05-15 Nephrology and urology

15 Nephrology and urology

382 • NEPHROLOGY AND UROLOGY Clinical examination of the kidney and urinary tract Blood pressure Often elevated Jugular venous pressure Elevated in fluid overload Hypertensive changes ‘Brown line’ pigmentation of nails Splinter haemorrhages Lungs Crepitations in fluid overload Observation • Tiredness • Respiratory rate and depth increased in metabolic acidosis • Pallor* Abdomen Renal mass Local tenderness Renal or other arterial bruits in renal vascular disease Rectal examination — prostate Heart Extra heart sounds in fluid overload Pericardial friction rub* *Features of advanced chronic kidney disease (see also Fig. 15.22) Phimosis Skin Yellow complexion* Bruising* Excoriation of pruritus* Reduced skin turgor in fluid depletion Fundoscopy

Hands

10 Sacral oedema 11 Ankle oedema 12 Peripheral neuropathy*

Genitalia Scrotal swellings Urinalysis for blood and protein Urine microscopy See Fig. 15.3

Many diseases of the kidney and urinary tract are clinically silent, at least in the early stages. Accordingly, it is common for these conditions to be detected first by routine blood tests or on dipstick testing of the urine. Several important abnormalities can also be picked up on physical examination, however, and these are summarised below.

Clinical examination techniques to evaluate urological and renal abnormalities. Inset (Dipstick): From Pitkin J, Peattie AB, Magowan BA. Obstetrics and gynaecology: An Iilustrated colour text. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2003. Blood pressure measurements

Blood tests for abnormal creatinine and electrolytes Urinalysis for protein, blood, nitrites and leucocytes

Abdominal examination for palpable kidneys Right kidney Left kidney Percussing for tenderness in renal angle Digital rectal examination for prostate enlargement Checking sacrum and ankles for pitting oedema Male lower urinary tract demonstrating the relationship of the bladder, urethra, vas deferens and testes. Bladder Pubic bones Corpus spongiosum Corpus cavernosum Urethra Glans penis Prepuce Scrotum Testis Epididymis Vas deferens Prostate gland Ejaculatory duct Anus Seminal vesicle Rectum Ureter

 proximal tubule termed Bowman’s capsule, which is composed of epithelial cells. The glomerular capillary endothelial cells contain pores (fenestrae), through which circulating molecules can pass to reach the underlying glomerular basement membrane (GBM), which is formed by fusion of the basement membranes of tubular epithelial and vascular endothelial cells (Fig. 15.1C and D). Glomerular epithelial cells (podocytes) have multiple long foot processes that interdigitate with those of the adjacent epithelial cells, thereby maintaining a selective barrier to filtration (Fig. 15.1E). Mesangial cells lie in the central region of the glomerulus. They have contractile properties similar to those of vascular smooth muscle cells and play a role in regulating glomerular filtration rate. Under normal circumstances, the glomerulus is impermeable to proteins the size of albumin (67 kDa) or larger, while proteins of 20 kDa or smaller are filtered freely. The ability of molecules between 20 and 67 kDa to pass through the GBM is variable and depends on the size (smaller molecules are filtered more easily) and charge (positively charged molecules are filtered more easily). Very little lipid is filtered by the glomerulus. Filtration pressure at the glomerulus is normally maintained at a constant level, in the face of wide variations in systemic blood pressure and cardiac output, by alterations in muscle tone within the afferent and efferent arterioles and mesangial cells. This is known as autoregulation. Reduced renal perfusion pressure increases local production of prostaglandins that mediate vasodilatation of the afferent arteriole, thereby increasing the intraglomerular pressure (Fig. 15.1D). In addition, renin is released by specialised smooth muscle cells in the juxtaglomerular apparatus in response to reduced perfusion pressure, stimulation of sympathetic nerves or low sodium concentration of fluid in the distal convoluted tubule at the macula densa. Renin cleaves angiotensinogen to release angiotensin I, which is further cleaved by angiotensin-converting enzyme (ACE) to produce angiotensin II. This restores glomerular perfusion pressure in the short term by causing vasoconstriction of the efferent arterioles within the kidney to raise intraglomerular pressure selectively (Fig. 15.1D), and by inducing systemic vasoconstriction to increase blood pressure and thus renal perfusion pressure. In the longer term, angiotensin II increases plasma volume by stimulating aldosterone release, which enhances sodium reabsorption by the renal tubules (see Fig. 18.18, p. 666). Consumption of non-steroidal anti-inflammatory preparations and renin–angiotensin system inhibitors in the context of volume depletion may impair the ability of the kidney to maintain glomerular filtration and exacerbate pre-renal failure (see Fig. 15.19, p. 413). Renal tubules, loop of Henle and collecting ducts The proximal renal tubule, loop of Henle, distal renal tubule and collecting ducts are responsible for reabsorption of water, electrolytes and other solutes, as well as regulating acid–base balance, as described in detail on page 350 and in Figure 14.3. They also play a key role in regulating calcium homeostasis by converting 25-hydroxyvitamin D to the active metabolite 1,25-dihydroxyvitamin D (p. 1049). Failure of this process contributes to the pathogenesis of hypocalcaemia and bone disease that occurs in chronic kidney disease (CKD, p. 415). Fibroblast-like cells that lie in the interstitium of the renal cortex are responsible for production of erythropoietin, which in turn is required for production of red blood cells. Erythropoietin synthesis is regulated by oxygen tension; anaemia and hypoxia increase production, whereas polycythaemia and hyperoxia inhibit it. This chapter describes the disorders of the kidneys and urinary tract that are commonly encountered in routine practice, as well as giving an overview of the highly specialised field of renal replacement therapy. Disorders of renal tubular function, which may cause alterations in electrolyte and acid–base balance, are described in Chapter 14. Functional anatomy and physiology The kidneys The kidneys play a central role in excretion of many metabolic breakdown products, including ammonia and urea from protein, creatinine from muscle, uric acid from nucleic acids, drugs and toxins. They achieve this by making large volumes of an ultrafiltrate of plasma (120 mL/min, 170 L/24 hrs) at the glomerulus, and selectively reabsorbing components of this ultrafiltrate at points along the nephron. The rates of filtration and reabsorption are controlled by many hormonal and haemodynamic signals to regulate fluid and electrolyte balance (p. 349), blood pressure (p. 447), and acid–base (p. 363) and calcium–phosphate homeostasis (pp. 367 and 368). In addition, the kidneys activate vitamin D and control the synthesis of red blood cells by producing erythropoietin. Strategies to replace each of these important functions are required when managing patients with kidney failure. Each kidney is approximately 11–14 cm in length in healthy adults; they are located retroperitoneally on either side of the aorta and inferior vena cava between the 12th thoracic and 3rd lumbar vertebrae (Fig. 15.1A). The right kidney is usually a few centimetres lower because the liver lies above it. Both kidneys rise and descend several centimetres with respiration. The kidneys have a rich blood supply and receive approximately 20–25% of cardiac output through the renal arteries, which arise from the abdominal aorta. The renal arteries undergo various subdivisions within the kidney, eventually forming interlobular arteries that run through the renal cortex. These eventually give rise to afferent glomerular arterioles that supply the glomeruli. The efferent arteriole, leading from the glomerulus, supplies the distal nephron and medulla in a ‘portal’ circulation (Fig. 15.1B). This highly unusual arrangement of two serial capillary beds reflects the role of the afferent and efferent arterioles in autoregulation of glomerular filtration. The nephron Each kidney contains approximately 1 million individual functional units, called nephrons. Each nephron consists of a glomerulus, which is responsible for ultrafiltration of blood, a proximal renal tubule, a loop of Henle, a distal renal tubule and a collecting duct, which together are responsible for selective reabsorption of water and electrolytes that have been filtered at the glomerulus (see Fig. 14.2, p. 350, and Fig. 15.1B). Under normal circumstances, more than 99% of the 170 L of glomerular filtrate that is produced each day is reabsorbed in the tubules. The remainder passes through the collecting ducts of multiple nephrons and drains into the renal pelvis and ureters. The glomerulus The glomerulus comprises a tightly packed loop of capillaries supplied by an afferent arteriole and drained by an efferent arteriole. It is surrounded by a cup-shaped extension of the

Fig. 15.1 Functional anatomy of the kidney. A Anatomical relationships of the kidney. B A single nephron. For the functions of different segments, see Figures 14.2 and 14.3 (pp. 350 and 351). C Histology of a normal glomerulus. D Schematic cross-section of a glomerulus, showing five capillary loops, to illustrate structure and show cell types. E Electron micrograph of the filtration barrier. (GBM = glomerular basement membrane) (C) Courtesy of Dr J.G. Simpson, Aberdeen Royal Infirmary. Distal convoluted tubule Endothelial cell Angiotensin II vasoconstricts Prostaglandins vasodilate Pelvis Cortex Calyx Medulla Vena cava Ureter Bladder Afferent arteriole Glomerulus Efferent arteriole Proximal convoluted tubule Collecting duct Thickwalled segment Loop of Henle Thin-walled segment Ureter Renal artery Renal vein Epithelial cell (podocyte) Urinary space Bowman's capsule Parietal epithelium Capillary loops Efferent arteriole Afferent arteriole Mesangial cell Mesangial matrix Juxtaglomerular apparatus Aorta Endothelial cell Epithelial cell (podocyte) Foot process GBM Macula densa Renal artery A B C D E

Investigation of renal and urinary tract disease Glomerular filtration rate The glomerular filtration rate (GFR) is the sum of the ultrafiltration rates from

plasma into the Bowman’s space in each nephron and is a measure of renal excretory function. It is proportionate to body size and the reference value is usually expressed after correction for body surface area as 120 ± 25 mL/min/1.73 m2. The GFR may be measured directly by injecting and measuring the clearance of compounds such as inulin or radiolabelled ethylenediamine-tetra-acetic acid (EDTA), which are completely filtered at the glomerulus and are not secreted or reabsorbed by the renal tubules (Box 15.1). This is not performed routinely, however, and is usually reserved for special circumstances, such as the assessment of renal function in potential live kidney donors. Instead, GFR is usually assessed indirectly in clinical 15.1 How to estimate glomerular filtration rate (GFR) Measuring GFR • Direct measurement using labelled ethylenediamine-tetra-acetic acid (EDTA) or inulin • Creatinine clearance (CrCl): Minor tubular secretion of creatinine causes CrCl to exaggerate

GFR when renal function is poor; can be affected by drugs (e.g. trimethoprim, cimetidine) Needs 24-hr urine collection (inconvenient and often unreliable) CrCl mL/min urine creatinine concentration mol/L volume ( ) ( )

× µ ( ) ( ) ( ) mL plasma creatinine concentration mol/L time min µ ×

Estimating GFR with equations • The Modification of Diet in Renal Disease (MDRD) study equation (see www.renal.org/eGFR): Requires knowledge of age and sex only; it can therefore be reported automatically by laboratories For limitations, see Box 15.2 eGFR * creatinine in mol/L/ age in yrs

× × − −

88 4 1 154

(.) ( ) . µ . (.) (.)

0 742 1 21 × × if female if black • The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: More accurately estimates the actual GFR than the MDRD eGFR in those with relatively preserved renal function eGFR min SCr

max SCr

/ / 12 9 Age

× × × × −

1 018

(,) (,) . . . κ κ α ( ) . ( ) if female if black ×1 159 Where SCr = serum creatinine in µmol/L κ = 61.9 if female and 79.6 if male α = − 0.329 if female and − 0.411 if male min = whichever is the minimum of serum creatinine/κ or 1 max = whichever is the maximum of serum creatinine/κ or 1 • No equations perform well in unusual circumstances, such as extremes of body (and muscle) mass or in acutely unwell patients (see Box 15.2) *A correction factor of 175 is used for isotope dilution mass spectrometry traceable creatinine measurements. To convert creatinine in mg/dL to µmol/L, multiply by 88.4. Failure of erythropoietin production plays an important role in the pathogenesis of anaemia in CKD. The ureters and bladder The ureters drain urine from the renal pelvis (Fig. 15.1A) and deliver it to the bladder, a muscular organ that lies anteriorly in the lower part of the pelvis, just behind the pubic bone. The function of the bladder is to store and then release urine during micturition. The bladder is richly innervated. Sympathetic nerves arising from T10–L2 relay in the pelvic ganglia to cause relaxation of the detrusor muscle and contraction of the bladder neck (both via α-adrenoceptors), thereby preventing release of urine from the bladder. The distal sphincter mechanism is innervated by somatic motor fibres from sacral segments S2–4, which reach the sphincter either by the pelvic plexus or via the pudendal nerves. Afferent sensory impulses pass to the cerebral cortex, from where reflex-increased sphincter tone and suppression of detrusor contraction inhibit micturition until it is appropriate. Conversely, parasympathetic nerves arising from S2–4 stimulate detrusor contraction, promoting micturition. The micturition cycle has a storage (filling) phase and a voiding (micturition) phase. During the filling phase, the high compliance of the detrusor muscle allows the bladder to fill steadily without a rise in intravesical pressure. As bladder volume increases, stretch receptors in its wall cause reflex bladder relaxation and increased sphincter tone. The act of micturition is initiated first by voluntary and then by reflex relaxation of the pelvic floor and distal sphincter mechanism, followed by reflex detrusor contraction. These actions are coordinated by the pontine micturition centre. Intravesical pressure remains greater than urethral pressure until the bladder is empty. The prostate gland The prostate gland is situated at the base of the bladder, surrounding the proximal urethra (p. 383). Exocrine glands within the prostate produce fluid, which comprises about 20% of the volume of ejaculated seminal fluid and is rich in zinc and proteolytic enzymes. The remainder of the ejaculate is formed in the seminal vesicles and bulbo-urethral glands, with spermatozoa arising from the testes. Smooth muscle fibres within the prostate, which are under sympathetic control, play a role in controlling urine flow through the bulbar urethra, and also contract at orgasm to move seminal fluid through ejaculatory ducts into the bulbar urethra (emission). Contraction of the bulbocavernosus muscle (via a spinal muscle reflex) then ejaculates the semen out of the urethra. The penis Blood flow into the corpus cavernosum of the penis is controlled by sympathetic nerves from the thoracolumbar plexus, which maintain smooth muscle contraction (p. 383). In response to afferent input from the glans penis and from higher centres, pelvic splanchnic parasympathetic nerves actively relax the cavernosal smooth muscle via neurotransmitters such as nitric oxide, acetylcholine, vasoactive intestinal polypeptide (VIP) and prostacyclin, with consequent dilatation of the lacunar space. At the same time, draining venules are compressed, trapping blood in the lacunar space with consequent elevation of pressure and erection (tumescence) of the penis.

practice by measuring serum levels of endogenously produced compounds that are excreted by the kidney. The most widely used is serum creatinine, which is produced by muscle at a constant rate, is almost completely filtered at the glomerulus, and is not reabsorbed. Although creatinine is secreted to a small degree by the proximal tubule, this is only usually significant in terms of GFR estimation in severe renal impairment, where it accounts for a larger proportion of the creatinine excreted. Accordingly, provided muscle mass remains constant, changes in serum creatinine concentrations closely reflect changes in GFR. The relationship between serum creatinine and GFR is not linear, however, and a modest elevation in serum creatinine above the normal range may therefore reflect a substantial decline in GFR (Fig. 15.2). For this reason, several methods have been developed to estimate GFR from serum creatinine measurements (see Box 15.1) but the most widely used is the Modification of Diet in Renal Disease (MDRD) equation. Routine reporting by laboratories of estimated GFR (eGFR) has increased recognition of moderate kidney damage and encouraged early deployment Fig. 15.2 Serum creatinine and the glomerular filtration rate (GFR). A The relationship between serum creatinine and estimated GFR (eGFR) is non-linear; small increases above the normal range (e.g. 80–100 μmol/L; green lines) can therefore indicate a substantial decline in renal function (e.g. 105–80 mL/min/1.73 m2; conversely, in the high range, large changes in creatinine (e.g. 400–600 μmol/L; blue lines) can occur with only small declines in renal function (e.g. 20–15 mL/ min/1.73m2). B Creatinine is dependent on muscle mass; the same creatinine value may therefore reflect very different levels of renal function depending on the age and sex of the individual. To convert creatinine in mg/dL to μmol/L, multiply by 88.4.

