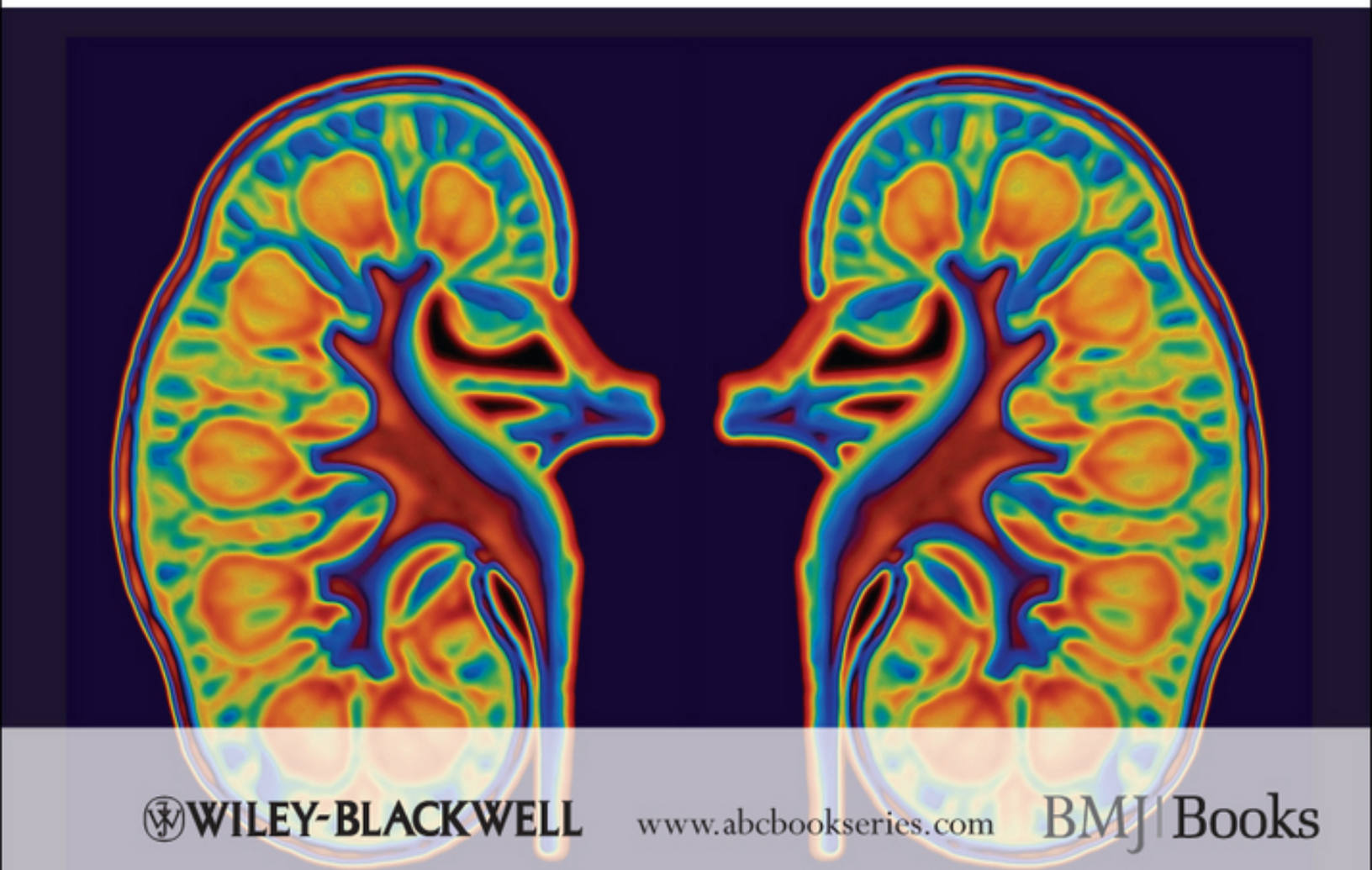
ABC of Kidney Disease

SECOND EDITION

Edited by David Goldsmith, Satish Jayawardene and Penny Ackland



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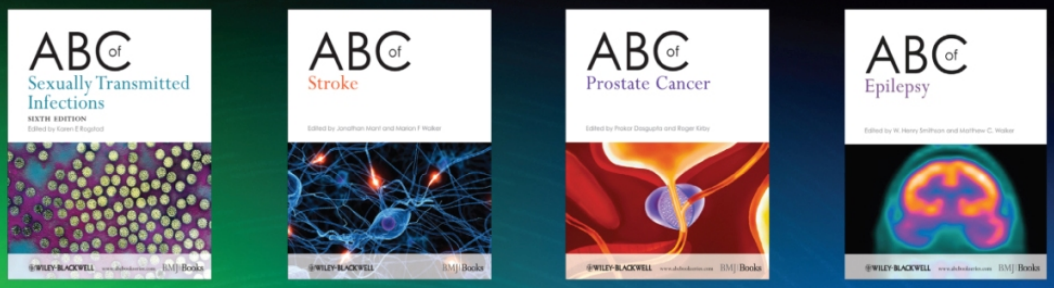

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Kidney Disease

Second Edition

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Preface

This is the second edition of this popular handbook on kidney disease. It is necessary because important advances have been made in several areas, including the treatment of the anaemia associated with chronic kidney disease. Moreover, with the passage of time, more is now known about the prevalence, and importance, of chronic kidney disease in the United Kingdom and the rest of the world. In this second edition, we refine the presentation of the information concerning chronic kidney disease, we expand on the importance of good preparation for dialysis and transplantation, where those options are relevant, and we expand on the important area of conservative, or non-dialytic, management of the symptoms of chronic kidney disease, an option which is taken by increasing numbers. We have also revised the appendices, which include a Top Ten Tips section for quick reference. All in all, we hope and feel that this new version is an improvement on its predecessor, and that readers (from students to non-kidney specialists) will find this book a useful guide to the best management of a growing number of patients.

Chapter 1

Diagnostic Tests in Chronic Kidney Disease

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Overview

- Urinary protein excretion of <150 mg/day is normal (~30 mg of this is albumin and about 70–100 mg is Tamm-Horsfall (muco)protein, derived from the proximal renal tubule). Protein excretion can rise transiently with fever, acute illness, urinary tract infection (UTI) and orthostatically. In pregnancy, the upper limit of normal protein excretion is around 300 mg/day. Persistent elevation of albumin excretion (microalbuminuria) and other proteins can indicate renal or systemic illness.
