINTS

- * CKD may cause a normocytic anaemia, most often in CKD stages 4 and 5*
- * In CKD stage 3, anaemia is often not due to kidney disease, and a careful search should be made for other causes of anaemia*

CALCIUM AND BONES

- Renal insufficiency is associated with a number of abnormalities of mineral metabolism that may cause symptomatic problems and later bone disease
- The aetiology of these abnormalities is multifactorial. Important factors include deficiency of activated vitamin D (this undergoes one of its activation steps in the kidney) and retention of phosphate. These may lead to hyperparathyroidism, with bone disease and ectopic calcification
- Serum calcium tends to be low, with high phosphate and alkaline phosphatase levels
- Patients with CKD may also be at risk of osteoporosis, in the same way as the general population
- Measurement of calcium or phosphate is not required in CKD stages 1 or 2 unless a problem is suspected
- In CKD stages 3–5, calcium and phosphate should be measured at the same intervals as eGFR. The RCGP/RA guidelines state the patients with confirmed abnormalities of calcium (corrected by the laboratory for the serum albumin level) or phosphate should be referred to (or at least discussed with) a nephrologist
- The RCGP/RA guidelines also state that the parathyroid hormone (PTH) level should be measured in primary care in everyone with CKD stage 3. This was thought to be unrealistic in terms of the numbers of cases and extra training required in primary care, and the guidelines consensus group that met in early 2007 indicated that PTH could essentially be measured when appropriate in secondary care
- If the corrected serum calcium level is low, the nephrologist will usually advise treatment with a vitamin D analogue. Note that vitamin D

PATIENT AND CARER INFORMATION:

CALCIUM AND BONES

- Problems with calcium, phosphate and a chemical messenger in the blood called parathyroid hormone (PTH) can occur in anyone with CKD, but are more common in people with CKD stages 4 and 5
- Sometimes there are symptoms – in other words someone feels unwell. In many cases, however, problems can start without any symptoms, and slowly cause irreversible damage to the bones, the heart or blood vessels over a period of years
- Pain in the bones is not common in the early stages of CKD-associated bone disease
- Preventative treatment can reduce the chances of this irreversible damage, and starts with measurement of the levels of calcium and phosphate in the blood. This can be done on a routine blood test from the same sample used to measure eGFR
- If the levels of calcium and phosphate are normal, it is not necessary to take further action. Some of the first signs of problems are a low calcium level or a high phosphate level. If either of these occurs, the GP may need to add treatment or ask a kidney specialist for advice. A low calcium level would usually be treated with a form of activated vitamin D, because someone with CKD may not be able to produce the active form of vitamin D in their kidneys. A high level of phosphate may need to be treated with restriction of the phosphate in the diet. This would not usually occur until someone has CKD stage 4 or 5, and individualised advice on diet will be given by a specialist renal dietitian

preparations such as calciferol are not useful as they require activation through the kidneys, a step that is likely to be impaired in CKD when hypocalcaemia is present

- If the serum corrected calcium is high, the nephrologist will reduce or stop any vitamin D or calcium-containing medications, and measure the PTH level

- If the phosphate level is high, the nephrologist will refer the patient to a dietitian and consider drugs to take at mealtimes to reduce phosphate absorption. Phosphate retention is normally only seen in CKD stages 4 and 5

HYPERKALAEMIA

- A high blood potassium level can be life-threatening and is an important complication of CKD
- This is the reason that biochemistry laboratories will report a high potassium level by telephone to the requesting doctor (usually at the most inconvenient time to organise effective action)
- The exact response to a telephoned high potassium level depends on the details of the case, but anyone in the community with a potassium level >6.5 mmol/l should have their blood rechecked immediately. Some patients with a potassium level that is high but is <6.5 mmol/l may be able to wait until the next day for repeated testing if they have a history of high potassium levels
- The emergency management of hyperkalaemia, if confirmed, includes assessing its immediate effect on the heart with an ECG. In the early stages hyperkalaemia may cause high peaked T waves in the chest leads, then later bradycardia with broadened QRS complexes. Eventually ventricular fibrillation (VF) or asystole occurs. The ECG may remain almost normal even when hyperkalaemia is immediately life-threatening, so a normal ECG does not mean that the patient is safe
- The emergency management of hyperkalaemia is usually performed in the emergency department, where there should be local guidelines
- Prevention of further episodes of hyperkalaemia is obviously important. If someone has CKD stage 5, their dialysis plan should be reviewed. In all stages of CKD, a medicines review is required. Drugs that may cause or exacerbate hyperkalaemia include ACEI/ARB (see p. 36 for more details), spironolactone, amiloride and triamterene
- Dietary restriction of potassium may be required in CKD stages 4 or 5, or if hyperkalaemia is recurrent despite appropriate medicines review. It is best to seek a specialist dietary review rather than simply to advise dietary restriction. However, some of the foods high in potassium include tomatoes, some fruits, such as bananas, and coffee. These may be restricted pending a full dietary review

VITAL POINTS

- * Hyperkalaemia may be life-threatening, and is an immediate emergency when >7.0 mmol/l*
- * If someone has had life-threatening hyperkalaemia they should not take spironolactone, amiloride or triamterene (ACEI/ARB should be stopped temporarily and their use reviewed)*