GFR (mL/min/1.73 m2) GFR (mL/min/1.73 m2)

A

Serum creatinine (μmol/L) Serum creatinine (μmol/L)

25-year-old male 80-year-old female B 15.2 Limitations of estimated glomerular filtration rate (eGFR) • It is only an estimate, with wide confidence intervals (90% of patients will have eGFR within 30% of their measured GFR, and 98% within 50%) • It is based on serum creatinine, and so may over-estimate actual GFR in patients with low muscle mass (e.g. those with cachexia, amputees) and under-estimate actual GFR in individuals taking creatine supplements (creatinine is a metabolite of creatine) or trimethoprim (inhibits secretion of creatinine) • Creatinine level must be stable over days; eGFR is not valid in assessing acute kidney injury • It tends to under-estimate normal or near-normal function, so slightly low values should not be over-interpreted • In the elderly, who constitute the majority of those with low eGFR, there is controversy about categorising people as having chronic kidney disease (Box 15.3) on the basis of eGFR alone, particularly at stage 3A, since there is little evidence of adverse outcomes when eGFR is > 45 mL/min/1.73 m2 unless there is also proteinuria • eGFR is not valid in under-18s or during pregnancy • Ethnicity is not taken into account in routine laboratory reporting; the laboratory eGFR value should therefore be multiplied by 1.21 for black people • Few patients will understand eGFR in terms of mL/min/1.73 m2; it may therefore be helpful to assume that a GFR of 100 mL/ min/1.73 m2 is approximately normal and to discuss eGFR values in terms of a percentage of normal, e.g. 25 mL/min/1.73 m2 = 25% of normal kidney function of protective therapies; however, some limitations remain (Boxes 15.2 and 15.3). In particular, the MDRD formula is based on the serum creatinine value and so is heavily influenced by muscle mass; eGFR may therefore be misleading in individuals whose muscle bulk is outside the normal range for their sex and age. Measurement of other endogenous metabolites, such as cystatin C, may provide a more accurate estimate of GFR in this setting; this test, however, is not yet widely available in routine clinical practice. Direct measurement of creatinine clearance by collecting a 24-hour urine sample and relating serum creatinine levels to urinary creatinine excretion (see Box 15.1) is now less commonly performed due to the difficulty in obtaining accurate 24-hour urine collections. It may still have a role in assessing renal function in patients at extremes of muscle mass, where the creatinine-based equations perform poorly. Urine investigations Screening for the presence of blood (p. 391), protein (p. 392), glucose, ketones, nitrates and leucocytes, and assessment of urinary pH and osmolality can be achieved by dipstick testing. The presence of leucocytes and nitrites in urine is indicative of renal tract infection. Urine pH can provide diagnostic information in the assessment of renal tubular acidosis (p. 365). Urine microscopy (Fig. 15.3) may detect dysmorphic erythrocytes, which suggest the presence of nephritis or red cell casts, indicative of glomerular disease. White cell casts are strongly suggestive of pyelonephritis. Microscopy may also detect the presence of bacteria in those with urinary infection and crystals in patients with renal stone disease. It should be noted that calcium oxalate and urate crystals can sometimes be found in normal urine that has been left to stand, due to crystal formation ex vivo.

 Fig. 15.3 Urine microscopy. A Erythrocytes due to bleeding from lower in the urinary tract (×400). B Dysmorphic erythrocytes due to glomerular inflammation (×400). C Hyaline casts in normal urine. D Erythrocytes and a red cell cast in glomerulonephritis (×100). Panels A–C are phase contrast images; D is a bright field image. (A, B) Courtesy of Dr G.M. Iadorola and Dr F. Quarello, B. Bosco Hospital, Turin (from www.sin-italia .org/imago/sediment/sed.htm). A B C D 15.3 Stages of chronic kidney disease (CKD) Stage1 Definition2 Description Prevalence4 Clinical presentation5

Kidney damage3 with normal or high GFR (> 90) Normal function 3.5% Asymptomatic

Kidney damage and GFR 60–89 Mild CKD 3.9% Asymptomatic 3A GFR 45–59 Mild to moderate CKD 7.6% (3A and 3B combined) Usually asymptomatic 3B GFR 30–44 Moderate to severe CKD Anaemia in some patients at 3B Most are non-progressive or progress very slowly

GFR 15–29 Severe CKD 0.4% First symptoms often at GFR < 20 Electrolyte problems likely as GFR falls

GFR < 15 or on dialysis Kidney failure 0.1% Significant symptoms and complications usually present Dialysis initiation varies but usually at GFR < 10 1Stages of CKD 1–5 were originally defined by the US National Kidney Foundation Kidney Disease Quality Outcomes Initiative 2002. In the 2013 Kidney Disease Outcomes Quality Initiative (K/DOQI) CKD guideline update, the suffices A1, A2 and A3 are recommended, indicating the presence of albuminuria of < 30, 30–300 and > 300 mg/ 24 hrs respectively, in view of the prognostic importance of albuminuria. 2Two GFR values 3 months apart are required to assign a stage. All GFR values are in mL/ min/1.73 m2. 3Kidney damage means pathological abnormalities or markers of damage, including abnormalities in urine tests or imaging studies. 4From Hill NR, Fatoba ST, Oke JL et al. Global prevalence of chronic kidney disease – a systematic review and meta-analysis. PLoS One 2016; 11:e0158765. 5For further information, see page 415. Urine collection over a 24-hour period may be performed to measure excretion of solutes, such as calcium, oxalate and urate, in patients with recurrent renal stone disease (p. 431). Proteinuria can also be measured on 24-hour collections but is usually now quantified by protein/creatinine ratio on spot urine samples. Other dynamic tests of tubular function, including concentrating ability (p. 688), ability to excrete a water load (p. 357) and ability to excrete acid (p. 415), and calculation of fractional calcium, phosphate or sodium excretion, are valuable in some circumstances but are usually performed in very specific contexts. The fractional excretion of these ions can be calculated by the general formula: 100 × (urine concentration of analyte × serum creatinine) / (serum concentration of analyte × urinary creatinine). Calculation of fractional excretion of sodium (FENa) can help in the setting of acute kidney injury (AKI) to differentiate volume depletion, when the tubules are avidly conserving sodium (FENa typically < 1.0%), from acute tubular necrosis, when the tubules are damaged and are less able to conserve sodium (FENa typically

> 1.0%). In clinical practice this is seldom required. Blood tests Haematology A normochromic normocytic anaemia is common in CKD and is due in part to deficiency of erythropoietin and bone marrow suppression secondary to toxins retained in CKD. Other causes of anaemia include iron deficiency from urinary tract bleeding, and haemolytic anaemia secondary to disorders such as haemolytic uraemic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). Other abnormalities may be observed that reflect underlying disease processes, such as neutrophilia and raised erythrocyte sedimentation rate (ESR) in vasculitis or sepsis, and lymphopenia and raised ESR in systemic lupus erythematosus (SLE). Fragmented red cells on blood film and low platelets may be observed in thrombotic microangiopathies such as HUS/TTP and malignant hypertension. Pancytopenia may occur in SLE or bone marrow suppression due to myeloma. Biochemistry Abnormalities of routine biochemistry are common in

> renal disease. Serum levels of creatinine may be raised, reflecting reduced GFR (see above), as may serum potassium. Serum levels of urea are often increased in kidney disease but this analyte has limited value as a measure of GFR since levels increase with protein intake, following gastrointestinal haemorrhage and in catabolic states. Conversely, urea levels may be reduced in patients with chronic liver disease or anorexia and in malnourished patients, independently of changes in renal function. In the absence of the other causes mentioned above, an elevated urea:creatinine

renal ultrasound is operator-dependent and the results are often less clear in obese patients. Computed tomography Computed tomography urography (CTU) is used to evaluate cysts and mass lesions in the kidney or filling defects within the collecting systems. It usually entails an initial scan without contrast medium, and subsequent scans following injection of contrast to obtain a nephrogram image and images during the excretory phases. CTU has largely replaced the previous gold-standard investigation of intravenous urography (IVU) for investigation of the upper urinary tract, having the advantage of providing complete staging information and details of surrounding organs. Contrast enhancement is particularly useful for characterising mass lesions within the kidney and differentiating benign from malignant lesions (see Fig. 15.32A, p. 435). CT without contrast gives clear definition of retroperitoneal anatomy regardless of obesity and is superior to ultrasound in this respect. Non-contrast CT of kidneys, ureters and bladder (CTKUB) is the method of choice for demonstrating stones within the kidney or ureter (see Fig. 15.29, p. 432). For investigation of patients with renal trauma, a triple-phase CT scan with a delayed phase, to assess the integrity of the collecting system, is performed. Drawbacks of contrast-enhanced CT scans include the fact that relatively large doses of contrast medium are required, which can cause renal dysfunction, and that the radiation dose is significant (Box 15.4). Magnetic resonance imaging Magnetic resonance imaging (MRI) offers excellent resolution and gives good distinction between different tissue types (see Fig. 15.15, p. 406). It is very useful for local staging of prostate, bladder and penile cancers. Magnetic resonance angiography (MRA) provides an alternative to CT for imaging renal vessels but involves administration of gadolinium-based contrast media, which may carry risks for patients with impaired renal function (Box 15.4). Whilst MRA gives good images of the main renal vessels, stenosis of small branch arteries may be missed. Renal arteriography Renal arteriography involves taking X-rays following an injection of contrast medium directly into the renal artery. The main indication is to investigate renal artery stenosis (p. 406) or haemorrhage following renal trauma. Renal angiography can often be combined with therapeutic balloon dilatation or stenting of the renal artery. It can be used to occlude bleeding vessels and arteriovenous fistulae by the insertion of thin platinum wires (coils). These curl up within the vessel and promote thrombosis, thereby securing haemostasis. ratio is indicative of volume depletion and pre-renal failure. Serum calcium tends to be reduced and phosphate increased in CKD, in association with high parathyroid hormone (PTH) levels caused by reduced production of 1,25-dihydroxyvitamin D (1,25(OH)2D) by the kidney (secondary hyperparathyroidism). In some patients, this may be accompanied by raised serum alkaline phosphatase levels, which are indicative of renal osteodystrophy. Serum bicarbonate may be low in renal failure and in renal tubular acidosis. Serum albumin may be low in liver disease, as a negative acute phase response or due to malnutrition/malabsorption, but if it is a new finding it should prompt urinalysis to exclude nephrotic syndrome. Other biochemical abnormalities may be observed that reflect underlying disease processes, such as raised glucose and HbA1c levels in diabetes mellitus (p. 726) and raised levels of C-reactive protein (CRP) in sepsis and vasculitis. Immunology Antinuclear antibodies, antibodies to extractable nuclear antigens and anti-double-stranded DNA antibodies may be detected in patients with renal disease secondary to SLE (p. 1034). Antineutrophil cytoplasmic antibodies (ANCAs) may be detected in patients with glomerulonephritis secondary to systemic vasculitis (p. 1040), as may antibodies to GBM in patients with Goodpasture's syndrome (p. 401), and low levels of complement may be observed in a number of kidney diseases (see Box 15.17, p. 401). Imaging Ultrasound Renal ultrasound is a valuable non-invasive technique that may be performed to assess renal size and to investigate patients who are suspected of having obstruction of the urinary tract (Fig. 15.4), renal tumours, cysts or stones. Ultrasound can also be used to provide images of the prostate gland and bladder, and to estimate the completeness of emptying in patients with suspected bladder outflow obstruction. In addition, it can reveal other abdominal, pelvic and retroperitoneal pathology. Ultrasonography may show increased signal in the renal cortex with loss of distinction between cortex and medulla, which is characteristic of CKD. Doppler imaging can be used to study blood flow in extrarenal and larger intrarenal vessels, and to assess the resistivity index (peak systolic velocity − end-diastolic velocity/peak systolic velocity in the intrarenal arteries), which may be elevated (> 0.7) in various diseases, including acute tubular necrosis and rejection of a renal transplant. However, Fig. 15.4 Renal ultrasound. A Normal kidney. The normal cortex is less echo-dense (blacker) than the adjacent liver. (RC = renal cortex; RS = renal sinus – calyx, renal pelvis, blood vessels, sinus fat) B Typical simple renal cyst: round, echo-free content, no septa, posterior acoustic enhancement. (C = calyx; P = thinned parenchyma; RP = renal pelvis; U = ureter) C The renal pelvis and calyces are dilated due to obstruction. The thinness of the parenchyma indicates chronic obstruction. D A typical renal stone with posterior shadowing. (AS = posterior acoustic shadow) E A T1b renal tumour. (K = kidney; L = liver; T = tumour) (A–E) Courtesy of Dr Tobias Klatte, Addenbrooke's Hospital, Cambridge. RC P C C C RP AS T K K L U RS Normal kidney A Simple renal cyst B Hydronephrosis C Renal stone D Renal tumour T1b E