- Repeat positive dipstick tests for blood and protein in the urine two or three times to ensure the findings are persistent.
- Microalbuminuria is an early sign of renal and cardiovascular dysfunction with adverse prognostic significance.
- Non-visible haematuria (NVH) is present in around 4% of the adult population—of whom at least 50% have glomerular disease.
- If initial glomerular filtration rate (GFR) is normal, and proteinuria is absent, progressive loss of GFR amongst those people with NVH of renal origin is rare, although long-term (and usually community-based) follow-up is still recommended.
- Adults aged 40 years old or more should undergo cystoscopy if they have NVH.
- Any patient with NVH who has abnormal renal function, proteinuria, hypertension and a normal cystoscopy should be referred to a nephrologist.
- Blood pressure control, reduction of proteinuria and cholesterol reduction are all useful therapeutic manoeuvres in those with renal causes of NVH.
- All NVH patients should have long-term follow-up of their renal function and blood pressure (this can, and often should be, community-based).
- Renal function is measured using creatinine, and this is now routinely converted into an estimated glomerular filtration rate (eGFR) value quickly and easily.
- The most common imaging technique now used for the kidney is the renal ultrasound, which can detect size, shape, symmetry of kidneys and presence of tumour, stone or renal obstruction.

Symptoms of chronic kidney disease (CKD) are often non-specific (Table 1.1). Clinical signs (of CKD, or of systemic diseases or syndromes) may be present and recognized early on in the natural history of kidney disease but, more often, both symptoms and signs are only present and recognized very late—sometimes too late to permit effective treatment in time to prepare for dialysis. However, the most

commonly performed test of renal function—plasma creatinine—is typically performed with every hospital inpatient and as part of investigations or screening during many GP surgery or hospital clinic outpatient episodes.