LOIN PAIN

- Pain from the kidney is felt in the loin, and may radiate down towards the groin. Kidney stone and acute bacterial pyelonephritis are conditions where loin pain often occurs
- Most other kidney conditions are not commonly regarded as a cause of loin pain, though most nephrologists will recognise that an acute exacerbation of IgA nephropathy may cause loin pain
- Studies into thoraco-lumbar back pain suggest that as many as 25% of the population may experience pain in the kidney area at some time or other. This pain is often presumed to be musculo-skeletal in origin
- Some patients with CKD experience very severe loin pain. It is very hard to tell, in many cases, whether this comes from the kidneys. Physical examinations and imaging cannot determine exactly the anatomical source of every pain
- A particular group of patients with severe loin pain also have haematuria, and the syndrome is called 'loin pain haematuria syndrome'. However, it has not been possible to determine a single causality for this condition. Indeed, whether it really exists is controversial. It is possible that since back pain and haematuria are both common, they may co-exist by chance in many cases
- Loin pain haematuria syndrome should be assessed by a nephrologist and urologist, but there may be little they can do to ameliorate the symptoms. Referral to a pain clinic, reassurance (patients hardly ever progress to CKD stages 4 or 5 if their initial eGFR is normal) and helping the patient develop effective coping strategies may be useful. The role of surgical intervention (eg denervation of the kidney or autotransplantation of the kidney) is controversial

GOUT

- Gout is caused by crystals of uric acid being deposited in joint spaces where they cause acute pain
- The risk of gout is associated with the blood urate level
- The blood urate level depends on several factors, including the eGFR – the lower the eGFR, the higher the blood urate level. This is because urate is excreted through the kidneys
- The risk of gout in CKD is particularly high in CKD stages 4–5
- If gout is suspected, remember the differential diagnosis for an acutely painful, red, swollen joint also includes septic arthritis
- The treatment of acute gout can be a problem in someone with CKD, where NSAID drugs are best avoided. Paracetamol and codeine may be used
- Colchicine can be used in people with CKD, and given at the usual dose with the usual advice about diarrhoea
- If pain relief is impossible to achieve with other drugs in acute gout, a few days of high-dose steroid treatment is usually effective. Be aware of the other possible adverse effects of steroids
- Allopurinol may be used as a preventative drug after recurrent attacks of gout. The dose should be reduced to 200 mg/day in people with CKD stage 3, and 100 mg/day in those with CKD stages 4–5. Note that allopurinol and azathioprine should not be co-prescribed as their interaction (causing neutropenia) can be life-threatening

DEPRESSION

- As with any chronic disease, CKD may be associated with depression, especially if there are physical symptoms associated with CKD stages 4 or 5
- Depression may present with low mood, but also with fatigue ('tired all the time'), impaired sex drive, and other non-specific symptoms. Depression may present at unexpected times – for example in the weeks after a successful kidney transplant, when it would be imagined that someone would normally be very happy

- The management of depression differs little from that in patients without CKD. However, if antidepressant drugs are to be used, it is important to check that they are prescribed in doses appropriate to the level of renal function and that they do not interact with any other prescribed medication
- Anaemia may exacerbate depression. The haemoglobin level should be reviewed and any anaemia treated as appropriate
- SSRIs can cause severe hyponatraemia, which can be missed in someone on other drugs that are more well known to cause it, eg thiazide or loop diuretics

This section looks at some of the other issues that may affect the lives of people with CKD. Broadly, CKD stages 1–2 do not usually impact much on normal life, CKD stages 4–5 have a great impact, and for CKD stage 3 the degree of impact depends on the level of kidney function, any likely progression in the future and other associated conditions

The important lifestyle advice in CKD is the same as the healthy living message that applies to anyone with, or at risk, of cardiovascular disease

VITAL POINTS

- * *Don't smoke*
- * *Have a healthy diet with five portions of fruit and vegetables a day*
- * *Watch your weight*
- * *Take some exercise*

DIET AND FLUID INTAKE

Diet

- For CKD stages 1–3, it is rare for anyone to need to start the dietary restrictions that apply in CKD stage 5 or on dialysis, with restriction potassium and phosphate in the diet and a modest restriction of protein
- People should be discouraged from making marked changes to their diet (such as phosphate and potassium restriction) unless advised by a renal dietitian. This will ensure that a balanced diet is taken – for example, just cutting protein intake down could result in an energy-deficient diet and a fast-track to malnutrition. Even without deliberate dietary changes, malnutrition is a greater problem in many elderly patients with CKD than any problems due to excessive dietary intake

- The current consensus in the UK is that marked dietary protein restriction does not significantly slow the progression of CKD. However, those patients with a declining eGFR should be referred to a nephrologist and will have access to a specialist renal dietitian for an individual assessment
- If someone has hyperkalaemia, it may be helpful to advise a modest potassium restriction. In its simplest form this means avoiding or reducing the intake of tomatoes, coffee and bananas. The dietitian on a renal unit will provide written information and more detailed advice on potassium restriction

VITAL POINTS

- * For most people with CKD the emphasis is on a healthy, balanced diet with five portions of fruit and vegetables a day*
- * For people with hypertension, restriction on salt intake is usually appropriate, with a ban on added salt and care with salt content in pre-prepared foods*
- * Additional dietary advice may be needed if someone has a high cholesterol level, or has another condition such as diabetes*

Fluid intake

- Most people with CKD do not need to make a conscious effort to change their fluid intake, and can stick to the government guidance of six to eight glasses or cups a day
- For some patients with CKD who get recurrent urine infections, increasing their fluid intake may reduce the frequency of infections
- A few people with CKD may have a tendency to salt and water retention, because of either nephrotic syndrome or reduced excretory ability of the kidneys in CKD 3–5, or an additional problem such as heart failure. Therefore a fluid restriction may be required. A restriction on the intake of fluids should be accompanied by salt restriction. Someone who restricts their water intake and has a high salt intake will become intolerably thirsty and will exceed their fluid restriction

Alcohol intake

- Drinking alcohol is not directly harmful to the kidneys
- The advice on alcohol intake given to the general population is a maximum safe consumption of three units a day in men and two units a day in women
- Alcohol consumption may increase blood pressure. For people with hypertension, NICE and SIGN (Scottish Intercollegiate Guidelines Network) advise sticking to the national guidance and do not advise further restrictions on alcohol consumption
- Some people feel that drinking alcohol while they have a urine infection slows the rate of recovery, or may predispose to urine infection. There is no hard evidence to support this