 Formal measurements of GFR can be made by radionuclide studies following the injection of diethylenetriamine penta-acetic acid (99mTc-DPTA). Static radionuclide studies are performed with dimercaptosuccinic acid labelled with technetium (99mTc-DMSA), which is taken up by proximal tubular cells. Following intravenous injection, images of the renal cortex are obtained that show the shape, size and relative function of each kidney (Fig. 15.6). This is a sensitive method for demonstrating cortical scarring in reflux nephropathy and a way of assessing the individual function of each kidney. Radionuclide bone scanning following the injection of methylene diphosphonate (99mTc-MDP) is indicated to assess the presence and extent of bone metastases in men with advanced prostate cancer (p. 438). Pyelography Pyelography involves direct injection of contrast medium into the collecting system from above (antegrade) or below (retrograde). It offers the best views of the collecting system and upper tract, and is often used to identify the cause of urinary tract obstruction (p. 391). Antegrade pyelography requires the insertion of a fine needle into the pelvicalyceal system under ultrasound or radiographic control. In addition to visualising the cause of obstruction, percutaneous nephrostomy drainage can be established and often stents can be passed through any obstruction. Retrograde pyelography can be performed by inserting a ureteric catheter into the ureteric orifice at cystoscopy (Fig. 15.5) and again a stent can be inserted to bypass any obstruction. Radionuclide studies These are functional studies requiring the injection of gamma ray-emitting radiopharmaceuticals that are taken up and excreted by the kidney, a process that can be monitored by an external gamma camera. Dynamic radionuclide studies are performed with mercaptoacetyltriglycine labelled with technetium (99mTc-MAG3), which is filtered by the glomerulus and excreted into the urine. Imaging following 99mTc-MAG3 injection can provide valuable information about the perfusion of each kidney but is not a reliable method for identifying renal artery stenosis. In patients with significant obstruction of the outflow tract, 99mTc-MAG3 persists in the renal pelvis and a loop diuretic fails to accelerate its disappearance. This can be useful in determining the functional significance of an equivocally obstructed collecting system without undertaking pyelography. Fig. 15.5 Retrograde pyelography. The best views of the normal collecting system are shown by pyelography. A catheter has been passed into the left renal pelvis at cystoscopy. The anemone-like calyces are sharp-edged and normal. Courtesy of Dr A.P. Bayliss and Dr P. Thorpe, Aberdeen Royal Infirmary. 15.4 Renal complications of radiological investigations Contrast nephrotoxicity • Acute deterioration in renal function commencing < 48 hrs after administration of IV radiographic contrast media Risk factors • Pre-existing renal impairment • Use of high-osmolality, ionic contrast media and repetitive dosing in short time periods • Diabetes mellitus • Myeloma Prevention • Provide hydration with free oral fluids plus IV isotonic saline 500 mL, then 250 mL/hr during procedure • Avoid nephrotoxic drugs; withhold non-steroidal anti-inflammatory drugs (NSAIDs). Omit metformin for 48 hrs after the procedure, in case renal impairment occurs • N-acetylcysteine may provide some protection but data are conflicting • If the risks are high, consider alternative methods of imaging Cholesterol atheroembolism • Typically follows days to weeks after intra-arterial investigations or interventions (p. 409) Nephrogenic sclerosing fibrosis after MRI contrast agents • Chronic progressive sclerosis of skin, deeper tissues and other organs, associated with gadolinium-based contrast agents • Only reported in patients with renal impairment, typically on dialysis or with GFR < 15 mL/min/1.73 m2, but caution is advised in patients with GFR < 30 mL/min/1.73 m2 Fig. 15.6 DMSA radionuclide scan. A posterior view is shown of a normal left kidney and a small right kidney (with evidence of cortical scarring at upper and lower poles) that contributes only 39% of total renal function. L LEFT = 61% RIGHT = 39% POSTERIOR R

with marked glycosuria. Urine volumes are variable in AKI due to intrinsic renal disease, but a rapid decline in urine volume may be observed. Anuria should prompt a differential including complete urinary obstruction, severe vascular compromise or rapidly progressive glomerulonephritis (Box 15.6). Obstruction of the renal tract can produce oliguria and anuria, but to do so, obstruction must be complete and occur distal to the bladder neck, be bilateral, or be unilateral on the side of a single functioning kidney. Unilateral ureteric obstruction may not lead to any noticeable reduction in urine output. The presence of pain that is exacerbated by a fluid load suggests an acute obstruction of the renal tract, and its characteristics may be of value in reaching a diagnosis. Obstruction at the bladder neck is associated with lower midline abdominal discomfort, whereas ureteric obstruction typically presents as loin pain radiating to the groin and at the level of the renal pelvis may present as flank pain. Chronic obstruction rarely produces pain but may give rise to a dull ache. Urethral strictures should be considered as a possible cause, especially in patients with a history of instrumentation of the renal tract. The presence of bladder enlargement in a middle-aged or elderly man suggests benign or malignant enlargement of the prostate gland as a potential cause of oliguria or anuria (pp. 437 and 438). It is important to note that many cases of acute urinary retention are observed after general anaesthesia, particularly in patients with pre-existing prostatic enlargement. Partial obstruction can be associated with a normal or even high urine volume due to chronic tubular injury, which causes loss of tubular concentrating ability. Management of oliguria and anuria should be directed at the underlying cause and is outlined later in the chapter (p. 413). Haematuria Healthy individuals may have occasional red blood cells in the urine (up to 12 500 cells/mL), but the presence of visible (macroscopic) haematuria or non-visible haematuria (microscopic, only detectable on dipstick testing) is indicative of significant bleeding from somewhere in the urinary tract (Fig. 15.7). Once infection, menstruation and causes of a positive urinary dipstick in the absence of red cells (haemoglobinuria/myoglobinuria) have 15.5 Renal biopsy Indications • Acute kidney injury and chronic kidney disease of uncertain aetiology • Nephrotic syndrome or glomerular proteinuria (protein:creatinine ratio > 100 mg/mol) in adults • Nephrotic syndrome in children that has atypical features or is not responding to treatment • Nephritic syndrome • Renal transplant dysfunction • Rarely performed for isolated haematuria or isolated low-grade proteinuria in the absence of impaired renal function or evidence of a multisystem disorder Contraindications • Disordered coagulation or thrombocytopenia. Aspirin and other antiplatelet agents increase bleeding risk • Uncontrolled hypertension • Kidneys < 60% predicted size • Solitary kidney* (except transplants) Complications • Pain, usually mild • Bleeding into urine, usually minor but may produce clot colic and obstruction • Bleeding around the kidney, occasionally massive and requiring angiography with intervention, or surgery • Arteriovenous fistula, rarely significant clinically *Relative contraindication. Renal biopsy Renal biopsy is used to establish the diagnosis and severity of renal disease in order to judge the prognosis and need for treatment (Box 15.5). The procedure is performed transcutaneously under local anaesthetic with ultrasound or contrast radiography guidance to ensure accurate needle placement into a renal pole. Light microscopy, electron microscopy and immunohistological assessment of the specimen may all be required. Presenting problems in renal and urinary tract disease Oliguria/anuria Oliguria is defined as being present when less than 400 mL of urine is passed per day, whereas anuria is deemed to exist when less than 100 mL of urine is passed per day. The volume of urine produced represents a balance between the amount of fluid that is filtered at the glomerulus and that reabsorbed by the renal tubules. When GFR is low, urine volumes may still be normal if tubular reabsorption is also reduced; hence urine volume alone is a poor indicator of the severity of kidney disease. Oliguria and anuria may be caused by a reduction in urine production, as in pre-renal AKI, when GFR is reduced and tubular homeostatic mechanisms increase reabsorption to conserve salt and water. A high solute load or associated tubular dysfunction may, however, produce normal or high urine volumes in such cases until the pre-renal insult becomes severe and GFR is markedly reduced, such as occurs in diabetic ketoacidosis 15.6 Causes of anuria (< 100 mL urine output per day) Condition Examples Urinary obstruction (complete) Urinary retention due to prostatic enlargement, urethral stenosis, bladder tumour Bilateral ureteric obstruction due to retroperitoneal fibrosis, cancer, radiation injury Bilateral renal stones (usually staghorn calculi) Massive crystalluria obstruction of tubules (rare) Lack of renal perfusion (bilateral) Aortic dissection involving renal arteries Severe acute tubular necrosis Severe functional hypoperfusion (cardiorenal, hepatorenal) Rapidly progressive glomerulonephritis Anti-glomerular basement membrane disease, severe antineutrophil cytoplasmic antibody (ANCA) vasculitis (100% glomerular crescents on biopsy)

 Dipstick test positive Urine microscopy Suggested cause Haematuria White blood cells Abnormal epithelial cells Infection Tumour Red cell casts Dysmorphic erythrocytes (phase contrast microscopy) Glomerular bleeding* Haemoglobinuria No red cells Intravascular haemolysis Myoglobinuria (brown urine) No red cells Rhabdomyolysis } 15.7 Interpretation of non-visible haematuria *Glomerular bleeding implies that the GBM is ruptured. It can occur physiologically following very strenuous exertion but usually indicates intrinsic renal disease and is an important feature of the nephritic syndrome. glomerular cause is not suspected (see below), it may be appropriate to manage them by periodic observation in primary care, although occasionally these individuals develop significant overt renal disease during follow-up. Glomerular bleeding occurs when inflammatory, destructive or degenerative processes disrupt the GBM, permitting passage of red blood cells into the urine. A characteristic feature of glomerular bleeding is an 'active urinary sediment' (the presence of dysmorphic red blood cells or red cell casts on microscopy); this is not always present, however. Patients with visible and non-visible haematuria should also be assessed for hypertension, proteinuria, reduced/declining renal function, family history of renal disease or features of systemic disease (Fig. 15.8). The presence of any of these features raises the possibility of intrinsic renal pathology and warrants referral to nephrology for further investigation, including consideration of renal biopsy. Nephritic syndrome The nephritic syndrome is characterised by the presence of haematuria in association with hypertension, oliguria, fluid retention and reduced/declining renal function. Many patients with glomerulonephritis, particularly those with milder disease, do not exhibit all of these features; their combined presence, however, is typical of a rapidly progressive glomerulonephritis and warrants urgent investigation. In many cases, investigation will include a renal biopsy to confirm diagnosis and guide management, but less invasive investigations may also be useful (Box 15.8). Patients with nephritic syndrome may also exhibit varying degrees of proteinuria, including nephrotic-range proteinuria; the prominence of haematuria on dipstick should, however, alert the physician to the possibility of a glomerulonephritis. Indeed, it is important to recognise that the characteristic features of nephritic syndrome and nephrotic syndrome do not always present in isolation, but should be considered to be the extreme phenotypes at either end of a spectrum of presentations (Fig. 15.9). Proteinuria While very small amounts of high-molecular-weight proteins and moderate amounts of low-molecular-weight proteins pass been excluded (Box 15.7), both visible and persistent non-visible haematuria require investigation, as they may be caused by malignancy or indicate glomerulonephritis. Visible haematuria is most likely to be caused by tumour, which can affect any part of the urogenital tract (Fig. 15.7), and patients with visible haematuria must therefore be referred to urology for imaging (ultrasound or CT scan) and cystoscopy (Fig. 15.8). Other common causes of visible haematuria are urine infection and stones. Visible haematuria may also be encountered in patients with IgA nephropathy, typically following an upper respiratory tract infection. Non-visible haematuria may also indicate an underlying tumour, and all patients over 40 years old with persistent (detected on at least 2 of 3 consecutive dipstick tests) non-visible haematuria should therefore undergo imaging and cystoscopy. In younger patients, an underlying tumour is much less likely, and if a Fig. 15.7 Causes of haematuria. Polyarteritis nodosa Vascular malformation Renal infarction Coagulation disorders Cysts Renal tumour Glomerulonephritis Small-vessel vasculitis Systemic lupus erythematosus Other glomerular diseases Interstitial nephritis Pyelonephritis Calculus Calculus Cystitis Bladder tumour Benign prostatic enlargement Prostate cancer Trauma Urethritis Trauma Trauma Ureteric tumour 15.8 Investigation of nephritic syndrome Cause Investigations Rapidly progressive glomerulonephritis (RPGN) Post-infectious glomerulonephritis ASOT, C3, C4 Anti-GBM disease Anti-GBM antibody Small-vessel vasculitis p-ANCA, c-ANCA Lupus nephritis ANA, dsDNA, C3, C4 Mild glomerulonephritic presentation IgA nephropathy Serum IgA (polyclonal rise in 50% of patients) Mesangioproliferative* *glomerulonephritis C3, C4, hepatitis B,C + HIV serology, ANA, dsDNA, immunoglobulins, PPE Alport's syndrome* Genetic screening, hearing test *Not a glomerulonephritis but may present in a similar manner with haematuria, variable proteinuria, hypertension and slowly declining renal function. (ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; ASOT = anti-streptolysin O titre; C3, C4 = complement proteins 3, 4; dsDNA = double-stranded DNA; GBM = glomerular basement membrane; HIV = human immunodeficiency virus; IgA = immunoglobulin A; PPE = plasma protein electrophoresis)

disease (see Box 15.20, p. 405). The presence of larger amounts of protein is usually indicative of significant renal disease. Proteinuria is usually asymptomatic and is often picked up by urinalysis, although large amounts of protein may make the urine frothy. Transient proteinuria can occur after vigorous exercise, during fever, in heart failure and in people with urinary through the healthy GBM, these proteins normally are completely reabsorbed by receptors on tubular cells. Hence, in healthy individuals, less than 150 mg of protein is excreted in the urine each day, much of which is derived from tubular cells. This includes Tamm–Horsfall protein (uromodulin), encoded by the UMOD gene that has recently been linked to tubulo-interstitial Fig. 15.8 Investigation of haematuria. *Symptomatic: lower urinary tract voiding symptoms such as hesitancy, frequency, urgency and dysuria. (ACR = albumin:creatinine ratio; BP = blood pressure; CT = computed tomography; eGFR = estimated glomerular filtration rate; NVH = non-visible haematuria; UTI = urinary tract infection) Persistent non-visible haematuria 2 of 3 positive dipsticks Exclude menstruation/UTI Refer to nephrology Consider renal biopsy Refer to urology Ultrasound/CT renal tracts Cystoscopy Observation Annual: urinalysis, BP, ACR, eGFR *Symptomatic NVH Assess: BP, eGFR, ACR Abnormal OR Normal <40 years

> 40 years Family history of renal disease Evidence of systemic disease Visible haematuria Exclude menstruation/UTI Check BP, eGFR Fig. 15.9 Nephritic and nephrotic syndrome. At one extreme, specific injury to podocytes causes proteinuria and nephrotic syndrome. The histology to the left shows diabetic nephropathy. At the other end of the spectrum, inflammation leads to cell damage and proliferation, breaks form in the glomerular basement membrane (GBM) and blood leaks into urine. In its extreme form, with acute sodium retention and hypertension, such disease is labelled nephritic syndrome. The histology to the right shows a glomerulus with many extra nuclei from proliferating intrinsic cells, and influx of inflammatory cells leading to crescent formation (arrows) in response to severe post-infectious glomerulonephritis. (FSGS = focal and segmental glomerulosclerosis; IgA = immunoglobulin A; MCGN = mesangiocapillary glomerulonephritis; SLE = systemic lupus erythematosus) Nephrotic Mechanism • Injury to podocytes • Changed architecture

Scarring

Deposition of matrix or other elements Clinical features • Overt proteinuria: usually > 3.5 g/24 hrs (urine may be frothy) • Hypoalbuminaemia (> 30 g/L) • Oedema and generalised fluid retention • Possible intravascular volume depletion with hypotension, or intravascular expansion with hypertension Nephritic Mechanism • Inflammation • Reactive cell proliferation • Breaks in GBM • Crescent formation Clinical features • Haematuria (red or brown urine) • Oedema and generalised fluid retention • Hypertension • Oliguria • Reduced renal function Haematuria Proteinuria SLE IgA nephropathy Minimal change nephropathy Diabetic nephropathy MCGN Anti-GBM disease FSGS Membranous nephropathy Amyloid Smallvessel vasculitis Post-streptococcal glomerulonephritis

394 • NEPHROLOGY AND UROLOGY 15.9 Quantifying proteinuria in random urine samples ACR1 PCR2 Typical dipstick results3 Significance < 3.5 (female) < 2.5 (male) < 25 – Normal 3.5–30 25–50 – Moderately elevated albuminuria 30–70 50–100

- to ++ Dipstick positive 70–300 100–350 ++ to +++ Glomerular disease more likely; equivalent to > 1 g/24 hrs