Table 1.1 Signs and symptoms of chronic kidney disease

Symptoms	Signs
Tiredness	Pallor
Anorexia	Leuconychia
Nausea and vomiting	Peripheral oedema
Itching	Pleural effusion
Nocturia, frequency, oliguria	Pulmonary oedema
Haematuria	Raised blood pressure
Frothy urine	
Loin pain	

Unlike ‘angina’ or ‘chronic obstructive airways disease’, where a history can be revealing (e.g. walking distance or cough), there is little that is quantifiable about CKD severity without blood and/or urine testing.

This is why serendipitous discovery of kidney problems (haematuria, proteinuria, structural abnormalities on kidney imaging or loss of kidney function) is a common ‘presentation’. A full understanding of what these abnormalities mean and a clear guide to ‘what to do next’ are particularly needed in kidney medicine, and filling this gap is one of the aims of this book.

Correct use and interpretation of urine dipsticks and plasma creatinine values (by far the commonest tests used for screening and identification of kidney disease) is the main focus of this chapter. Renal imaging and renal biopsy will also be described briefly.

Urine Testing

Urinalysis is a basic test for the presence and severity of kidney disease. Testing urine during the menstrual period in

women, and within 2–3 days of heavy strenuous exercise in both genders, should be avoided, to avoid contamination or artefacts. Fresh ‘mid-stream’ urine is best, again to reduce accidental contamination. Refrigeration of urine at temperatures from +2 to +8°C assists preservation. Specimens that have languished in an overstretched hospital laboratory specimen reception area, before eventually undergoing analysis, will rarely reveal all of the potential information that could have been gained.

Changes in urine colour are usually noticed by patients. Table 1.2 shows the main causes of different-coloured urine. Chemical parameters of the urine that can be detected using dipsticks include urine pH, haemoglobin, glucose, protein, leucocyte esterase, nitrites and ketones. Figure 1.1 shows the dipstick in its ‘dry’ state and an example of a positive test. Table 1.3 shows the main false negative and false positive results that can interfere with correct interpretation.

Table 1.2 The main causes of differently coloured urine

Pink–red–brown–black	**Yellow–brown**	**Blue–green**
Gross haematuria (e.g. bladder or renal tumour; IgA nephropathy)	**Jaundice** **Drugs**: chloroquine, nitrofurantoin	**Drugs**: triamterene
		Dyes: methylene blue
Haemoglobinuria (e.g. drug reaction)		
Myoglobinuria (e.g. rhabdomyolysis)		
Acute intermittent porphyria		
Alkaptonuria		
Drugs: phenytoin, rifampicin (red); metronidazole, methyldopa (darkening on standing)		
Foods: beetroot, blackberries		

Figure 1.1 Urine dipstick—the urine on the right is normal and the colours of all of the squares on the urine dipstick are normal/negative. The urine on the left is from someone with acute glomerulonephritis, looks pink-brown macroscopically and has maximal blood and protein on the dipstick.