SMOKING

- People with CKD must be advised not to smoke
- As CKD is a risk factor for cardiovascular disease, the risks of smoking are higher than in someone with completely normal kidneys
- If bupropion (Zyban) is to be used, the manufacturers advise a maximum recommended dose of 150 mg in renal impairment (roughly equivalent to CKD stages 3–5)
- Nicotine should be used with caution in severe renal impairment (roughly equivalent to CKD stages 4–5)

EXERCISE

- The advice for exercise in CKD does not differ substantially from that in the general population
- If someone with CKD is particularly fatigued, they may benefit from exercise to improve physical fitness. Their haemoglobin level should be reviewed in case anaemia is causing any symptoms

WORK

- CKD should not directly affect anyone's ability to work
- Many people in CKD stages 4 and 5, or with any stage of CKD and comorbid conditions, may find it difficult to work and require individual assessment

TRAVEL

- CKD stages 1–2 by itself should not impact seriously on travel or holidays. At stages 3 or 4, where there is a possibility that intercurrent illness or dehydration can precipitate stage 5 and dialysis, it is advisable to have extra insurance
- People with CKD should be advised to plan holidays well in advance, and if they do have CKD stages 3–5 to be careful with choosing an appropriate holiday. Three months caravanning in the Sahara may not be a good idea for someone with CKD stage 4 because of the risk of volume depletion and lack of a readily available specialist medical help
- It is always difficult to remember what vaccinations to take for any given destination, or whether malaria prophylaxis is required. Patients should consult their travel operator or one of the many websites that gives up-to-date information. If there is any doubt about the safety of particular vaccines or drugs, information is available on kidney charity websites (see p. 91). The most important principle of vaccination to consider is that live vaccines should be avoided if possible in people who are immunosuppressed (for example, for a kidney transplant or for vasculitis)
- People with CKD may be at risk of getting dehydrated in hot weather, and should be advised about taking plenty of fluids
- Some patients who get urinary tract infections may ask for a course of antibiotics to take on holiday, so they can start treatment immediately there are any symptoms of infection without having to find a doctor

INSURANCE

- Anyone with CKD will almost certainly have to declare this when applying for life insurance, critical illness insurance or holiday insurance
- After receiving a medical report, insurance companies may then decide either to load insurance premiums or apply exclusions
- CKD stages 1–2 should have little impact on insurance, unless the kidney disease is likely to be progressive (eg polycystic kidneys or diabetic nephropathy) or if the kidney disease has caused repeated hospitalisation
- CKD stage 3 may have an impact on insurance depending on an individual company's estimations of risk. In older people, CKD stage 3 has little impact on mortality rate, whereas for a young person, CKD stage 3 may represent a significant added long-term risk. Because of the uncertainty over some of the risks associated with CKD stage 3, it may be worth a patient shopping around if they are not satisfied with their first quotation
- If someone is having difficulty getting an insurance policy, it may be worth their while checking one of the patient association's websites or contacting their telephone helpline, as they have details of companies or brokers who may be able to help
- If there is a risk of inherited kidney disease (eg polycystic kidneys), some people believe that if they avoid having a diagnostic test, they can avoid declaring the risk on an insurance application. However, by failing to declare a material risk on their application the likelihood is that any claim against the policy would be refused, even if the claim were for a condition that appeared to be unrelated to the kidney disease. They are far better off having the diagnostic test – after all, if the tests prove to be normal, their insurance premiums should not be affected at all

SEX

- CKD does not prevent anyone from getting sexually transmitted diseases, so the usual precautions about safe sex should apply
- Men and women with CKD stages 4–5 may have sexual problems, with both libido and arousal. This is in addition to the increased incidence of sexual problems as people get older

- The effects of CKD stage 3 on sexual function are not well documented
- People should be encouraged to report any sexual problems they have to their healthcare team. Not everyone on the healthcare team will have the expertise or confidence to manage these problems, but there should be a local referral pathway
- If someone with CKD does have a sexual problem, their haemoglobin level should be reviewed, as sexual problems are more frequent with anaemia and treatment of the anaemia can improve sexual function. Medicines should be reviewed – erectile dysfunction in men taking beta-blockers is probably the most frequent avoidable problem. Sexual problems are also more common in people with diabetes, especially if they have an autonomic neuropathy
- Emotional problems can also cause or exacerbate sexual problems, and should be considered
- Erectile dysfunction can be treated with drugs such as sildenafil (Viagra), although care should be taken with the assessment of cardiovascular disease and other medications. Other treatments include penile injections and pump devices
- Other medical management of sexual problems in CKD patients may include measurement of the testosterone level, as testosterone deficiency can cause loss of libido in men and women

PREGNANCY

Getting pregnant

- Men in CKD stages 4–5 may have a reduced sperm count
- Women in CKD stages 4–5 may have reduced fertility and some may stop having periods
- Less is known about the effects of CKD stage 3 on fertility
- CKD stages 1–2 probably have little effect on fertility in men or women, unless there are additional problems such as diabetes
- A woman planning to get pregnant should discuss the possible risks of pregnancy with their medical team and have a medication review. Antihypertensive drugs may need adjusting if a pregnancy is planned (eg switching from an ACE inhibitor to labetalol)

- If a woman with CKD 4 is planning a pregnancy, her options include waiting until she has received a kidney transplant before getting pregnant