> 300 350 +++ to ++++ Nephrotic range: almost always glomerular disease, equivalent to > 3.5 g/24 hrs 1Urinary albumin (mg/L)/urine creatinine (mmol/L). 2Urine protein (mg/L)/urine creatinine (mmol/L). (If urine creatinine is measured in mg/dL, reference values for PCR and ACR can be derived by dividing by 11.31.) 3Dipstick results are affected by urine concentration and are occasionally weakly positive on normal samples. tract infection. Patients should be assessed for the presence of these conditions and urine testing repeated once the potential trigger has been treated or resolved. Testing for proteinuria is best done on an early morning sample, as some individuals exhibit orthostatic proteinuria. In these patients, typically less than 1 g/24 hrs of protein is excreted only in association with an upright posture, the first morning sample being negative. Orthostatic proteinuria is regarded as a benign disorder that does not require treatment. Moderately elevated albuminuria (microalbuminuria) In healthy individuals, there is virtually no urinary excretion of large-molecular-weight serum proteins, such as albumin, in contrast to modest urinary excretion of tubule-derived proteins. The presence of even moderate amounts of albuminuria (previously referred to as microalbuminuria) is therefore abnormal, and may indicate early glomerular pathology, at a time when the standard dipstick test remains negative (Box 15.9). Screening for moderately elevated albuminuria should be performed regularly in patients with diabetes, as persistently elevated levels warrant therapy with inhibitors of the renin–angiotensin–aldosterone system, even in normotensive individuals, to reduce the rate of loss of renal function (see Box 20.39, p. 758). Persistent moderately increased albuminuria has also been associated with cardiovascular mortality in patients with and without diabetes, but an explanation for this association has not yet been established. Overt (dipstick-positive) proteinuria Urinary dipstick testing is a valuable screening tool for the detection of proteinuria; it is only semi-quantitative, however, as it is highly dependent on

the concentration of the urine. Typically, standard dipsticks test positive for protein once the urinary protein exceeds approximately 0.5 g/24 hrs; however, trace to 1+ on dipstick may be observed in very concentrated urine from individuals with no evidence of renal pathology. Hence all patients with persistent proteinuria on dipstick should have the amount of protein quantified to guide further investigations (Fig. 15.10). When more than 1 g of protein per day is being excreted, glomerular disease is likely and this is an indication for renal biopsy. Since quantification by 24-hour urine collection is often inaccurate, the protein:creatinine ratio (PCR) in a spot sample of urine is preferred. This makes an allowance for the variable degree of urinary dilution and can be used to extrapolate to 24-hour values (Box 15.9). Changes in PCR also give valuable information about the progression of renal disease and response to therapy in CKD. It is possible to measure albumin:creatinine ratio (ACR), but this requires a more expensive immunoassay and is usually reserved for situations when high sensitivity is required, such as detection of the early stages of diabetic nephropathy (p. 757). It is sometimes helpful to identify the type of protein in the urine. Large amounts of low-molecular-weight proteins, such as β2-microglobulin (molecular weight 12 kDa), in the urine suggest renal tubular damage and are referred to as tubular proteinuria. This rarely exceeds 1.5–2 g/24 hrs (maximum PCR 150–200 mg/ mmol; see Box 15.9 for conversion of mg/mmol to mg/dL). Free immunoglobulin light chains (molecular weight 25 kDa) are filtered freely at the glomerulus but are poorly identified by Fig. 15.10 Investigation of proteinuria. (ACR = albumin:creatinine ratio; PCR = protein:creatinine ratio.) Substantial Total 24-hr protein > 1 g PCR > 100 mg/mmol ACR > 70 mg/mmol Yes Quantify Repeated proteinuria on dipstick Features of significant renal disease? Hypertension Abnormal renal function Family history of renal disease Signs of systemic disease No Consider renal biopsy Observation Urinalysis, blood pressure, creatinine every 6 – 12 mths Re-assess if anything changes Moderate or low-grade Total 24-hr protein < 1 g PCR < 100 mg/mmol ACR < 70 mg/mmol

scarring or deposition of exogenous material such as amyloid into the glomerulus. Investigation of nephrotic syndrome usually involves renal biopsy, although non-invasive tests may also be helpful in suggesting the underlying cause (Box 15.10). In children, minimal change disease is by far the most common cause of nephrotic syndrome and therefore renal biopsy is not usually required unless the patient fails to respond to high-dose glucocorticoid therapy. Similarly, most patients with diabetes presenting with nephrotic syndrome will have diabetic nephropathy, and so renal biopsy is usually not performed unless the course of the disease is atypical (rapidly increasing proteinuria or rapid decline in renal function; p. 757). Management of nephrotic syndrome should be directed at the underlying cause. In addition, nephrotic syndrome is associated with a number of complications (Box 15.11), which may require supportive management unless the nephrosis is expected to resolve rapidly, such as in glucocorticoid-responsive minimal change disease. Oedema Oedema is caused by an excessive accumulation of fluid within the interstitial space. Clinically, this can be detected by persistence of an indentation in tissue following pressure on the affected area (pitting oedema). Pitting oedema tends to accumulate in the ankles during the day and improves overnight as the interstitial fluid is reabsorbed. Non-pitting oedema is typical of lymphatic obstruction and may also occur as the result of excessive matrix deposition in tissues: for example, in hypothyroidism (p. 639) or systemic sclerosis (p. 1037). Clinical assessment Dependent areas, such as the ankles and lower legs, are typically affected first but oedema can be restricted to the sacrum in bed-bound patients. With increasing severity, oedema spreads to affect the upper parts of the legs, the genitalia and abdomen. Ascites is common and often an earlier feature in children or young adults, and in liver disease. Pleural effusions are common but frank pulmonary oedema is rare. Facial oedema on waking is common. Features of intravascular volume depletion (tachycardia, postural hypotension) may occur when oedema is due to decreased 15.10 Investigation of nephrotic syndrome Cause Typical age group Investigations Fulminant presentation Minimal change disease Children, young adults, occasionally seen in older patients None specific Primary focal segmental glomerulosclerosis Young adults None specific Subacute presentation Membranous nephropathy Middle-aged to older patients Hepatitis B, C + HIV serology, ANA, dsDNA Amyloid Older patients Immunoglobulins, PPE, Bence Jones protein, serum free light chains Gradual progression Diabetic nephropathy Any age, but rarely < 10 years from diagnosis of type 1 diabetes Glucose, glycosylated haemoglobin (ANA = antinuclear antibody; dsDNA = double-stranded DNA; HIV = human immunodeficiency virus; PPE = plasma protein electrophoresis) dipstick tests. Hence, electrophoresis of the urine and specific immunodetection methods are required to detect immunoglobulin light chains, known as ‘Bence Jones protein’. This may occur in AL amyloidosis (p. 81) and in B-cell dyscrasias but is particularly important as a marker for myeloma (p. 966). Nephrotic syndrome Nephrotic syndrome is characterised by very heavy proteinuria (> 3.5 g/24 hrs), hypoalbuminaemia and oedema (see below). Blood volume may be normal, reduced or increased. Renal sodium retention is an early and universal feature; the mechanisms of this are shown in Figure 14.5 (p. 354). The diseases that cause nephrotic syndrome all affect the glomerulus (see Fig. 15.9), either directly, by damaging podocytes, or indirectly, by causing 15.11 Consequences of the nephrotic syndrome and their management Feature Mechanism Consequence Management Hypoalbuminaemia Urinary protein losses exceed synthetic capacity of liver Reduced oncotic pressure Oedema Treatment of underlying cause Avid sodium retention Secondary hyperaldosteronism Additional poorly characterised intrarenal mechanisms Oedema Diuretics and a low-sodium diet* Hypercholesterolaemia Non-specific increase in lipoprotein synthesis by liver in response to low oncotic pressure High rate of atherosclerosis Statins, ezetimibe Hypercoagulability Relative loss of inhibitors of coagulation (antithrombin III, protein C and S) and increase in liver synthesis of procoagulant factors Venous thromboembolism Consideration of prophylaxis in chronic or severe nephrotic syndrome Infection Hypogammaglobulinaemia due to urinary loss of immunoglobulins Pneumococcal and meningococcal infection Consideration of vaccination *Severe nephrotic syndrome may need very large doses of combinations of diuretics acting on different parts of the nephron (e.g. loop diuretic plus thiazide plus amiloride). In occasional patients with hypovolaemia, intravenous salt-poor albumin infusions may help to establish a diuresis, although efficacy is controversial. Over-diuresis risks secondary impairment of renal function through hypovolaemia.

 at risk of developing CKD and current recommendations are that hypertensive patients should have renal function checked annually. Control of hypertension is very important in patients with renal impairment because of its close relationship with further decline of renal function (p. 420) and because of the exaggerated cardiovascular risk associated with CKD. Pathophysiology and management are discussed on pages 509 and 510. Loin pain Loin pain is often caused by musculoskeletal disease but can be a manifestation of renal tract disease; in the latter case, it may arise from renal stones, ureteric stones, renal tumours, acute pyelonephritis and urinary tract obstruction. Acute loin pain radiating anteriorly and often to the groin is termed renal colic. When combined with haematuria, this is typical of ureteric obstruction due to calculi (p. 431). Precipitation of loin pain by a large fluid intake (Dietl's crisis) suggests upper urinary tract obstruction caused by a congenital abnormality of the pelvi-ureteric junction (p. 433). Dysuria Dysuria refers to painful urination, often described as burning, scalding or stinging, and commonly accompanied by suprapubic pain. It is often associated with frequency of micturition and a feeling of incomplete emptying of the bladder. By far the most common cause is urinary tract infection, as described on page 426. Other diagnoses that need to be considered in patients with dysuria include sexually transmitted infections (p. 329) and bladder stones (p. 431). Frequency Frequency describes daytime micturition more often than a patient would expect. It may be a consequence of polyuria, when urine volume is normal or high, but is also found in patients with dysuria and prostatic diseases, when the urine volume is normal. Polyuria Polyuria is defined as a urine volume in excess of 3 L/24 hrs. Various underlying conditions, both renal and extrarenal, may be responsible, as outlined in Box 15.13. Investigation of polyuria includes measurement of urea, creatinine and electrolytes, glucose, calcium and albumin. A 24-hour urine collection may be helpful to confirm the severity of polyuria. The presence of nocturnal polyuria suggests a oncotic pressure or increased capillary permeability. If oedema is localised – for example, to one ankle but not the other – then venous thrombosis, inflammation or lymphatic disease should be suspected. Investigations Oedema may be due to a number of causes (Box 15.12), which are usually apparent from the history and examination of the cardiovascular system and abdomen. Blood should be taken for measurement of urea and electrolytes, liver function and serum albumin, and the urine tested for protein. Further imaging of the liver, heart or kidneys may be indicated, based on history and clinical examination. Where ascites or pleural effusions occur in isolation, aspiration of fluid with measurement of protein and glucose, and microscopy for cells, will usually help to clarify the diagnosis in differentiating a transudate (typical of oedema) from an exudate (more suggestive of local pathology, p. 564). Management Mild oedema usually responds to elevation of the legs, compression stockings, or a thiazide or a low dose of a loop diuretic, such as furosemide or bumetanide. In nephrotic syndrome, renal failure and severe cardiac failure, very large doses of diuretics, sometimes in combination, may be required to achieve a negative sodium and fluid balance. Restriction of sodium intake and fluid intake may be required. Diuretics are not helpful in the treatment of oedema caused by venous or lymphatic obstruction or by increased capillary permeability. Specific causes of oedema, such as venous thrombosis, should be treated. Hypertension Hypertension is a very common feature of renal disease. Additionally, the presence of hypertension identifies a population 15.13 Causes of polyuria • Excess fluid intake • Osmotic diuresis: hyperglycaemia, hypercalcaemia • Cranial diabetes insipidus • Nephrogenic diabetes insipidus: Rare inherited mutations in vasopressin receptor or aquaporin 2 genes Lithium Diuretics Interstitial nephritis Hypokalaemia Hypercalcaemia 15.12 Causes of oedema Increased total extracellular fluid • Congestive heart failure • Renal failure • Liver disease High local venous pressure • Deep venous thrombosis or venous insufficiency • Pregnancy • Pelvic tumour Low plasma oncotic pressure/serum albumin • Nephrotic syndrome • Liver failure • Malnutrition/malabsorption Increased capillary permeability • Leakage of proteins into the interstitium, reducing the osmotic pressure gradient that draws fluid into the lymphatics and blood • Infection/inflammation • Severe sepsis • Calcium channel blockers Lymphatic obstruction • Infection: filariasis, lymphogranuloma venereum (pp. 290 and 341) • Malignancy • Radiation injury • Congenital abnormality

Most types of glomerulonephritis are immunologically mediated and several respond to immunosuppressive drugs. Deposition of antibody occurs in many types of glomerulonephritis and testing for circulating or glomerular deposition of antibodies may aid diagnosis (see Fig. 15.11 and Boxes 15.8 and 15.10). In small-vessel vasculitis, no glomerular antibody deposition is observed (pauci-immune), but the antibodies may be indirectly pathogenic by activating neutrophils to promote endothelial injury (Fig. 15.11). Glomerulonephritis is generally classified in terms of the histopathological appearances, as summarised in Box 15.15 and Figure 15.12. Many non-specialists find the terminology used in describing glomerulonephritis to be confusing; some definitions are provided in Box 15.16. It is important to stress that the histological appearance rarely confirms a specific renal disease but rather suggests a limited range of diagnoses, which may be confirmed by further investigation. Conversely, some diseases, such as lupus, are associated with more than one histological pattern of injury. The most common histological subtypes may be categorised according to their typical clinical presentation, as discussed below. Genetic disorders associated with glomerular disease are described later (p. 403). pathological cause. Investigation and management of suspected diabetes insipidus are described on page 688. Nocturia Nocturia is defined as waking up at night to void urine. It may be a consequence of polyuria but may also result from increased fluid intake or diuretic use in the late evening (including caffeine). Nocturia also occurs in CKD, and in prostatic enlargement when it is associated with poor stream, hesitancy, incomplete bladder emptying, terminal dribbling and urinary frequency due to partial urethral obstruction (p. 437). Nocturia may also occur due to sleep disturbance without any functional abnormalities of the urinary tract. Urinary incontinence Urinary incontinence is defined as any involuntary leakage of urine. It may occur in patients with a normal urinary tract, as the result of dementia or poor mobility, or transiently during an acute illness or hospitalisation, especially in older people (see Box 15.54, p. 436). The pathophysiology, investigation and management of urinary incontinence are discussed in detail later in the chapter (p. 436). Glomerular diseases Glomerular diseases account for a significant proportion of acute and chronic kidney disease. Most patients with glomerular disease do not present acutely and are asymptomatic until abnormalities are detected on routine screening of blood or urine samples. There are many causes of glomerular damage, including immunological injury, inherited diseases such as Alport’s syndrome (p. 403), metabolic diseases such as diabetes mellitus (p. 757), and deposition of abnormal proteins such as amyloid in the glomeruli (p. 81). The glomerular cell types that may be the target of injury are shown in Figure 15.11. Proteinuria is the hallmark of glomerular disease; however, the response of the glomerulus to injury and hence the predominant clinical features vary according to the nature of the insult, ranging from fulminant nephrotic syndrome to rapidly progressive glomerulonephritis (see Fig. 15.9). Several prognostic indicators are common to all causes of glomerulonephritis (Box 15.14) and may be helpful in assessing the need for immunosuppressive therapy. Glomerulonephritis While glomerulonephritis literally means ‘inflammation of glomeruli’, the term is often used more broadly to describe all types of glomerular disease, even though some of these (e.g. minimal change nephropathy) are not associated with inflammation. Fig. 15.11

Glomerulonephritis associated with antibody production. Antibodies and antigen–antibody (immune) complexes may target or be deposited in specific components of the glomerulus, resulting in different patterns of histological injury and clinical presentation. Testing for antibody deposition in the glomerulus by immunofluorescence (IF) on renal biopsy tissue or for antibodies in the serum may aid diagnosis. Diagnostic tests are shown in italics. (ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; dsDNA = double-stranded DNA; GBM = glomerular basement membrane; IgA = immunoglobulin A; SLE = systemic lupus erythematosus) Endothelium (indirectly) Small-vessel vasculitis ANCA (serum) GBM Goodpasture's disease Anti-GBM antibody (serum + IF on biopsy; see Fig.15.12H) Podocyte Membranous nephropathy Anti-phosphilipase A2 receptor 1 (serum + IF on biopsy; experimental at present; see Fig.15.12F) Planted antigens SLE – ANA, anti-dsDNA (serum) Post-infectious glomerulonephritis Circulating immune complexes Cryoglobulinaemia (Cryoglobulins in serum) Serum sickness Endocarditis Mesangium IgA nephropathy (polyclonal rise in serum IgA in 50% patients; IF on biopsy; see Fig.15.12G) 15.14 Poor prognostic indicators in glomerular disease • Male sex • Hypertension • Persistent and severe proteinuria • Elevated creatinine at time of presentation • Rapid rate of decline in renal function • Tubulo-interstitial fibrosis observed on renal biopsy