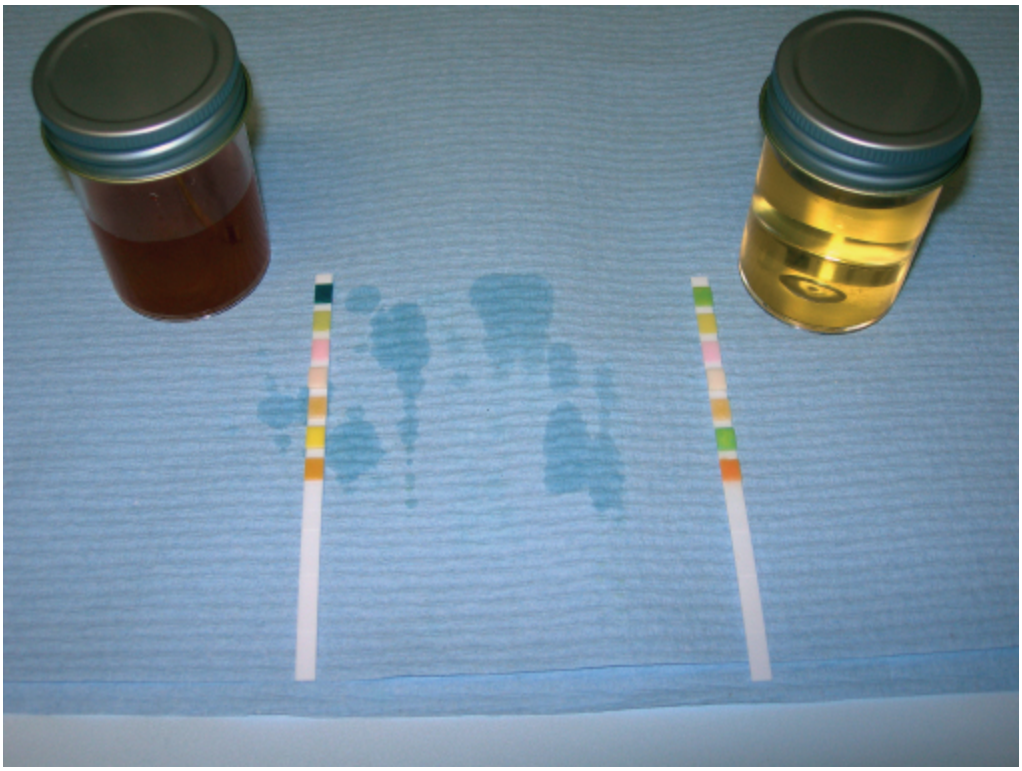


Table 1.3 The main causes of false negative and false positive testing from use of urine dipsticks

Test	False positive	False negative
Haemoglobin	Myoglobin	Ascorbic acid
	Microbial peroxidases	Delayed examination
Proteinuria	Very alkaline urine (pH 9)	Tubular proteins
	Chlorhexidine	Immunoglobulin light chains
		Globulins
Glucose	Oxidizing detergents	UTI
		Ascorbic acid

Discounting contamination from menstrual—or other—bleeding, and exercise-induced haematuria and proteinuria.

Urine microscopy can only add useful information to urinalysis when there is a reliable methodology for

collection, storage and analysis. This is often lacking, even in hospitals. Early-morning urine is best, with rapid sample centrifugation. Under ideal circumstances *cells* (erythrocytes, leucocytes, renal tubular cells and urinary epithelial cells), *casts* (cylinders of proteinaceous matrix), *crystals, lipids* and *organisms* can be reliably identified where present in urine. Figure 1.2 shows a red cell cast in urine (indicative of acute renal inflammation). Figure 1.3 shows urinary crystals.

Figure 1.2 Microscopy of centrifuged fresh urine. There is a red cell cast (protein skeleton with incorporated red blood cells). This is characteristic of acute glomerulonephritis.