Being pregnant

- Women in CKD stages 1–3 should be able to progress through pregnancy, though with extra monitoring
- Some hospitals run joint nephrology/obstetric clinics
- A woman with hypertension who has CKD stage 3 may well develop increased levels of hypertension in the third trimester, requiring early delivery of the baby in some cases
- Pregnancy in a woman with CKD stages 4–5 requires a lot of specialist intervention. Anaemia may be a particular problem, as it can affect development of the placenta. The use of ESA should be considered, preferably in a combined nephrology/obstetric clinic
- Blood pressure and renal function should be monitored carefully in the early post-delivery period

CHILDREN AND INHERITED CKD

- Most causes of CKD are not directly passed onto patients' children, and so routine screening is not required
- Polycystic kidney disease is an exception, and screening may help identify those at risk of developing renal failure and targeting for increased blood pressure control (see p. 47)
- Reflux nephropathy is another condition where screening may help, especially as affected children are at risk of urine infection and renal scarring in the first 3 years of life. Reducing this early renal damage may reduce their chances of developing kidney failure in later years
- In most other common kidney conditions, routine family screening is not required, although may be considered in individual cases according to the family history and wishes of the parents/those who may wish to be screened

LIFE EXPECTANCY

- The relative life expectancy by age and CKD stage obtained in a research study in Coventry is shown on pp. 26–27. These results are comparable with those from other research studies
- This shows that life expectancy seems to be reduced in CKD stages 4 and 5 at any age, and in CKD stage 3 in younger people. The significance of CKD stage 3 in older people, especially for eGFR 45–59 ml/min per 1.73 m², is uncertain, but there is not a large effect on life expectancy
- It should be stressed again that anyone with CKD is more likely to die of cardiovascular disease than of kidney failure. Only about 10% of people with CKD stage 4 will progress to CKD stage 5 and established renal failure

PATIENT AND CARER INFORMATION:

CKD AND LIFE EXPECTANCY

- Research has shown an increased risk of death in people with CKD compared with other people of the same age with normal renal function
- Very few people with CKD stage 3 or 4 actually die of kidney failure, and seem to have death rates due to circulatory diseases that are about two to five times higher than people of their own age without CKD
- However, people aged over 70 years who have stage 3 CKD with an eGFR of 45–59 ml/min per 1.73 m² may have a life expectancy that is very similar to those of a similar age without CKD
- It is difficult to give exact survival rates for an individual, as the survival of someone with CKD depends very much on whether they already have another condition, such as heart disease

END-OF-LIFE CARE

- End-of-life care for CKD patients falls into three main categories:
 - ◆ Care for those who are dying primarily of comorbidities (such as heart failure)
 - ◆ Care for those who develop established renal failure but who are not suitable for dialysis
 - ◆ Care for those already on dialysis or have had a transplant
- The principles of management do not differ greatly from end-of-life care in other conditions
- There can be some tension if someone is dying with established renal failure and dialysis is not planned, but the patient or their family requests that dialysis is given. In many cases this would not be appropriate and the symptoms that require palliation should be treated. Occasionally someone who has opted for non-dialysis care of established renal failure will change their minds and may be dialysed. This needs to be discussed with their nephrologist in the first instance
- Links between renal units and palliative care teams have developed over the last few years, and hospices or other services that were once considered to be for people dying of cancer are now open to those dying of CKD
- Established renal failure by itself does not normally cause severe pain. Symptom relief normally concentrates on treating nausea or sickness, itching, and in the terminal stages of uraemia there may be confusion or agitation and some distress. Combinations of opiates, haloperidol or other anti-emetics are usually helpful

For those readers who prefer a case-oriented approach rather than a standard textbook approach, here are some case studies of referrals from secondary to primary care. These have been chosen because they cover most of the reasons for referral to secondary care, and also illustrate some of the uncertainties in management.

So let's sit through a CKD new patient clinic.

REFERRAL FOR CKD STAGE 3

'Please see this 55-year-old woman whose eGFR was 55 ml/min per 1.73 m² three years ago, and is now 35 ml/min per 1.73 m²'

- Uncomplicated CKD stage 3 can be managed in primary care, and there are various triggers for referral to a specialist. One of these is a fall in eGFR >5 ml/min per 1.73 m² per year. Therefore this is an appropriate referral
- On the face of it, this woman could need dialysis in 3 years' time if the eGFR keeps falling at the present rate. Therefore the aim of nephrology intervention is to try and prevent established renal failure, and if this is not possible, to plan dialysis or transplantation well in advance
- The first step is to establish more data points for creatinine/eGFR. Sometimes it turns out that the eGFR of 35 ml/min per 1.73 m² has been obtained during an inter-current illness, and that the true chronic stable level of eGFR is much better
- If there is progressive loss of renal function, my job is to establish a diagnosis, using initially urine dipstick for blood and protein, renal ultrasound, and bloods, including screening for myeloma and autoantibodies. Renal biopsy might be indicated if there is haematuria or proteinuria and preserved renal sizes
- Usually there is no renal disease that will respond to specific treatment, so management would be to optimise lifestyle, blood pressure and lipid levels

- The patient should understand that the aim of treatment is to try and prevent established renal failure. She would be followed up in the clinic to monitor her progress and to introduce her to renal failure education at an appropriate time if her eGFR continues to fall

REFERRAL FOR CKD STAGE 4

AND HEART FAILURE

‘Please see this 82-year-old man who has an eGFR of 22 ml/min per 1.73 m², which fell to 12 ml/min per 1.73 m² during a recent episode of heart failure and then recovered. His serum sodium is 132 mmol/l and serum potassium is 5.9 mmol/l – both levels are stable. At his best he is limited by breathlessness. Medications are: furosemide 80 mg bd; lisinopril 15 mg od; cocodamol prn; ibuprofen prn; gliclazide 40 mg bd; metformin 500 mg tds; spironolactone 25 mg od; carvedilol 6.25 mg bd; atorvastatin 40 mg od’