398 • NEPHROLOGY AND UROLOGY discussed elsewhere, including diabetic nephropathy (p. 757) and amyloid (p. 81). Minimal change nephropathy Minimal change disease occurs at all ages but accounts for most cases of nephrotic syndrome (see Box 15.15) in children and about one-quarter of adult cases. It is caused by reversible dysfunction of podocytes. On light microscopy, the glomeruli appear normal (Fig. 15.12A), but fusion of podocyte foot processes is observed on electron microscopy. The presentation is with nephrotic syndrome, which typically is severe; it remits Diseases typically presenting with nephrotic syndrome In these diseases, the injury is focused on the podocyte and there is little histological evidence of inflammation or cell proliferation in the glomerulus (non-proliferative, Fig. 15.12). Minimal change and primary focal segmental glomerulosclerosis (FSGS) typically present with fulminant nephrotic syndrome, whereas in membranous nephropathy and secondary FSGS, the nephrosis tends to be more indolent in nature. Other causes of nephrotic syndrome due to systemic disease are 15.15 Glomerulonephritis categorised by clinical presentation and histological classification Histology Immune deposits Pathogenesis Associations Comments Nephrotic presentation Minimal change Normal, except on electron microscopy, where fusion of podocyte foot processes is observed (non-specific finding) None Unknown; probable circulating factor promoting podocyte injury Some cases are genetic (p. 403) Atopy Drugs, most commonly NSAIDs Haematological malignancies Acute and often severe nephrotic syndrome Good response to glucocorticoids Dominant cause of idiopathic nephrotic syndrome in childhood Focal segmental glomerulosclerosis (FSGS) Segmental scars in some glomeruli No acute inflammation Podocyte foot process fusion seen in primary FSGS Non-specific trapping in focal scars Unknown; circulating factors may increase glomerular permeability Injury to podocytes may be common feature Some cases are genetic (p. 403) APOL1 variant in people of West African descent Causes of secondary FSGS include: Healing of previous local glomerular injury HIV infection Heroin misuse Morbid obesity Chronic hypertension Primary FSGS presents as idiopathic nephrotic syndrome but is less responsive to treatment than minimal change; may progress to renal impairment, and can recur after transplantation Secondary FSGS presents with variable proteinuria and outcome Membranous nephropathy Thickening of GBM Progressing to increased matrix deposition and glomerulosclerosis Granular subepithelial IgG Antibodies to a podocyte surface antigen (commonly phospholipase A2 receptor 1), with complementdependent

podocyte injury HLA-DQA1 (for idiopathic) Drugs: Penicillamine, NSAIDs, heavy metals Hepatitis B virus Malignancy Lupus1 Common cause of adult idiopathic nephrotic syndrome One-third progress, one-third spontaneously remit and one-third remain stable; may respond to glucocorticoids and immunosuppressants Mild glomerulonephritic presentation IgA nephropathy Increased mesangial matrix and cells Focal segmental nephritis in acute disease Mesangial IgA (and C3) Unknown Mucosal infections (e.g. helminths) may be involved Usually idiopathic, flares triggered by upper respiratory infection Liver disease Coeliac disease Common disease with range of presentations, usually including haematuria and hypertension Henoch–Schönlein purpura is an acute IgA variant common in children Mesangiocapillary glomerulonephritis Immunoglobulin type Immunoglobulins Deposition of circulating immune complexes or 'planted' antigens Infections, autoimmunity or monoclonal gammopathies Most common pattern found in association with subacute bacterial infection, but also with cryoglobulinaemia ± hepatitis C virus, and others Complement type Complement components Complement abnormalities, inherited or acquired Dense deposit disease is associated with abnormal activation of alternative complement pathway Complement gene mutations C3 nephritic factor and partial lipodystrophy In dense deposit disease, intramembranous deposits No proven treatments Continued

15.15 Glomerulonephritis categorised by clinical presentation and histological classification – continued Histology Immune deposits Pathogenesis Associations Comments Rapidly progressive glomerulonephritis presentation Focal necrotising glomerulonephritis Segmental inflammation and/or necrosis in some glomeruli ± crescent formation Variable according to cause but typically negative (or 'pauciimmune') Small-vessel vasculitis, often ANCA-mediated Primary or secondary small-vessel vasculitis Often occurs in systemic disease Responds to treatment with glucocorticoids and immunosuppressants Diffuse proliferative glomerulonephritis 2 Infection-related diffuse proliferative glomerulonephritis 3 Diffuse proliferation of endothelial and mesangial cells Infiltration by neutrophils and macrophages ± crescent formation Subendothelial and subepithelial Immune complex-mediated (e.g. to streptococcal infection with presumed cross-reactive epitopes) Post-streptococcal Concurrent infection with staphylococci, endocarditis Presents with severe sodium and fluid retention, hypertension, haematuria, oliguria Usually resolves spontaneously Anti-glomerular basement membrane disease Usually crescentic nephritis Linear IgG along GBM Autoantibodies to α3 chain of type IV collagen in GBM HLA-DR15 (previously known as DR2) Associated with lung haemorrhage but renal or lung disease may occur alone Treat with glucocorticoids, cyclophosphamide and plasma exchange 1Systemic lupus erythematosus can cause almost any histological injury pattern, most commonly membranous nephropathy or diffuse proliferative glomerulonephritis. 2In addition to the association with infection and anti-GBM disease, a diffuse proliferative glomerulonephritis picture may also be seen with lupus and occasionally IgA nephropathy. 3Infection may also present with mesangioproliferative glomerulonephritis and membranous nephropathy (HIV). (ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; APOL1 = apolipoprotein L1; GBM = glomerular basement membrane; HLA = human leucocyte antigen; IgA = immunoglobulin A; NSAIDs = non-steroidal anti-inflammatory drugs) Fig. 15.12 Histopathology of glomerular disease. (A – E Light microscopy) A A normal glomerulus. Note the open capillary loops and thinness of their walls. B Focal segmental glomerulosclerosis (GS). The portion of the glomerulus arrowed shows loss of capillary loops and cells, which are replaced by matrix. C Focal necrotising glomerulonephritis (GN). A portion of the glomerulus (N = focal necrotising lesion) is replaced by bright pink material with some ‘nuclear dust’. Neutrophils may be seen elsewhere in the glomerulus. There is surrounding interstitial inflammation (I). This is most commonly associated with small-vessel vasculitis and may progress to crescentic nephritis (see E). D Membranous glomerulonephritis. The capillary loops (C) are thickened (compare with the normal glomerulus) and there is expansion of the mesangial regions by matrix deposition (M). However, there is no gross cellular proliferation or excess of inflammatory cells. E Crescentic glomerulonephritis. The lower part of Bowman’s space is occupied by a semicircular formation (‘crescent’, Cr) of large pale cells, compressing the glomerular tuft. This is seen in aggressive inflammatory glomerulonephritis. Antibody deposition in the glomerulus. (F – H Direct immunofluorescence) F Granular deposits of IgG along the basement membrane in a subepithelial pattern, typical of membranous GN. G Immunoglobulin A (IgA) deposits in the mesangium, as seen in IgA nephropathy. H Ribbon-like linear deposits of anti-GBM antibodies along the glomerular basement membrane in Goodpasture’s disease. The glomerular structure is well preserved in all of these examples. (A, C, D, E) Courtesy of Dr J.G. Simpson, Aberdeen Royal Infirmary. (F, G, H) Courtesy of Dr R. Herriot. A B C D E F G H Normal glomerulus Focal segmental GS Membranous GN Focal necrotising GN Crescentic GN Membranous GN IgA nephropathy Anti-GBM disease C N I Cr M

 rarely exhibit full-blown nephrotic syndrome. Management of secondary FSGS is focused on treating the underlying cause and reducing proteinuria by inhibiting the renin–angiotensin system (p. 417). Membranous nephropathy Membranous nephropathy is the most common cause of nephrotic syndrome in Caucasian adults. It is caused by antibodies (usually autoantibodies) directed at antigen(s) expressed on the surface of podocytes, including the M-type phospholipase A2 receptor 1. While most cases are idiopathic, a proportion are associated with other causes, such as heavy metal poisoning, drugs, infections, lupus and tumours (see Box 15.15 and Fig. 15.12D and F). Approximately one-third of patients with idiopathic membranous nephropathy undergo spontaneous remission, one-third remain in a nephrotic state, and one-third develop progressive CKD. High doses of glucocorticoids and cyclophosphamide may improve both the nephrotic syndrome and the long-term prognosis. However, because of the toxicity of these regimens, many nephrologists reserve such treatment for those with severe nephrotic syndrome or deteriorating renal function. Treatment of secondary membranous nephropathy is directed at the underlying cause. Diseases typically presenting with mild nephritic syndrome Patients with mild glomerulonephritis typically present with nonvisible haematuria and modest proteinuria, and their renal disease tends to follow a slowly progressive course. IgA nephropathy and mesangiocapillary glomerulonephritis (MCGN) typically fall in this category. Their presentation is highly variable, however; IgA nephropathy occasionally presents with rapidly progressive glomerulonephritis while MCGN may present with nephrotic syndrome. Other diseases that present with haematuria, modest proteinuria and slow progression include Alport’s syndrome (p. 403). IgA nephropathy This is one of the most common types of glomerulonephritis and can present in many ways. Haematuria is the earliest sign and non-visible haematuria is almost universal, while hypertension is also very common. These are often detected during routine screening: for example, at occupational medical examinations. Proteinuria can also occur but is usually a later feature. In many cases, there is slowly progressive loss of renal function leading to end-stage renal disease (ESRD). A particular hallmark of IgA nephropathy in young adults is the occurrence of acute self-limiting exacerbations, often with visible haematuria, in association with minor respiratory infections. This may be so acute as to resemble acute post-infectious glomerulonephritis, with fluid retention, hypertension and oliguria with dark or red urine. Characteristically, the latency from clinical infection to nephritis is short: a few days or less. Asymptomatic presentations dominate in older adults, with non-visible haematuria, hypertension and reduction in GFR. Occasionally, IgA nephropathy progresses rapidly in association with crescent formation on biopsy. Management is largely directed towards the control of blood pressure, with renin–angiotensin system inhibitors preferable in those with proteinuria. There is some evidence for additional benefit from several months of high-dose glucocorticoid treatment in those at high-risk of progressive disease (see Box 15.14), but no strong evidence for other immunosuppressive agents. A role for other therapies, such as fish oil, remains uncertain. with high-dose glucocorticoid therapy (1 mg/kg prednisolone for 6 weeks), though the response to therapy is often less satisfactory in older patients. Some patients who respond incompletely (glucocorticoid-resistant) or relapse frequently need maintenance glucocorticoids (glucocorticoid dependence), cytotoxic therapy or other agents. Glucocorticoid resistance in children warrants a biopsy to exclude an alternative diagnosis, but if minimal change is confirmed, a genetic cause should be considered (p. 403). Minimal change disease typically does not progress to CKD but can present with problems related to the nephrotic syndrome (see Box 15.11) and complications of treatment. Focal segmental glomerulosclerosis Primary focal segmental glomerulosclerosis (FSGS) (Fig. 15.12B) can occur in all age groups but is particularly common in people of West African descent, who, compared with other ethnicities, have a much higher carriage rate of an apolipoprotein L1 (APOL1) gene variant that is associated with increased risk of FSGS. Histological analysis shows sclerosis initially limited to segments of the glomeruli, which may also show positive staining for deposits of C3 and IgM on immunofluorescence. Since FSGS is a focal process, abnormal glomeruli may not be seen on renal biopsy if only a few are sampled, leading to an initial diagnosis of minimal change nephropathy. In most cases the underlying cause is unknown (primary FSGS) and these patients typically present with abrupt onset of severe nephrotic syndrome. Primary FSGS may respond to high-dose glucocorticoid therapy (0.5–2.0 mg/ kg/day) but the response is rarely as rapid or complete as for minimal change disease. Immunosuppressive drugs, such as ciclosporin, cyclophosphamide and mycophenolate mofetil, have also been used but their efficacy is uncertain. Progression to CKD is common in patients who do not respond to glucocorticoids and the disease frequently recurs after renal transplantation. FSGS may also be secondary to other diseases such as human immunodeficiency virus (HIV) renal disease (particularly in African Americans), morbid obesity or chronic hypertension. In addition, it may reflect scarring from previous focal glomerular injury resulting from HUS, cholesterol embolism or vasculitis. Patients with secondary FSGS typically present with more modest proteinuria than those with primary disease and 15.16 Terminology used in glomerulonephritis Light microscopy • Focal: affecting some but not all glomeruli • Diffuse: affecting > 50% of glomeruli • Segmental: affecting a portion of a glomerulus • Global: affecting all of the glomerulus • Necrotising: severe injury leading to an area of necrosis, usually associated with vasculitis • Crescentic: a crescent-shaped area of inflammatory cells responding to severe glomerular injury Electron microscopy • Subendothelial immune deposits: found between the endothelial cell and the GBM – often found in nephritic presentations • Intramembranous immune deposits: found within the GBM – found in the dense deposit variant of mesangiocapillary glomerulonephritis • Subepithelial immune deposits: found between the epithelial cell and the GBM – often found in nephrotic presentations, including membranous presentation of lupus (GBM = glomerular basement membrane)

Anti-glomerular basement membrane disease Anti-GBM disease is a rare autoimmune disease in which antibodies develop against the α3 chain of type 4 collagen GBM. Expression of the α3 chain is largely restricted to the basement membranes of glomeruli and lungs, and hence the disease may present with rapidly progressive glomerulonephritis, lung haemorrhage, or disease of both organs, when it is known as Goodpasture's disease. Goodpasture's disease is more common in younger patients, while elderly patients often present with renal-limited disease. Patients with anti-GBM disease should be treated with plasma exchange combined with glucocorticoids and immunosuppressants, but early diagnosis is essential, as renal function is rarely recoverable in those requiring dialysis at presentation. The combination of glomerulonephritis and pulmonary haemorrhage (Goodpasture's syndrome) may also be observed with small-vessel vasculitis (particularly granulomatosis with polyangiitis, previously known as Wegener's granulomatosis) and lupus. Infection-related glomerulonephritis RPGN may occur either during or following an infection. In both cases, circulating immune complexes are present and activation of the complement system promotes consumption of complement factors, resulting in low serum C3 and C4 concentration, as observed in many causes of glomerulonephritis (Box 15.17). Post-infectious glomerulonephritis is observed most commonly in children and young adults, and typically presents 10 days after a streptococcal throat infection or longer after a skin infection. The clinical presentation ranges from mild abnormalities on urinalysis to RPGN with severe AKI. The anti-streptolysin (ASO) test is positive in up to 95% of patients with streptococcal throat infections. Treatment is supportive, with control of blood pressure and fluid overload with salt restriction, diuretics and dialysis if required. Antibiotic therapy is rarely needed, as the renal disease occurs after the infection has subsided. The medium-term prognosis for children and most adults is good, with recovery of renal function typical even in those requiring dialysis therapy. Some patients may develop CKD 20–30 years after the original presentation, however. An immune complex-mediated disease may also be observed during an infection, typically a staphylococcal infection such as endocarditis, skin infection or pneumonia, but also with subacute endocarditis due to Streptococcus viridans. This occurs more commonly in older adults and the presentation tends not to be as fulminant as with post-streptococcal disease. In addition to supportive measures, antibiotic therapy is required, as infection is usually concurrent with renal disease. Tubulo-interstitial diseases These diseases primarily affect the renal tubules and interstitial components of the renal parenchyma. They are characterised Henoch–Schönlein purpura This condition most commonly occurs in children but can also be observed in adults. It is a systemic vasculitis that often arises in response to an infectious trigger. It presents with a tetrad of features: • a characteristic petechial rash typically affecting buttocks and lower legs • abdominal pain due to vasculitis involving the gastrointestinal tract • arthralgia • renal disease characterised by visible or non-visible haematuria, with or without proteinuria. Renal biopsy shows mesangial IgA deposition and appearances that are indistinguishable from acute IgA nephropathy (Fig. 15.12G). Treatment is supportive in nature; in most patients, the prognosis is good, with spontaneous resolution, though relapses are common. Some patients, particularly adults and those with severe or persistent proteinuria, progress to develop ESRD. Mesangiocapillary glomerulonephritis Mesangiocapillary glomerulonephritis (MCGN), also known as membranoproliferative glomerulonephritis, is a pattern of injury seen on renal biopsy that is characterised by an increase in mesangial cellularity with thickening of glomerular capillary walls. The typical presentation is with proteinuria and haematuria. Several underlying causes have been identified, as summarised in Box 15.15. It can be classified into two main subtypes. The first is characterised by deposition of immunoglobulins within the glomeruli. This subtype is associated with chronic infections, autoimmune diseases and monoclonal gammopathy.