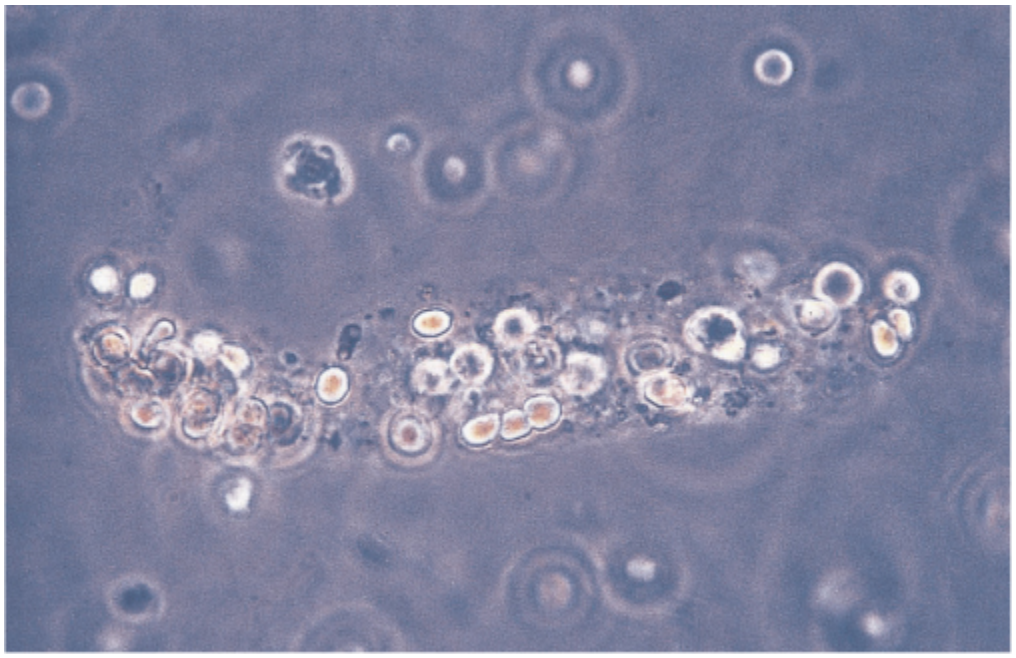
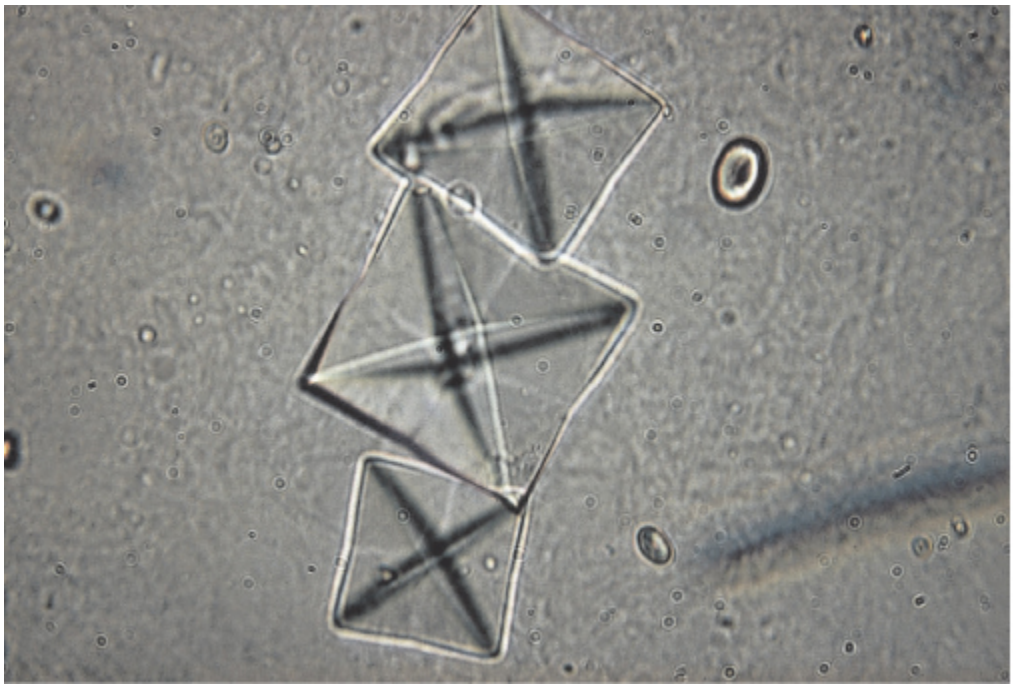


Figure 1.3 Crystalluria.



Non-visible Haematuria

Definition and Background

In healthy people red blood cells (rbc) are not present in the urine in > 95% of cases. Large numbers of rbcs make the urine pink or red.

Non-visible haematuria (NVH) (formerly known as microscopic haematuria) is commonly defined as the presence of greater than two rbcs per high power field in a centrifuged urine sediment. It is seen in 3–6% of the normal population, and in 5–10% of those relatives of kidney patients who undergo screening for potential kidney donation.

NVH can be an incidental finding of no prognostic importance, or the first sign of intrinsic renal disease or urological malignancy. It always requires assessment, and most often requires referral to a kidney specialist or to a urologist.

Clinical Features

The finding of NVH is usually as a result of routine medical examination for employment, insurance or GP-registration purposes in an otherwise apparently healthy adult. Initially, therefore, NVH is an issue for primary healthcare workers. The goal of an assessment is to understand whether:

- there are any clues available from the patient's history, his/her family history or from examination to point to a particular diagnosis, e.g. connective tissue disease, sickle cell disease;
- the haematuria is transient or persistent;
- there is any evidence of renal disease, e.g. abnormal renal function, accompanying proteinuria, raised blood pressure (BP);
- the haematuria represents glomerular (i.e. from the kidney) or extra-glomerular (urological) bleeding.

Investigations

Typically, the full evaluation of NVH requires hospital-based investigations. Box 1.1 lists these in a logical order.