- This man would appear to have CKD stage 4. Although an eGFR of 12 ml/min per 1.73 m² is within CKD stage 5, this fall was not sustained and does not reflect the level of his chronic kidney disease
- He has heart failure, which may be ischaemic in origin, but I should double check the urine protein dipstick to make sure there is not heavy proteinuria that would be suggestive of diabetic nephropathy
- More often, patients have a long history of hypertension and minimal proteinuria, and I would think it most likely there was hypertensive nephrosclerosis causing his CKD
- Renal artery stenosis would be a possibility, though at this level of renal function treating it with angioplasty may not help the eGFR
- I would talk to the patient about his experience with fluid balance: how often he gets fluid overloaded, how he responds to this, and if he is prone to volume depletion. I’d give advice about salt restriction and keeping a steady fluid intake each day. The fluid intake and/or the diuretic dosage could be varied to pre-empt any episodes of serious heart failure
- The medications require considerable review. At this level of eGFR, especially with the fairly high potassium level, the spironolactone should be stopped. Even if the potassium is normal now, it could increase sharply during an illness

- Metformin is not a good drug at this level of renal function, as acidosis can occur. Replacement with a ‘-glitazone’ may not be straightforward, as these can cause fluid retention, especially with CKD. So I’d suggest increasing the gliclazide dose and monitoring carefully
- Ibuprofen may cause fluid retention and have an additional adverse effect on the kidneys. He should avoid this, and the reason he takes the drug should be explored. He should be advised on how to avoid over-the-counter ibuprofen, and reminded that topical NSAIDs can have the same problems as tablet NSAIDs
- This patient probably does not need long-term specialist follow-up

REFERRAL FOR CKD STAGE 5

‘Please see this 87-year-old lady with a creatinine of 510 $\mu\text{mol/l}$. She is diabetic, is in a wheelchair, and has required several blood transfusions in the last 6 months’

- This referral sounds quite appropriate, but it might be months and months later than it should have been
- From the letter alone, it is clear that if the creatinine is sustained at this level, and is taken during an acute episode, she has CKD stage 5, indeed established renal failure with an eGFR below 10 ml/min per 1.73 m². This patient should already have had a management plan for established renal failure some time ago
- If she is transfusion-dependent, this is likely to be due to the anaemia of renal failure, and perhaps the transfusions could have been prevented if an ESA had been prescribed at the right time
- Therefore this patient will need an urgent assessment either as an inpatient, or with rapid-response outpatient visits. Ideally this might include a home visit from a specialist renal nurse, who can discuss with the patient and family at home what treatment plan they want
- The plan may be not to dialyse, and to give palliation. However, discussions about the use of dialysis or not should be made with more forward planning than this
- At this level of creatinine it is likely that the lady already has symptoms, such as loss of appetite or itching, and these should be addressed urgently

REFERRAL FOR MICROSCOPIC HAEMATURIA

'Please see this 52-year-old lady with persistent microscopic haematuria, who has a normal creatinine level'

- On the basis of the information in the letter, the patient has CKD stage 1 with no complications, and can be followed up in primary care. So if I had seen this letter before the clinic, I would have refused the referral and spoken to the GP
- Referral to secondary care would be triggered if there were additional abnormalities, such as significant proteinuria, an abnormal ultrasound scan, recurrent urinary tract infections or persistent loin pain
- So the GP should measure the blood pressure and urine dipstick. If the dipstick shows '+ protein' or more, the PCR should be measured. If these are normal and the patient is well, the patient can be seen annually in primary care
- Should the patient be referred to a urological haematuria clinic? These clinics have been developed to diagnose structural lesions, especially cancer. NICE guidance states that anyone aged over 50 years with microscopic haematuria should be referred, and she falls into this category. The NICE referral criteria for haematuria clinics have been 'watered down' by many urology services, who state that they should only see 'unexplained' microscopic haematuria in patients aged over 50 years. Therefore, if this lady had dipstick positive for protein with a PCR of 120 mg/mmol and a slightly reduced eGFR, a nephrologist might feel that the haematuria could be explained by a glomerular lesion, even if this was not severe enough to trigger renal biopsy. In this circumstance a urology service might not feel that a haematuria clinic referral is required. If in doubt, though, it is probably better to refer to a haematuria clinic, as missing even the occasional renal tract tumour can have very severe consequences

REFERRAL FOR PROTEINURIA

'Please see this 22-year-old man who has an ACR of 105 mg/mmol, a normal eGFR and a blood pressure of 140/80 mmHg'

- The patient would appear to have CKD stage 1 or 2, and at this level of proteinuria referral to me is appropriate

- The GP gives an ACR, not PCR. The PCR is generally 20–50% higher than the ACR on a given urine specimen, as there is protein in the urine that is not albumin. In this setting, there is no problem my seeing the patient with an ACR instead of a PCR
- The protein loss is not enough to be associated with nephrotic syndrome or to make him unwell in any way, but is a marker of some sort of renal damage, albeit slight at this time
- The main renal pathologies that would cause this level of proteinuria are reflux nephropathy and a minor glomerular lesion
- To look for reflux nephropathy, I would ask him if there was a family history of kidney disease and whether he had ever had any urine infections. I would request a renal ultrasound scan, and as the operator would look for any evidence of reduced renal size, renal scarring or loss of cortical thickness
- If reflux nephropathy did seem likely, I would advise him of the risk of hypertension and kidney damage in the future, and strongly advise careful follow up; this could be done initially in primary care. He should be aware of the chance of other family members inheriting the condition
- To look for glomerular disease, I would see if urine dipstick testing showed any haematuria. The renal ultrasound should be normal if he has glomerular disease at this level of eGFR. Renal biopsy is unlikely to be indicated in this case scenario
- What about the blood pressure? It does not reach the formal definition of hypertension (140/90 mmHg), but is above the treatment limit for someone with significant proteinuria (130/80 mmHg) (see p. 33). I would ask for careful monitoring of his blood pressure and proteinuria, with treatment started if they remain at these levels
- This patient should not need long-term routine follow-up in a secondary care clinic. But I might offer a second appointment to answer any further questions, and make sure he understands the importance of a management plan, and that re-referral to my clinic would be needed if the proteinuria increases, eGFR decreases or his blood pressure goes out of control