The second is characterised by deposition of complement in the glomeruli and is associated with inherited or acquired abnormalities in the complement pathway. This category comprises 'dense deposit disease', which is typified by electron-dense deposits within the GBM, and C3 glomerulonephritis that shows deposits similar to immunoglobulin-type MCGN. Treatment of MCGN associated with immunoglobulin deposits consists of the identification and treatment of the underlying disease, if possible, and the use of immunosuppressive drugs such as mycophenolate mofetil or cyclophosphamide. There are few specific treatments for MCGN associated with complement dysregulation, although eculizumab, the anti-C5 inhibitor that prevents formation of the membrane attack complex, has shown promise. Diseases typically presenting with rapidly progressive glomerulonephritis Rapidly progressive glomerulonephritis (RPGN) is characterised by rapid loss of renal function over days to weeks, usually in association with hypertension and oedema. Non-visible haematuria is almost always present with variable amounts of proteinuria, while characteristic red cell casts and dysmorphic red cells may be observed on urine microscopy (see Fig. 15.3). Renal biopsy typically shows crescentic lesions (see Fig. 15.12E), often associated with necrotising lesions within the glomerulus (Fig. 15.12C), particularly in small-vessel vasculitides. This pattern of presentation is typical of post-infectious glomerulonephritis, anti-GBM disease and small-vessel vasculitides (p. 1040). It can also be observed in SLE (p. 1034) and occasionally in IgA and other nephropathies (see Fig. 15.9). 15.17 Causes of glomerulonephritis associated with low serum complement • Post-infectious glomerulonephritis • Subacute bacterial infection, especially endocarditis • Systemic lupus erythematosus • Cryoglobulinaemia • Mesangiocapillary glomerulonephritis, usually complement type

 signs of a generalised drug hypersensitivity reaction with fever, rash and eosinophilia. Proteinuria is generally modest (PCR < 100 mg/mmol) and tubular in type (see Box 15.25, p. 412). The urine may contain white blood cells and white cell casts but is sterile on culture. Eosinophils are present in up to 70% of patients but this is a non-specific finding. AIN should always be considered in patients with non-oliguric AKI. There may be a rapid deterioration of renal function in some cases of drug-induced AIN, causing the condition to be mistaken for RPGN. Investigations Renal biopsy is usually required to confirm the diagnosis (Fig. 15.13D). This typically shows evidence of intense inflammation, with infiltration of the tubules and interstitium by polymorphonuclear leucocytes and lymphocytes. Eosinophils may also be observed, especially in drug-induced AIN. Often granulomas may be evident, especially in drug-induced AIN or sarcoidosis (p. 608). The degree of chronic inflammation in a biopsy is a useful predictor of long-term renal function. Eosinophiluria may be present but is not a good discriminator for AIN. Management Some patients with drug-induced AIN recover following withdrawal of the drug alone, but high-dose glucocorticoids (prednisolone 1 mg/kg/day) may accelerate recovery and prevent long-term scarring. Other specific causes (see Box 15.18) should be treated, if possible. Chronic interstitial nephritis Chronic interstitial nephritis (CIN) is characterised by renal dysfunction with fibrosis and infiltration of the renal parenchyma by lymphocytes, plasma cells and macrophages, in association with tubular damage. by tubular dysfunction with electrolyte abnormalities, moderate levels of proteinuria and varying degrees of renal impairment. Often the urinary output may be relatively preserved for any given GFR, and indeed there may be polyuria and nocturia. Acute interstitial nephritis Acute interstitial nephritis (AIN) is an immune-mediated disorder, characterised by acute inflammation affecting the tubulointerstitium of the kidney. It is commonly drug-induced, with proton pump inhibitors (PPIs) fast becoming the most common cause, but can be caused by other toxins, and can complicate a variety of systemic diseases and infections (Box 15.18). Clinical features The clinical presentation is typically with renal impairment but, in some patients with drug-induced AIN, there may be 15.18 Causes of acute interstitial nephritis Allergic Many drugs but particularly: • Penicillins • Non-steroidal antiinflammatory drugs (NSAIDs) • Proton pump inhibitors • Mesalazine (delayed) Immune • Autoimmune nephritis ± uveitis • Transplant rejection Infections • Acute bacterial pyelonephritis • Leptospirosis • Tuberculosis • Hantavirus Toxic • Myeloma light chains • Mushrooms (Cortinarius) Fig. 15.13 Tubular histopathology. A Normal tubular histology. The tubules are back to back. Brush borders can be seen on the luminal borders of cells in the proximal tubule. B Acute tubular necrosis. There are scattered breaks (B) in tubular basement membranes, swelling and vacuolation of tubular cells, and, in places, apoptosis and necrosis of tubular cells with shedding of cells into the lumen. During the regenerative phase, there is increased tubular mitotic activity. The interstitium (I) is oedematous and infiltrated by inflammatory cells. The glomeruli (not shown) are relatively normal, although there may be endothelial cell swelling and fibrin deposition. C Acute bacterial pyelonephritis. A widespread inflammatory infiltrate that includes many neutrophils is seen. Granulocyte casts (G) are forming within some dilated tubules (T). Other tubules are scarcely visible because of the extent of the inflammation and damage. D Acute (allergic) interstitial nephritis. In this patient who received a non-steroidal anti-inflammatory drug (NSAID), an extensive mononuclear cell infiltrate (no neutrophils) involving tubules (T) is seen. This inflammation does not involve the glomeruli (not shown). Sometimes eosinophils are prominent. Transplant rejection looks similar to this. A B C D T G T I B Normal tubular histology Acute tubular necrosis Acute pyelonephritis Acute interstitial nephritis

Clinical features Most patients with CIN present in adult life with CKD, hypertension and small kidneys. Urinalysis abnormalities are non-specific. A minority present with salt-losing nephropathy, characterised by hypotension, polyuria and features of sodium and water depletion. People with CIN have an impairment of urine-concentrating ability and sodium conservation, which puts them at risk of AKI due to salt and water depletion during an acute illness. Renal tubular acidosis (p. 365) may complicate CIN but is seen most often in myeloma, sarcoidosis, cystinosis, amyloidosis and Sjögren’s syndrome. Management Management is supportive in nature, with correction of acidosis and hyperkalaemia; replacement of fluid and electrolytes, as required; and renal replacement therapy if irreversible renal damage has occurred. Papillary necrosis The renal papillae lie within a hypertonic environment in the renal medulla, at the end of the vasa recta. They are susceptible to ischaemic damage because of this and can undergo necrosis when their vascular supply is impaired as the result of diabetes mellitus, sickle-cell disease or long-term ingestion of NSAIDs. The condition may occasionally occur in other diseases. There is an association with pyelonephritis but it is difficult to determine whether this is a cause of papillary necrosis or a complication. The clinical presentation is variable. Some patients are asymptomatic and clinically silent, whereas others present with renal colic and renal impairment as necrosed papillae slough off and cause ureteric obstruction. Urinalysis may be normal but more frequently haematuria and sterile pyuria are present. Significant proteinuria is unusual, unless there is renal failure. The imaging method of choice to make the diagnosis is CTU or intravenous pyelography. Management is based on relieving obstruction, where present, and withdrawal of the offending drugs. Genetic renal diseases The advent of modern genetic techniques such as next-generation sequencing has allowed us to understand the breadth of inherited renal diseases on a much deeper level than before. Inherited glomerular diseases Alport’s syndrome A number of uncommon diseases may involve the glomerulus in childhood but the most important one affecting adults is Alport’s syndrome. Most cases arise from a mutation or deletion of the COL4A5 gene on the X chromosome, which encodes type IV collagen, resulting in inheritance as an X-linked recessive disorder (p. 48). Mutations in COL4A3 or COL4A4 genes are less common and cause autosomal recessive disease. The accumulation of abnormal collagen results in a progressive degeneration of the GBM (Fig. 15.14). Affected patients progress from haematuria to ESRD in their late teens or twenties. Female carriers of COL4A5 mutations usually have haematuria but less commonly develop significant renal disease. Some other basement membranes containing the same collagen isoforms are similarly involved, notably in the cochlea, so that Alport’s syndrome is associated with sensorineural deafness and ocular abnormalities. Pathophysiology This disease may follow on from AIN that does not resolve, or may be associated with ingestion of various toxins and drugs, or with metabolic and chronic inflammatory diseases, as summarised in Box 15.19. In many patients, CIN presents at a late stage and no underlying cause can be identified. Genetic causes may underlie many of these cases (p. 404). Toxins that have been associated with CIN include those contained within the plant Aristolochia clematitis (birthwort). These are probably responsible for the severe nephrotoxicity that can be associated with treatment with herbal medicines in Asia and for Balkan nephropathy, which affects isolated rural communities in Bosnia, Bulgaria, Croatia, Romania and Serbia, possibly through contaminated flour. The nephropathy is commonly linked with tumours of the collecting system and is probably due to the mutagenic effects of the plant toxin on the urothelial epithelium. Ingestion of mushrooms within the Cortinarius genus can cause a devastating and irreversible renal tubular toxicity. It is encountered occasionally in Scandinavia and Scotland. 15.19 Causes of chronic interstitial nephritis Acute interstitial nephritis • Any of the causes of acute interstitial nephritis, if persistent (see Box 15.18) Glomerulonephritis • Varying degrees of interstitial inflammation occur in association with most types of inflammatory glomerulonephritis Immune/inflammatory • Sarcoidosis • Sjögren’s syndrome • Chronic transplant rejection • Systemic lupus erythematosus, primary autoimmune Toxic • Aristolochia in herbal medicines • Lead • Balkan nephropathy • Mushrooms (Cortinarius) Drugs • All drugs causing acute interstitial nephritis • Tenofovir • Lithium toxicity • Analgesic nephropathy • Ciclosporin, tacrolimus Infection • Consequence of severe pyelonephritis Congenital/developmental • Vesico-ureteric reflux: associated but causation not clear • Renal dysplasias: often associated with reflux • Inherited: now well recognised but mechanisms unclear • Other: Wilson’s disease, sickle-cell nephropathy, medullary sponge kidney (nephrocalcinosis) Metabolic and systemic diseases • Calcium phosphate crystallisation after excessive phosphate administration (e.g. phosphate enemas in patients with chronic kidney disease) • Hypokalaemia • Hyperoxaluria

 all code for podocyte proteins, including nephrin (‘Finnish-type’ nephropathy) and podocin, which both cause early congenital nephrotic syndrome. Autosomal dominant mutations in various genes may cause FSGS as part of systemic syndromes; the genes include INF2 (Charcot–Marie–Tooth disease), LMX1B (nail–patella syndrome) and WT1 (abnormal genitalia, Wilms’ tumour, mental retardation). Inheriting variants in the APOL1 gene, which is observed predominantly in people of West African ancestry, leads to a greatly increased risk of kidney disease including FSGS (p. 400). Inherited tubulo-interstitial diseases It has become evident in recent years that a significant number of cases of CKD with low or absent proteinuria have genetic causes, which may be inherited in an autosomal dominant or recessive pattern (Box 15.20). The histological pattern of injury is identical to other forms of CIN (p. 402). This is a heterogeneous group of inherited disorders. Small cysts are sometimes evident, explaining the previous name of medullary cystic kidney disease, but tubulo-interstitial nephritis is the predominant pattern of injury. Many of these conditions, especially those formerly known as nephronophthisis, are associated with retinal dystrophies and brain or other abnormalities, and some may be associated with hyperuricaemia or gout (UMOD or HNF1-beta mutations). Modern genetics have brought clarity to a disease spectrum comprising many different conditions with inexact previous names. Angiotensin-converting enzyme (ACE) inhibitors may slow but not prevent loss of kidney function. Patients with Alport's syndrome are good candidates for renal replacement therapy (RRT), as they are young and usually otherwise healthy. They can develop an immune response to the normal collagen antigens present in the GBM of the donor kidney and, in a small minority, anti-GBM disease develops and destroys the allograft. Thin glomerular basement membrane disease In thin glomerular basement membrane disease there is glomerular bleeding, which is usually non-visible, without associated hypertension, proteinuria or a reduction in GFR. The glomeruli appear normal by light microscopy but, on electron microscopy, the GBM is abnormally thin. The condition may be familial and some patients are carriers of Alport mutations. This does not appear to account for all cases, and in many patients the cause is unclear. Monitoring of these patients is advisable, as proteinuria may develop in some and there appears to be an increased rate of progressive CKD in the long term. Hereditary nephrotic syndrome Many genes have been discovered that cause early-onset nephrotic syndrome, often with an FSGS pattern of injury. Inheritance may be autosomal dominant or recessive, the former conditions having a less severe and later-onset phenotype and often exhibiting incomplete penetrance. The involved genes almost Fig. 15.14 Alport's syndrome. A Diagrammatic structure of the normal glomerular basement membrane (GBM). B The normal GBM (electron micrograph) contains mostly the tissue-specific (α3, α4 and α5) chains of type IV collagen. C In Alport's syndrome, this network is disrupted and replaced by α1 and α2 chains. Although the GBM appears structurally normal in early life, in time thinning appears, progressing to thickening, splitting and degeneration. (B, C) Courtesy of Dr J. Collar, St Mary's Hospital, London. Urinary space Foot process of podocyte Endothelial cell Glomerular capillary GBM A B C 15.20 Hereditary tubulo-interstitial kidney diseases Inheritance Gene(s) Other name(s) Clinical features Autosomal dominant UMOD MCKD type 2 Juvenile hyperuricaemic nephropathy Gout MUC1 MCKD type 1 Progressive CKD without other manifestations HNF1-beta Juvenile hyperuricaemic nephropathy Cystic kidneys, solitary kidney; gout; MODY; abnormal LFTs; pancreatic atrophy; hypomagnesaemia REN (codes for renin) Juvenile hyperuricaemic nephropathy Gout; hyperkalaemia; salt-losing nephropathy Autosomal recessive NPHP genes (17 discovered so far) Nephronophthisis Part of many syndromes (Bardet–Biedl) Common cause of paediatric ESRD Occurs earlier than AD interstitial nephritis Extrarenal manifestation common (learning difficulty, eye/limb problems) (AD = autosomal dominant; CKD = chronic kidney disease; ESRD = end-stage renal disease; LFTs = liver function tests; MCKD = medullary cystic kidney disease; MODY = maturity-onset diabetes of the young)