Box 1.1 : Investigations required for the work-up of patients with non-visible haematuria

- Protein:creatinine ratio on fresh urine (if present on urinary dipstick testing)
- Urine microscopy and culture
- Plasma biochemistry and eGFR
- Autoantibody screen, e.g. antinuclear antibody (ANA) and antineutrophil cytoplasmic antibody (ANCA) and complement levels (C3 and C4)
- Renal ultrasound
- Renal CT/MRI (in certain cases)
- Cystoscopy for adults > 40 years of age
- Renal biopsy in certain circumstances

- *Urine microscopy and culture* should also be undertaken. The presence of dysmorphic red cells in the urine increases the possibility of intrinsic/parenchymal kidney disease as opposed to urological disease. This can only be ascertained in a specialist laboratory.
- *Renal structure* can be assessed with a renal ultrasound scan (this can show stones, cysts and tumours). A plain abdominal film will show radio-opaque renal, ureteric or bladder calculi. Renal function should be assessed by measurement of plasma biochemistry and estimated glomerular filtration rate (eGFR). In addition, proteinuria should be looked for by dipstick analysis of the urine and, if present, a protein/creatinine ratio measured. Proteinuria > 0.5 g/24 h (protein:creatinine ratio > 50) suggests glomerular disease and a referral to a kidney specialist is warranted for NVH with significant proteinuria, raised BP or abnormal renal function.

Management

Any patient who presents with persistent non-visible haematuria over the age of 40 should be referred to a urologist. A renal ultrasound, urine cytology and a flexible cystoscopy to exclude urological cancer would normally be undertaken.

Any patient who has abnormal renal function, proteinuria, hypertension and a normal cystoscopy should be referred to a kidney specialist.

Renal biopsy is required to establish a diagnosis with absolute certainty in most cases of ‘renal haematuria’. Those patients who additionally have renal impairment, heavy proteinuria, hypertension, positive autoantibodies, low complement levels or have a family history of renal disease should be considered for a renal biopsy.

Please also see the 2008 NICE CKD guidelines for further information on NVH, http://www.nice.org.uk/nicemedia/live/12069/42119/42119.pdf.

Prognosis

The prognosis for most patients with asymptomatic NVH without urological malignancy and no evidence of intrinsic renal disease is very good. It is beyond the scope of this chapter to discuss the prognosis of all the causes of non-visible haematuria, as listed in Table 1.4. However, some general observations apply for those patients in whom there is no structural cause for NVH and bleeding is glomerular, and these are given below.

Table 1.4 Causes of non-visible haematuria

Renal causes	**Systemic causes**	**Miscellaneous and urological causes**
IgA nephropathy	Systemic lupus erythematosus	Cystic diseases of the kidney
Thin basement membrane disease	Henoch–Schönlein purpura	Papillary necrosis
Alport's syndrome		Urothelial tumours
Focal segmental glomerulosclerosis		Renal and bladder stones
Membranoproliferative glomerulonephritis		Exercise-induced haematuria
Post-infectious glomerulonephritis		

In the presence of impaired renal function, it is mandatory to try to achieve blood pressure control (<130/80 mmHg) and reduction of microalbuminuria or proteinuria (if present). Angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) are useful agents, as they achieve both of these desired effects. It is very important to recheck plasma creatinine and potassium about 7–14 days after starting ACE or ARB, and regularly

thereafter—an increase of ≥ 30% in plasma creatinine or a fall of ≥ 25% eGFR, or a rise of plasma potassium to exceed 5.5 mmol/L, should occasion recall to consider abandoning the drugs or reducing the dose, further investigations, and dietary advice for potassium restriction if relevant.

It is important that these patients, whether monitored in the community or at a hospital-based clinic, have their urine tested, BP measured and renal function monitored regularly. If not under renal specialist follow-up, the development of hypertension, proteinuria or deterioration in renal function are all indications for referral to a specialist unit (see Chapter 3).

Microalbuminuria and Proteinuria

Protein is normally present in urine in small quantities. Tubular proteins (e.g. Tamm-Horsfall) and low amounts of albumin can be detected in healthy people. Microalbuminuria (MAU) refers to the presence of elevated urinary albumin concentrations (see Table 1.5); MAU is a sign of either systemic or renal malfunction.