REFERRAL FOR DIABETES AND REDUCED eGFR

‘Please see this 64-year-old man with diabetes and an eGFR of 45 ml/min per 1.73 m² and PCR of 85 mg/mmol’

- This is an appropriate referral to nephrology outpatients, even if the rate of change of eGFR is not fully clear
- The important question is whether the diagnosis is diabetic nephropathy. If this is the case, there is a high risk of progression to established renal failure over the next few years, and a high chance of developing other problems, such as heart attack, stroke or serious diabetic eye disease
- Diabetic nephropathy is more likely if the kidneys are normal on ultrasound, there is no haematuria and diabetic retinopathy is present. I would not ask for a renal biopsy to confirm the diagnosis if I thought the diagnosis was diabetic nephropathy. I would only ask for a biopsy if I thought something else was going on, especially if it was treatable (not often the case in nephrology, sadly)
- Management is likely to consist of the usual measures of lifestyle, and control of blood pressure (including ACEI/ARB) and blood lipids and glucose. A nephrologist should not be necessary to achieve these treatment goals, and many patients referred from primary care have little a nephrologist can add to treatment at this stage
- I would assess the risk of progression to established renal failure in the future, and probably follow up the patient at intervals so that assessment and education on dialysis and transplantation can be made at the appropriate time

REFERRAL FOR UNCONTROLLED HYPERTENSION

IN SOMEONE WITH VASCULAR DISEASE

‘Please see this 76-year-old woman with CKD stage 3, blood pressure 185/90 despite three antihypertensive drugs. She has previous coronary artery surgery’

- The level of blood pressure on three antihypertensive drugs makes this referral appropriate

- She may have hypertensive nephrosclerosis, but in someone who has already clearly had macrovascular disease, it is important to assess whether the patient has atherosclerotic renal artery stenosis. If this is the case, she should have either none or a little protein in her urine, and unequal sized kidneys on ultrasound. I would also look through any previous data to see if her renal function had declined if an ACEI has been started, though a lack of effect of ACEI/ARB on renal function does not exclude renal artery stenosis
- If I suspected renal artery stenosis, I would organise a CT or MR scan of her renal arteries, and consider angioplasty if she has significant disease, as this could improve her blood pressure. However, the effects of successful renal artery angioplasty on blood pressure are not consistent. While there could be some improvement, she would undoubtedly still require some antihypertensive medication
- Her normal day-to-day blood pressure level needs to be established. If there is a question of 'white coat hypertension', ambulatory blood pressure monitoring or home blood pressure monitoring may be helpful
- If she requires more antihypertensive therapy, it is a matter of going carefully through different classes of drug. Some patients do require five different classes of antihypertensive. I refer some patients on to a specialist hypertension clinic. These are often (but not always) run by nephrologists. Even within nephrology, some practitioners are more skilled than others in hard-to-control hypertension



Appendix 1

NICE GUIDANCE RELEVANT TO CKD

Type 2 diabetes, renal disease. Inherited guideline, published 2002

Type 1 diabetes. Clinical guideline 15, published 2004

Hypertension. Clinical guideline 34, published 2006

Anaemia management in chronic kidney disease. Clinical guideline 39, published 2006

Urinary incontinence. Clinical guideline 40, published 2006

Urinary tract infection in children. Clinical guideline 54, published 2007

Chronic kidney disease. Clinical guideline, published 2008

Type 2 diabetes, update. Clinical guideline, to be published 2008

THE NATIONAL SERVICE FRAMEWORK

Part 2 of the Renal National Service Framework (NSF) is about CKD, and was published in 2005. The full document can be found on the Department of Health website:

www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4101902



Appendix 2

GP CARE AND THE QUALITY

AND OUTCOMES FRAMEWORK

- The Quality and Outcomes Framework (QOF) is a national initiative to incentivise (pay) GPs and their practices for achieving a series of outcomes
- The QOF was introduced in 2004, and points were accrued for various organisational achievements (eg holding an annual patient survey), and also for the management of certain chronic medical conditions, such as hypertension, coronary heart disease, diabetes, asthma and chronic obstructive pulmonary disease
- CKD was introduced into the QOF in 2006
- Broadly speaking, points were given for having a register of patients with CKD stages 3–5, measuring their blood pressure and renal function, and treating as many patients as possible with ACE inhibitors
- The aims of the QOF were to reduce the numbers of patients progressing to CKD stage 5, and also to reduce cardiovascular morbidity and mortality in all people with CKD
- A large proportion of patients with CKD stages 3–5 were already on one or all of the hypertension, diabetes or coronary heart disease registers, and were having their blood pressure monitored and treated
- However, the CKD QOF did drive laboratories to standardise their measurements of serum creatinine and to calculate the eGFR
- Primary care had to become used to the notion of eGFR and CKD stages, something that not all nephrologists had thought useful until recently
- The QOF labels many older people who appear to be fit and well as having CKD stage 3

- For those with eGFR 45-60 ml/min per 1.73 m², the value of being told that they have a kidney condition has been questioned by some, and has focused attention on how to refine the QOF so that treatment and information about health is targeted more accurately
- The QOF criteria for CKD will be refined over time, perhaps using proteinuria to identify better those at greatest risk
- The QOF arrived a little before long-term epidemiological and interventional studies have defined fully the importance of CKD stage 3 in the elderly
- It is to be hoped there will be a consensus between those who feel that the QOF is a case of action before evidence, and those who feel the QOF is a brave initiative to improve the health of the population