Clinical features Common clinical features are shown in Box 15.21. Affected people are usually asymptomatic until later life but hypertension usually occurs from the age of 20 onwards. One or both kidneys may be palpable and the surface may feel nodular. About 30% of patients with PKD also have hepatic cysts (see Fig. 22.39, p. 893) but disturbance of liver function is rare. Sometimes (almost always in women) this causes massive and symptomatic hepatomegaly, usually concurrent with renal enlargement but occasionally with only minor renal involvement. Berry aneurysms of cerebral vessels are an associated feature in about 5% of patients with PKD. This feature appears to be largely restricted to certain families (and presumably specific mutations). Mitral and aortic regurgitation is frequent but rarely severe, and colonic diverticula and abdominal wall hernias may occur. Investigations The diagnosis is usually based on family history, clinical findings and ultrasound examination. Ultrasound demonstrates cysts in approximately 95% of affected patients over the age of 20 and is the screening method of choice, but may not detect small developing cysts in younger subjects. Cysts may also be identified by other imaging modalities, such as MRI (Fig. 15.15). Simple renal cysts may occur in normal individuals but are uncommon below the age of 30. The following criteria exist for an ultrasound diagnosis of PKD in patients with a family history but unknown genotype: • 15–39 years of age: at least three unilateral or bilateral kidney cysts • 40–59 years of age: at least two cysts in each kidney • 60 years or older: at least four cysts in each kidney. It is now possible to make a molecular diagnosis by mutation screening of PDK1 or PDK2 but this is seldom used in routine clinical practice because the PKD1 gene is so large and has many possible mutations. Next-generation sequencing allows faster and simpler genetic screening for PKD1 and PKD2. This is likely to be used in cases with an uncertain diagnosis (young patients, few cysts, lack of family history), for workup of living kidney donors, or for screening for mutations associated with a worse prognosis (see below). Screening for intracranial aneurysms is not generally indicated but can be done by MR angiography in families with a history of subarachnoid haemorrhage. The yield of screening is low, however, and the risk:benefit ratio of intervention in asymptomatic aneurysms in this disease is not clear. Management Blood pressure control is important because cardiovascular morbidity and mortality are so common in renal disease, but evidence is lacking that controlling blood pressure to generally recommended CKD targets (e.g. <130/80 mmHg) influences renal outcomes. There are data suggesting that targeting a very low blood pressure (<110/75 mmHg) with ACE inhibitors or angiotensin II Isolated defects of tubular function An increasing number of disorders have been identified that are caused by specific defects in transporter molecules expressed in renal tubular cells. Only the most common are mentioned here. Renal glycosuria is a benign autosomal recessive defect of tubular reabsorption of glucose, caused by mutations of the sodium/glucose co-transporter SGLT2. Glucose appears in the urine in the presence of a normal blood glucose concentration. It is notable that SGLT2 inhibitors have been developed as a treatment for diabetes mellitus and evidence suggests they may improve renal and cardiovascular outcomes. Cystinuria is a rare condition, in which reabsorption of filtered cystine, ornithine, arginine and lysine is defective. It is caused by mutations in the SLC3A1 amino acid transporter gene. The high concentration of cystine in urine leads to cystine stone formation (p. 431). Other uncommon tubular disorders include hereditary hypophosphataemic rickets (p. 1052), in which reabsorption of filtered phosphate is reduced; nephrogenic diabetes insipidus (p. 687), in which the tubules are resistant to the effects of vasopressin (antidiuretic hormone, ADH); and Bartter’s and Gitelman’s syndromes, in which there is sodium-wasting and hypokalaemia (p. 361). The term ‘Fanconi’s syndrome’ is used to describe generalised proximal tubular dysfunction. The condition typically presents with low blood phosphate and uric acid concentrations, glycosuria, aminoaciduria and proximal renal tubular acidosis. In addition to the causes of interstitial nephritis described above, some congenital metabolic disorders are associated with Fanconi’s syndrome, notably Wilson’s disease, cystinosis and hereditary fructose intolerance. Renal tubular acidosis describes the common end-point of a variety of diseases affecting distal (classical or type 1) or proximal (type 2) renal tubular function. These syndromes are described on page 365. Cystic diseases of the kidney It is common to encounter patients with a single renal cyst or even multiple cysts as an incidental finding, especially in those aged 50 years and over. Usually, these cysts are of no clinical consequence and are asymptomatic, but occasionally they can cause pain or haematuria. In addition, several specific diseases are recognised as being caused by the formation of multiple renal cysts. These are discussed in more detail below. Adult polycystic kidney disease Adult polycystic kidney disease (PKD) is a common condition, with a prevalence of approximately 1:1000, and is inherited as an autosomal dominant trait. Small cysts lined by tubular epithelium develop from infancy or childhood and enlarge slowly and irregularly. The surrounding normal kidney tissue is compressed and progressively damaged. Mutations in the PKD1 gene account for 85% of cases and those in PKD2 for about 15% (coding for polycystin 1 and 2, respectively). ESRD occurs in approximately 50% of patients with PKD1 mutations, with a mean age of onset of 52 years, but in a minority of patients with PKD2 mutations, with a mean age of onset of 69 years. It has been estimated that between 5% and 10% of patients on RRT have PKD. 15.21 Adult polycystic kidney disease: common clinical features • Vague discomfort in loin or abdomen due to increasing mass of renal tissue • Acute loin pain or renal colic due to haemorrhage into a cyst • Hypertension • Haematuria (with little or no proteinuria) • Urinary tract or cyst infections • Renal failure

 causes cysts but also may cause a tubulo-interstitial pattern of injury or congenital absence of a kidney. It also causes a form of MODY (p. 733). Autosomal recessive PKD is caused by mutations in the PKHD1 gene, encoding fibrocystin. It is less common than autosomal dominant PKD (about 1:20 000 live births). Patients often present in infancy or young childhood with renal cysts and congenital hepatic fibrosis. Some uncommon autosomal dominantly inherited conditions are associated with multiple renal cysts and tumours in adult life. In tuberous sclerosis (p. 1264), replacement of renal tissue by multiple angiomyolipomas may occasionally cause renal failure in adults. Patients may also develop renal cysts and have a higher risk of renal cell carcinoma. Other organs affected include the skin (adenoma sebaceum on the face) and brain (causing seizures and mental retardation). The von Hippel–Lindau syndrome (p. 1132) is associated with multiple renal cysts, renal adenomas and renal adenocarcinoma. Other involved organs include the central nervous system (haemangioblastomas), pancreas (serous cystadenomas) and adrenals (phaeochromocytoma). A number of other rarer inherited cystic diseases are recognised that have some similarities to PKD but distinct genetic causes. Multicystic dysplastic kidneys are often unilateral and are a developmental abnormality found in children. Most of these seem to involute during growth, leaving a solitary kidney in adults. Acquired cystic kidney disease can develop in patients with a very long history of renal failure, so it is not an inherited cystic disease. It is associated with increased erythropoietin production and sometimes with the development of renal cell carcinoma. Renal vascular diseases Diseases that affect renal blood vessels may cause renal ischaemia, leading to acute or chronic kidney disease or secondary hypertension. The rising prevalence of atherosclerosis and diabetes mellitus in ageing populations has made renovascular disease an important cause of ESRD. Renal artery stenosis A stenosis of more than 50% may be observed on imaging of the renal arteries in up to 20% of older patients with advanced kidney disease; however, a haemodynamically significant effect will be present in only a relatively small proportion. Renal artery stenosis is the most common cause of secondary hypertension, with an estimated prevalence of about 2% in unselected patients, but this may increase to 4% in older patients who have evidence of atherosclerotic disease elsewhere. Most cases of renal artery stenosis are caused by atherosclerosis but fibromuscular dysplasia involving the vessel wall may be responsible in younger patients. Rare causes include vasculitis, thromboembolism and aneurysms of the renal artery. Pathophysiology Renal artery stenosis results in a reduction in renal perfusion pressure, which activates the renin–angiotensin system, leading to increased circulating levels of angiotensin II. This results in hypertension by provoking vasoconstriction and increasing aldosterone production by the adrenal, causing sodium retention by the renal tubules (p. 351). Significant reduction of renal blood flow occurs when there is more than 70% narrowing of the artery, and this is commonly associated with distal, post-stenotic Fig. 15.15 MRI images of the kidneys. A Normal kidneys. B Polycystic kidneys; although the kidney enlargement is extreme, this patient had only slightly reduced GFR. A B receptor blocker (ARBs) leads to slower increases in kidney volume, but no improvements in eGFR decline were observed and these targets are often not tolerated. This tight blood pressure target did lead to a greater decline in left ventricular mass index, which may have implications for improved cardiovascular risk later in life. The vasopressin V2 receptor antagonist tolvaptan may retard kidney volume increase and slow the rate of GFR decline. It has now been licensed in many countries for patients at high risk of progression. Risk factors for progression include large kidneys (more specifically height-adjusted kidney volume), truncating PKD1 mutations, and family history of early progression, as well as male sex, hypertension, proteinuria and development of early symptomatic cysts. Patients with PKD are usually good candidates for dialysis and transplantation. Sometimes kidneys are so large that one or both have to be removed to make space for a renal transplant. Otherwise, they are usually left in situ unless they are a source of pain or infection. Other cystic diseases Renal cysts and diabetes syndrome is caused by HNF1-beta mutations (see above); it has a varying renal phenotype that often

although this is insufficiently sensitive or specific to be of value in diagnosis of renovascular disease in hypertensive patients. Management The first-line management in patients with renal artery stenosis is medical therapy with antihypertensive drugs, supplemented, where appropriate, by statins and low-dose aspirin in those with atherosclerotic disease. Interventions to correct the vessel narrowing should be considered in: • young patients (age below 40) suspected of having renal artery stenosis • those whose blood pressure cannot easily be controlled with antihypertensive agents • those who have a history of ‘flash’ pulmonary oedema • those with accelerated phase (malignant) hypertension • those whose renal function is deteriorating. The most commonly used technique is angioplasty. The best results are obtained in non-atheromatous fibromuscular dysplasia, where correction of the stenosis has a high chance of success in improving blood pressure and protecting renal function. Beyond the indications above, angioplasty and stenting is now rarely dilatation. Atherosclerotic lesions are typically ostial and are associated with more widespread atherosclerosis within the aorta and other vessels, particularly the iliac vessels. There is often concurrent small-vessel disease in affected kidneys, due to subclinical atheroemboli. As the stenosis becomes more severe, global renal ischaemia leads to shrinkage of the affected kidney and may cause renal failure if bilateral, or if unilateral in the presence of a single kidney (ischaemic nephropathy). In younger patients, fibromuscular dysplasia is a more likely cause of renal artery stenosis. This is an uncommon disorder of unknown cause. It is characterised by hypertrophy of the media (medial fibroplasia), which narrows the artery but rarely leads to total occlusion. It may be associated with disease in other arteries; for example, those who have carotid artery dissections are more likely to have renal arteries with this appearance. It most commonly presents with hypertension in patients aged 15–30 years, and women are affected more frequently than men. Irregular narrowing (beading) may occur in the distal renal artery and this sometimes extends into the intrarenal branches of the vessel. Rarely, renal artery stenosis may occur as a complication of large-vessel vasculitis, such as Takayasu's arteritis and polyarteritis nodosa (pp. 1041 and 1042). Untreated, atheromatous renal artery stenosis is thought to progress to complete arterial occlusion in about 15% of cases. This figure increases with more severe degrees of stenosis. If the progression is gradual, collateral vessels may develop and some function may be preserved, preventing infarction and loss of kidney structure. Conversely, at least 85% of patients with renal artery stenosis will not develop progressive renal impairment, and many patients die from coronary, cerebral or other vascular disease rather than renal failure. Unfortunately, methods of predicting which patients are at risk of progression or who will respond to treatment are still imperfect. Clinical features Renal artery stenosis can present in various ways including hypertension, acute pulmonary oedema, progressive renal failure (with bilateral disease) or a deterioration in renal function when ACE inhibitors or ARBs are administered. Although many patients experience a slight drop in GFR when commencing these drugs, an increase in serum creatinine of 30% or more raises the possibility of renal artery stenosis. Acute pulmonary oedema is particularly characteristic of bilateral renovascular disease. It typically occurs at night and is associated with severe hypertension, often in the context of normal or only mildly impaired renal and cardiac function. Clinical evidence of generalised vascular disease may be observed, particularly in the legs and in older patients with atherosclerotic renal artery stenosis. Clinical features associated with an increased risk of renal artery stenosis in hypertensive patients are summarised in Box 15.22. However, given the risk of imaging and angiography in patients with renal disease (see Box 15.4, p. 390), further investigation should only be performed if intervention is being contemplated (see below). Investigations When appropriate, imaging of the renal vasculature with either CT angiography or MR angiography should be performed to confirm the diagnosis (Fig. 15.16). Both give good views of the main renal arteries, the vessels predominantly involved and the most amenable to intervention. Biochemical testing may reveal impaired renal function and an elevated plasma renin activity, sometimes with hypokalaemia due to hyperaldosteronism. Ultrasound may also reveal a discrepancy in size between the two kidneys, 15.22 Presentation and clinical features of renal artery stenosis Renal artery stenosis is more likely if: • hypertension is severe, of recent onset or difficult to control • kidneys are asymmetrical in size • flash pulmonary oedema occurs repeatedly* • there is peripheral vascular disease of the lower limbs • there is renal impairment* • renal function has deteriorated on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers *Particularly with bilateral disease. Fig. 15.16 Renal artery stenosis. A magnetic resonance angiogram following injection of contrast. The abdominal aorta is severely irregular and atheromatous. The left renal artery is stenosed (arrow).