Table 1.5 Equivalent ranges for urinary protein loss

	Urine dipstick	Albumin excretion rate (AER) (μg/min; mg/24 h)		Urinary albumin:creatinine ratio (mg/mmol)	Protein (mg)/ creatinine (mmol)	Urinary protein (mg/24 h)
Normal	0	6–20	10–30	<2.5 (m) <3.5 (w)	<15	<150
Microalbuminuria	0	>20–200	30–300	>2.5 (m) >3.5 (w)	<15	<150
'Trace' proteinuria	Trace	>200	>300	15–29	15–29	150–299
Proteinuria	+, ++	N/A	N/A	N/A	30–350	300–3500
Nephrotic	+++	N/A	N/A	N/A	>350	>3.5 g

m, men; w, women.

MAU is measured by quantitative immunoassay—and is an important first and early sign of many renal conditions, particularly diabetic renal disease and other glomerulopathies. It is also strongly associated with adverse

cardiovascular outcomes. Around 10% of the population can be shown to have persistent MAU. For confirmation, two out of three consecutive analyses should show MAU in the same three-month period.

UAER (urinary albumin excretion rate)—in a healthy population the normal range for UAER is 1.5–20 µg/min. UAER increases with strenuous exercise, a high-protein diet, pregnancy and urinary tract infections (UTIs). Daytime UAER is 25% higher than at night (so for daytime urine, an upper normal limit of 30 µg/min is often used). Overnight timed collections can be performed (and microalbuminuric range is an overnight UAER of 20–200 µg/min), but for unselected population screening the albumin:creatinine ratio (ACR) in early-morning urine is preferable. An ACR of > 2 predicts a UAER of > 30 µg/min with a high sensitivity.

Increasingly favoured as a screening tool is the urinary protein:creatinine ratio (**PCR**). This is best done on 'spot' early-morning urine samples (as renal protein excretion has a diurnal rhythm; see below). This is now preferable to relying on 24-hour urine collections. There is an inherent assumption in using PCR that urinary creatinine concentration is 10 mmol/L (in practice it can range from 2 to 30), but this is of little practical importance for its use as a screening tool. A PCR of 100 mg/mmol corresponds roughly to 1 g/L of proteinuria.

One question often asked is how to 'convert' an ACR to a PCR. At low levels of proteinuria (<1 g/day), a rough conversion is that doubling the ACR will give you the PCR. At proteinuria excretion rates of > 1 g/day, the relationship is more accurately represented by 1.3×ACR = PCR.

Table 1.5 attempts to display all of the different ways to express urinary protein to allow for comparisons between methods.

Please note that the normal range for protein excretion in pregnancy is up to 300 mg/day, with clinical significance

(pre-eclampsia or renal disease) being more likely once 500 mg or more is excreted per day. See Chapter 6.

Please also see the 2008 NICE CKD guidelines on albuminuria, proteinuria and eGFR, http://www.nice.org.uk/nicemedia/live/12069/42119/42119.pdf.

Tests of Kidney Function

The kidney has exocrine and endocrine functions. The most important function to assess, however, is renal excretory capacity, which we measure as glomerular filtration rate (GFR). Each kidney has about 1 million nephrons, and the measured GFR is the composite function of all nephrons in both kidneys. Conceptually, it can be understood as the (virtual) clearance of a substance from a volume of plasma into the urine per unit of time. The substance can be endogenous (creatinine, cystatin C) or exogenous (inulin, iohexol, iothalamate, ^{51}Cr-EDTA, ^{99m}Tc-DTPA). This 'ideal substance' to measure kidney function does not exist—ideal characteristics being free filtration across the glomerulus, neither reabsorption from nor excretion into renal tubules, existing in a steady state concentration in plasma, and being easily and reliably measured. Despite creatinine failing several of these criteria, it is universally used, and we shall concentrate on interpreting creatinine concentration in urine and blood as it aids derivation of GFR.

The basic anatomy of the kidney and the anatomy and basic physiology of the 'nephron' (the functional component of the kidney), are shown in Figure 7.1.

Table 1.6 shows the different ways in which both plasma urea and plasma creatinine may be 'artefactually' elevated or reduced, which can lead to misunderstanding and miscalculation of renal function. Creatinine is measured by