Glossary

ACEI/ARB angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. Classes of drug that vasodilate arterioles by reducing the action of angiotensin, a natural vasoconstrictor. May reduce the blood pressure, improve symptoms of heart failure, and have additional benefit in CKD by reducing glomerular pressure and so damage to the glomeruli. Rarely may cause problems if there is renal artery stenosis, so their use in CKD requires careful monitoring

ACR albumin to creatinine ratio, the ratio of these two compounds in the urine, gives a measurement of whether there is significant albumin loss in the urine

ARAS atherosclerotic renal artery stenosis

Creatinine a waste substance produced by muscles. The higher the creatinine level, the less well the kidneys are working

CT computerised tomography, a method of obtaining detailed internal images using x-rays. Commonly used to examine the renal arteries and to diagnose and to stage cancer. Can also be used in combination with intravenous contrast to obtain a more detailed examination than an IVU used to image the renal arteries (CT angiography, or CTA)

Dialysis an artificial process by which the toxic waste products of food and excess water are removed from the body

DMSA scan a scan of the kidneys obtained after the injection of a compound labelled with a radio-isotope. Gives information on the distribution of functional tissue in the kidneys, can be useful to diagnose localised scarring

DTPA scan a scan of the kidneys obtained after the injection of a compound labelled with a radio-isotope. Gives information on rate of excretion of isotope by each kidney, can measure the relative function of each kidney, and detect obstruction to the outflow of urine

eGFR estimated glomerular filtration rate, a measurement of renal function obtained from the serum creatinine and MDRD formula

End stage renal failure (ESRF) life-threatening reduction in kidney function, effectively CKD stage 5. The term ERF is now preferred

Established renal failure (ERF) life-threatening reduction in kidney function, effectively CKD stage 5

Erythropoiesis-stimulating agent (ESA) a drug that treats anaemia by stimulating the bone marrow to produce red cells (at one time these agents were all types of EPO, now some of the newer drugs are not strictly speaking EPO, the term ESA is used to include all the drugs)

Erythropoietin (EPO) the natural hormone that stimulates the bone marrow to produce red blood cells, and the name also given to some of the drugs used to treat anaemia

FSGS focal and segmental glomerulosclerosis, a type of glomerulonephritis associated with proteinuria. A firm diagnosis can only be made by renal biopsy

GFR glomerular filtration rate, the rate in ml/min that plasma is filtered from the blood in the kidneys

Hyperkalaemia an elevated level of blood potassium

IVU intravenous urogram, x-ray imaging of the kidneys, ureters and bladder obtained after an intravenous injection of contrast. Still useful in the management of patients with suspected stone disease, but less use in patients with CKD

MCGN mesangiocapillary glomerulonephritis, a type of glomerulonephritis associated with proteinuria. A firm diagnosis can only be made by renal biopsy

MDRD initials of a clinical trial performed some years ago in the USA: Modification of Diet in Renal Disease. A very large number of trial participants had both serum creatinine and GFR measured, so it was possible to get the best statistical fit between blood creatinine levels and GFR, ie the estimated GFR

MR magnetic resonance, a method of imaging that uses a magnetic to excite atoms in the body, rather than using x-rays. It can be used to image the renal arteries, when it is termed magnetic resonance angiography (MRA)

NICE National Institute for Health and Clinical Excellence. Produces guidance for the NHS (www.nice.nhs.uk)

NSAIDs non-steroidal anti-inflammatory drugs, for example ibuprofen and diclofenac. They may reduce renal blood flow and can affect renal function

Palliative treatment treatment directed to reducing symptom burden in end-of-life care

PCR protein to creatinine ratio, the ratio of these two compounds in the urine, gives a measurement of whether there is significant protein loss in the urine

Phosphate a mineral important in the bones and cellular metabolism. Normally phosphate is excreted by the kidneys. In CKD stages 4 and 5 the blood level of phosphate may rise, and dietary restriction or drug treatment may be required

Proteinuria the presence of protein in the urine. Normally it is only present in very small quantities. Measured by dipstick as a screening tool, then by ACR or PCR

PTH parathyroid hormone, a substance that when secreted raises the level of calcium in the blood. May be stimulated by low calcium levels in CKD

Renal artery stenosis narrowing of artery to the kidney. Most commonly caused by atheroma. It may cause reduced kidney function, hypertension or fluid overload with pulmonary oedema. Suspected especially when ultrasound shows unequal sized kidneys, diagnosed by CT or MR scans

SLE systemic lupus erythematosus, a multi-system autoimmune disease characterised by autoantibodies against double-stranded DNA. Can cause kidney disease, usually a glomerulonephritis with proteinuria

Sodium a mineral important in the metabolism of the body, but which also contributes to hypertension in CKD. Sodium is found in salt, and CKD patients with hypertension should restrict their salt intake



Resources

You will find many information leaflets from the National Kidney Federation.

A DVD featuring patients and kidney specialists is available from Kidney Research UK: www.kidneyresearchuk.org

The following books are also likely to be helpful:

Auer J (2004) *Living Well With Kidney Failure*. London: Class Publishing

Cameron SA (1996) *Kidney Failure: the facts*. Oxford: Oxford University Press

Higgins R (2005) *Help I've got Kidney Failure*. London: Class Publishing

Higgins R (2007) *CKD Health Check*. London: Class Publishing

Jackson H, Cassidy A, James G (2005) *Eating Well With Kidney Failure*.

London: Class Publishing

Stein A, Wild J (2002) *Kidney Dialysis and Transplants: the 'at your fingertips' guide*. London: Class Publishing

Stein A, Wild J (2002) *Kidney Failure Explained*. London: Class Publishing

PATIENTS' ASSOCIATIONS

British Kidney Patient Association (BKPA)

Bordon

Hants GU35 9JZ

Tel: 01420 472021/2

Fax: 01420 475831

Website: www.britishkidney-pa.co.uk

Diabetes UK

10 Parkway

London NW1 7AA

Tel: 020 7424 1000

Fax: 020 7424 1001

Helpline: 0845 1202 960

Website: www.diabetes.org.uk

Kidney Research UK

King's Chambers

Priestgate

Peterborough PE1 1FG

Tel: 01733 704650

Fax: 01733 704699

Helpline: 0845 300 1499

Website: www.kidneyresearchuk.org

National Kidney Federation

The Point

Coach Road

Shireoaks

Worksop

Notts S81 8BW

Tel: 01909 544999

Fax: 01909 481723

Helpline: 0845 601 02 09

Website: www.kidney.org.uk

KEY WEBSITES

As well as the websites listed above, there are very many more that you may find useful. Here are some suggestions:

www.aakp.org

The American Association of Kidney Patients

www.bhf.org.uk

The British Heart Foundation

www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Renal/fs/en

Department of Health publications for the NHS on kidney diseases

www.edren.org

The website of the Edinburgh Renal Unit. For general information go to the EdRenInfo link at the top of the home page

www.kidney.org

The National Kidney Foundation, America

www.kidneydirections.com

Information for kidney patients, and suggestions for ways to plan treatment

www.kidney.org.uk/Medical-Info/drugs/vacc2.html

The section of the NKF website giving information about medicines and vaccinations that can and can't be used for people with kidney transplants

www.kidneypatientguide.org.uk

Information for people with kidney failure and those who care for them

www.nephron.com

Exhaustive information on everything to do with kidney diseases

www.nice.org.uk

The National Institute for Health and Clinical Excellence produces clinical guidelines for the NHS, which include treatment of anaemia in CKD, diabetes and high blood pressure. CKD guidance was published in 2008

www.patients-association.com

Provides advice on patients' rights

www.renal.org

Renal Association, the UK national body of kidney specialists. Has a useful section on CKD, with information on how eGFR is calculated and links to national guidance

www.renalpatientview.org

This site enables patients in some UK kidney units to view their own results and care pathways on the Internet

www.uktransplant.org.uk

National Health Service site giving information about transplantation and organ donation

REFERENCES

There are no other short textbooks on CKD produced in the UK. A good general textbook of nephrology, aimed at nephrologists rather than primary care, is:

Feehally J, Floege J, Johnson RJ (2007) *Comprehensive Clinical Nephrology*, 3rd edn. Edinburgh: Mosby

The Renal Association has a comprehensive package of resources about CKD, ranging from detailed information to support eGFR reporting to links to patient information: www.renal.org/pages/pages/other-info/ckd-info.php

The UK CKD guidelines were published in 2005 under the auspices of the Royal College of Physicians and the Renal Association, and in February 2007 the Renal Association, the Scottish Renal Association and the Royal College of Physicians of Edinburgh published a consensus statement on CKD. These documents can be accessed via the Renal Association website: www.renal.org/CKDguide/ckd.html

General issues in primary care

Carter JL, Tomson CRV, Stevens PE, Lamb EJ (2006) Does urinary tract infection cause proteinuria or microalbuminuria? A systematic review. *Nephrology Dialysis Transplantation* 21: 3031–7

Francis RS, Tomson CR (2004) A GP guide to glomerulonephritis. *Practitioner* 248: 848–55

Roderick PJ, Atkins RJ, Smeeth L *et al.* (2008) Detecting chronic kidney disease in older people: what are the implications? *Age Ageing* 37:179–86

Tomson C, Porter T (2002) Asymptomatic microscopic or dipstick haematuria in adults: which investigations for which patients? *BJU International* 90: 185–8

Tomson CR (2003) Indications for renal biopsy in chronic kidney disease. *Clinical Medicine* 3: 513–7

Epidemiology

- Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS (2003) Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. *American Journal of Kidney Disease* 41: 1–12
- Coresh J, Selvin E, Stevens LA, *et al.* (2007) Prevalence of chronic kidney disease in the United States. *JAMA* 298: 2038–47
- Glasscock RJ, Winearls C. (2008) An epidemic of chronic kidney disease: fact or fiction? *Nephrology Dialysis Transplantation* 23: 117–21
- Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY (2004) Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. *New England Journal of Medicine* 351: 1296–1305
- Manjunath G, Tighiouart H, Coresh J, *et al.* (2003) Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney International* 63:1121–9.
- Raymond NT, Zehnder D, Smith SCH *et al.* (2007) Elevated relative mortality risk with mild-to-moderate chronic kidney disease decreases with age. *Nephrology Dialysis Transplantation* 22: 3214–20
- Shlipak MG, Sarnak MJ, Katz R, *et al.* (2005) Cystatin C and the risk of death and cardiovascular events among elderly persons. *New England Journal of Medicine* 352: 2049–60

Impact of interventions

- Baigent C, Landray M, Leaper C *et al.* (2005) First United Kingdom Heart and Renal Protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. *American Journal of Kidney Disease* 45: 473–84
- Richards N, Harris K, Whitfield M *et al.* (2007) Primary care-based disease management of chronic kidney disease (CKD), based on estimated glomerular filtration rate (eGFR) reporting, improves patient outcomes. *Nephrology Dialysis Transplant* 23: 549–55
- Richards N, Harris K, Whitfield M *et al.* (2007) The impact of population-based identification of chronic kidney disease using estimated glomerular filtration rate (eGFR) reporting. *Nephrology Dialysis Transplant* 23: 556–61

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KIDNEY FAILURE EXPLAINED

Dr Andy Stein
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