 Diseases of small intrarenal vessels Thrombotic microangiopathies A number of conditions are associated with acute damage and occlusion of small blood vessels (arterioles and capillaries) in the kidney (Box 15.23) and other organs. A common feature of these syndromes is microangiopathic haemolytic anaemia (MAHA), in which haemolysis and red cell fragmentation arise as consequences of damage incurred to red blood cells during passage through the abnormal vessels. The red blood cell fragments (schistocytes) may be observed on blood films, together with laboratory features of intravascular haemolysis (p. 947), including an elevated unconjugated bilirubin level, raised serum LDH concentration and decreased circulating levels of haptoglobin. A reticulocytosis is often seen. Endothelial injury is pronounced, leading to increased platelet adherence and a marked reduction in the platelet count. These abnormal blood parameters should alert the physician to the possibility of a thrombotic microangiopathy and may also be useful in monitoring response to treatment. The key is to distinguish between the various aetiologies, as the management differs according to the primary cause (Box 15.23). Haemolytic uraemic syndrome Haemolytic uraemic syndrome (HUS) is characterised by thrombotic microangiopathy that predominantly affects the renal microcirculation, with involvement of other organs (including the brain) observed in more severe cases. The most common cause of HUS is infection with organisms that produce enterotoxins called Shiga-like toxin or verotoxins. The organisms most commonly implicated are enterohaemorrhagic Escherichia coli (p. 263) and Shigella dysenteriae (p. 265). The performed in atherosclerotic disease, as randomised trials such as ASTRAL and CORAL have produced no convincing evidence for overall benefit in terms of renal function, blood pressure control or cardiovascular outcomes. The risks of angioplasty and stenting include renal artery occlusion, renal infarction and atheroemboli (p. 409) from manipulations in a severely diseased aorta. Small-vessel disease distal to the stenosis may preclude substantial functional recovery. Acute renal infarction This is an uncommon condition that occurs as the result of sudden occlusion of the renal arteries. The presentation is typically with loin pain of acute onset, usually in association with non-visible haematuria, but pain may be absent in some cases. Severe hypertension is common but not universal. Blood levels of lactate dehydrogenase (LDH) and CRP are commonly raised. The condition may be caused by thrombosis of a renal artery or by thromboemboli from a distant source, when occlusion may occur in branch arteries distal to the main renal artery. This can cause multiple infarcts within the renal parenchyma of both kidneys, which may be visualised by CT scanning. If occlusion of the main renal arteries is bilateral or if there is occlusion in a single functioning kidney, the presentation is with AKI and the patient is typically anuric. Patients with bilateral occlusion usually have evidence of widespread vascular disease and may show evidence of aortic occlusion, with absent femoral pulses and reduced lower limb perfusion. Management is largely supportive, and includes anticoagulation if a source of thromboembolism is identified. It is sometimes possible to perform stenting of an acutely blocked main renal artery to try to restore renal blood flow; in most cases, however, presentation is too late to salvage renal function. 15.23 Thrombotic microangiopathies associated with acute renal damage Condition Typical features Management Primary thrombotic microangiopathies Haemolytic uraemic syndrome: Renal failure prominent in all causes Shiga toxin +ve HUS Bloody diarrhoea; check stool for Escherichia coli O157:H7 Supportive therapy Complement-mediated Positive family history; screen for complement factor mutations Plasma exchange, eculizumab Drug-induced: quinine, calcineurin and VEGF-A inhibitors Drug exposure, fever with quinine Cessation of offending drug Thrombotic thrombocytopenic purpura Neurological manifestations prominent; check ADAMTS-13 activity Plasma exchange (p. 979) Thrombotic microangiopathy associated with systemic disorders Disseminated intravascular coagulation (DIC) Clotting system involvement: elevated D-dimers, low fibrinogen, prolonged PT and APTT Treatment of primary cause (p. 979) Malignancy May occur with breast, prostate, lung, pancreas and GI tumours Treatment of tumour where possible Systemic sclerosis Cutaneous features of systemic sclerosis Blood pressure control with ACE inhibitors (p. 1037) Pre-eclampsia and HELLP syndrome Typically in third trimester; abnormal LFTs Resolution with delivery (p. 1276) Malignant hypertension Blood pressure typically very high; evidence of hypertensive retinopathy including papilloedema Blood pressure control (ACE = angiotensin-converting enzyme; ADAMTS-13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; APTT = activated partial thromboplastin time; GI = gastrointestinal; HELLP = haemolysis, elevated liver enzymes and low platelets; HUS = haemolytic uraemic syndrome; LFTs = liver function tests; PT = prothrombin time; VEGF = vascular endothelial growth factor)

E. coli O157:H7 serotype is the best known but other serotypes that produce verotoxins may also be responsible. Although these bacteria live as commensals in the gut of cattle and other livestock, they can cause haemorrhagic diarrhoea in humans when the infection is contracted from contaminated food products, water or other infected individuals. In a proportion of cases, verotoxin produced by the organisms enters the circulation and binds to specific glycolipid receptors that are expressed on the surface of microvascular endothelial cells. Most cases are sporadic but large outbreaks related to poor sanitation may occur. In developed countries, Shiga-like toxin-associated HUS is now the most common cause of AKI in children. Recovery is good in most patients but sometimes RRT may be required for up to 14 days. No other specific treatments have been shown to accelerate renal recovery. In the absence of bloody diarrhoea, other (atypical) causes of HUS should be considered: in particular, abnormalities of the complement system. Familial forms are due to mutations in various genes that encode components or regulators of the complement cascade, including factor H (CFH), factor B (CFB), membrane co-factor protein (MCP) and complement component 3 (C3). The penetrance of familial HUS is incomplete, indicating that environmental triggers are also involved: often infection, including diarrhoea. Sporadic cases may be associated with the development of autoantibodies to complement factor H. In addition to supportive care, including RRT if necessary, management of complement-mediated HUS includes plasma exchange to replace complement component and remove pathogenic autoantibodies. Recently, impressive results have been reported with the anti-C5 monoclonal antibody, eculizumab, which binds to C5, thereby preventing activation of the terminal complement cascade. Thrombotic thrombocytopenic purpura Like HUS, thrombotic thrombocytopenic purpura (TTP) is characterised by microangiopathic haemolytic anaemia and thrombocytopenia; in contrast, however, the brain is more commonly affected in TTP and involvement of the kidney is usually less prominent. TTP is an autoimmune disorder caused by antibodies against ADAMTS-13, which is involved in regulating platelet aggregation, and a low (< 10%) serum ADAMTS-13 activity level may be useful in distinguishing TTP from HUS. This distinction is important, as early therapy with plasma exchange is crucial in TTP. More details are provided on page 979. Cholesterol emboli These present with renal impairment, haematuria, proteinuria and sometimes eosinophilia with inflammatory features that can mimic a small-vessel vasculitis. The symptoms are provoked by showers of cholesterol-containing microemboli, arising in atheromatous plaques in major arteries. The diagnosis should be suspected when these clinical features occur in patients with widespread atheromatous disease, who have undergone interventions such as surgery or arteriography. They may also be precipitated by anticoagulants and thrombolytic agents. On clinical examination, signs of large-vessel disease and microvascular occlusion in the lower limbs (ischaemic toes, livedo reticularis) are common but not invariable (Fig. 15.17). There is no specific treatment. Small-vessel vasculitis Renal disease caused by small-vessel vasculitis usually presents with a clinical picture typical of a glomerulonephritis (see Figs 15.9 and 15.12C, pp. 393 and 399). More information is given on page 410. Renal involvement in systemic conditions The kidneys may be directly involved in a number of multisystem diseases or secondarily affected by diseases of other organs. Involvement may be at a pre-renal, renal (glomerular or interstitial) or post-renal level. Many of the diseases are described in other sections of this chapter or in other chapters of the book. Diabetes mellitus Diabetic nephropathy is the most common cause of CKD in developed countries. In patients with diabetes, there is a steady advance from moderately elevated albuminuria (microalbuminuria) to dipstick-positive proteinuria, in association with evolving hypertensive and progressive renal failure, as described on page 757. Few patients require renal biopsy to establish the diagnosis, but atypical features such as very rapid progression of proteinuria/decline in renal function or the absence of other microvascular damage, including retinopathy, should lead to suspicion that an alternative condition could be present. Management with ACE inhibitors and ARBs to slow progression is described on page 757. In some patients, proteinuria may be eradicated and progression completely halted, even if renal function is abnormal, although most still have progressive disease, albeit at a slower rate. Emerging evidence suggests that SGLT2 inhibitors, such as empagliflozin, a new agent for diabetes that causes glycosuria (p. 748), may lead to improved cardiovascular and renal outcomes, at the expense of increased genital infections. Multiple myeloma In myeloma, a malignant clone of plasma cells produces a paraprotein, often a monoclonal light chain (p. 966). Renal manifestations are dominated by these toxic light chains, which may cause a variety of insults (Box 15.24). Hypercalcaemia may also occur due to bony metastases. Hepatic–renal disease Severe hepatic dysfunction may cause a haemodynamically mediated type of renal failure, hepatorenal syndrome (HRS), described on page 864. Patients with chronic liver disease are also predisposed to develop AKI (acute tubular necrosis) in response to relatively minor insults, including bleeding, diuretic therapy and infection. Differentiating true HRS from AKI can be difficult. Patients with true HRS are often difficult to treat Fig. 15.17 The foot of a patient who suffered extensive atheroembolism following coronary artery stenting.

 neuropathy may also occur. Serological testing for antibodies to myeloperoxidase (MPO) and proteinase 3 (PR3) is usually positive but these are not specific and a biopsy of affected tissue should be obtained, if possible, to confirm the diagnosis. The standard treatment of glomerulonephritis associated with systemic vasculitis is high-dose glucocorticoids combined with cyclophosphamide, or mycophenolate mofetil (p. 1041). Recent studies indicate that rituximab (p. 1006), when combined with highdose glucocorticoids, is as effective as oral cyclophosphamide and high-dose glucocorticoids in the treatment of ANCA-associated vasculitis. Plasma exchange can offer additional benefit in patients with progressive renal damage who are not responding adequately to immunosuppressive therapy. Glomerulonephritis secondary to vasculitis may rarely be seen in rheumatoid arthritis, SLE and cryoglobulinaemia, although SLE usually involves the kidney in different ways (see below). Medium- to large-vessel vasculitis, such as polyarteritis nodosa (p. 1042), does not cause glomerulonephritis but can cause hypertension, renal aneurysms and infarction if the renal vessels are involved. Systemic sclerosis Renal involvement is a serious complication of systemic sclerosis, which is more likely to occur in diffuse cutaneous systemic sclerosis (DCSS) than in limited cutaneous systemic sclerosis (LCSS) (p. 1037). The renal lesion is caused by intimal cell proliferation and luminal narrowing of intrarenal arteries and arterioles. There is intense intrarenal vasospasm and plasma renin activity is markedly elevated. Renal involvement usually presents clinically with severe hypertension, microangiopathic features and progressive oliguric renal failure (‘scleroderma renal crisis’). Use of ACE inhibitors to control the hypertension has improved the 1-year survival from 20% to 75% but about 50% of patients continue to require RRT. Onset or acceleration of the syndrome after glucocorticoid use or cessation of ACE inhibitors is well described. Systemic lupus erythematosus Subclinical renal involvement, with non-visible haematuria and proteinuria but minimally impaired or normal renal function, is common in systemic lupus erythematosus (SLE). Usually, this is due to glomerular disease, although interstitial nephritis may also occur, particularly in patients with overlap syndromes such as mixed connective tissue disease and Sjögren’s syndrome (p. 1038). Almost any histological pattern of glomerular disease can be observed in SLE and the clinical presentation ranges from florid, rapidly progressive glomerulonephritis to nephrotic syndrome. The most common presentation is with subacute disease and inflammatory features (haematuria, hypertension, variable renal impairment), accompanied by heavy proteinuria that often reaches nephrotic levels. In severely affected patients, the most common histological pattern is a proliferative glomerulonephritis with substantial deposits of immunoglobulins on immunofluorescence. Randomised controlled trials have shown that the risk of ESRD in lupus nephritis is significantly reduced by high-dose glucocorticoids administered in combination with cyclophosphamide, usually given as regular intravenous pulses. Subsequently, it has been shown that the combination of glucocorticoids and mycophenolate mofetil is equally as effective, for both induction and maintenance treatment. Many patients with SLE who develop ESRD go into remission, possibly because of immunosuppression related to the ESRD. by dialysis and have a poor prognosis. Where treatment is justified – for example, if there is a good chance of recovery or of a liver transplant – slow or continuous treatments are less likely to precipitate or exacerbate hepatic encephalopathy. IgA nephropathy (p. 400) is more common in patients with chronic liver disease. Sarcoidosis The most common renal manifestation of sarcoidosis is hypercalcaemia from 1-α-vitamin D formation in granulomas. Less commonly, it may lead to a granulomatous interstitial nephritis, sometimes presenting acutely, where renal function may improve with glucocorticoid therapy. Postmortem examinations reveal a chronic interstitial nephritis in 15–30% of patients with sarcoidosis but clinically relevant disease appears to be much less common. Systemic vasculitis Small-vessel vasculitis (p. 1040) commonly affects the kidneys, with rapid and profound impairment of glomerular function. Histologically, there is a focal inflammatory glomerulonephritis, usually with focal necrosis (see Box 15.15, p. 398, and Fig. 15.12C, p. 399) and often with crescentic changes (see Fig. 15.12C). Typically, the patient is systemically unwell with an acute phase response, weight loss and arthralgia. In some patients, it presents as a kidney-limited disorder, with rapidly deteriorating renal function and crescentic nephritis (a rapidly progressive glomerulonephritis). In others, pulmonary haemorrhage may occur, which can be life-threatening. The most important cause is ANCA vasculitis (p. 1041). Two subtypes are recognised, microscopic polyangiitis (MPA) and granulomatosis with polyangiitis. Both may present with glomerulonephritis and pulmonary haemorrhage, along with constitutional symptoms. Gastrointestinal involvement and 15.24 Renal manifestations of multiple myeloma Condition Presentation Pathogenesis Cast nephropathy (‘myeloma kidney’) AKI Little/no proteinuria Light chains combine with Tamm–Horsfall protein precipitating in tubules Fanconi’s syndrome Aminoaciduria, phosphaturia, glycosuria Proximal (type II) RTA Proximal tubular injury due to light chain deposition in tubular epithelium AL (primary) amyloidosis* Proteinuria/nephrotic syndrome Renal impairment Misfolded lights chains (usually lambda) form amyloid, which is deposited in glomeruli Monoclonal immunoglobulin deposition disease* Proteinuria (may be in nephrotic range) Renal impairment Usually light chains (frequently kappa) are deposited in glomeruli, causing a nodular glomerulosclerosis Hypercalcaemia Thirst, polyuria, bony and abdominal pain, headache Bony destruction from metastases *These may also occur as primary conditions without myeloma being present. (AKI = acute kidney injury; RTA = renal tubular acidosis)

renal injury over time (several weeks). Recovery of renal function depends on the duration of obstruction and also the pre-morbid GFR. Clinical features Early recognition and intervention is important in AKI; all emergency admissions to hospital should have renal function, blood pressure, temperature and pulse checked on arrival and should undergo a risk assessment for the likelihood of developing AKI. This includes looking at coexisting diseases such as diabetes and vascular and liver disease, which make AKI more likely, as well as gathering information on drug treatments such as ACE inhibitors and NSAIDs, which may be associated with renal dysfunction. If a patient is found to have a high serum creatinine, it is important to establish whether this is an acute or acute-on-chronic phenomenon, or a sign of CKD (see Fig. 15.22, p. 416). Previous measurements of renal function can be of great value in differentiating these possibilities. Patients with AKI need to be assessed quickly to determine the likely underlying cause. Clinical features and pertinent investigations for the different causes of AKI are shown in Box 15.25. Various criteria have been proposed to classify AKI and to help identify high-risk patients, guide treatment and provide information regarding prognosis but are mostly used in a research setting to standardise diagnosis. The most commonly used are the KDIGO, AKIN and RIFLE criteria. Pre-renal AKI Patients with pre-renal AKI are typically hypotensive and tachycardic with signs of poor peripheral perfusion, such as delayed capillary return. Tachycardia and postural hypotension (a fall in blood pressure of > 20/10 mmHg from lying to standing) are valuable signs of early hypovolaemia. Many patients with sepsis Patients with ESRD caused by SLE are usually good candidates for dialysis and transplantation. Although it may recur in renal allografts, the immunosuppression required to prevent allograft rejection usually controls SLE. Sickle-cell nephropathy Improved survival of patients with sickle-cell disease (p. 951) means that a high proportion now live to develop chronic complications of microvascular occlusion. In the kidney, these changes are most pronounced in the medulla, where the vasa recta are the site of sickling because of hypoxia and hypertonicity. Loss of urinary concentrating ability and polyuria are the earliest changes; distal renal tubular acidosis and impaired potassium excretion are typical. Papillary necrosis may also occur (p. 403). A minority of patients develop ESRD. This is managed according to the usual principles, but response to recombinant erythropoietin is poor because of the haemoglobinopathy. Patients with sickle trait have an increased incidence of unexplained non-visible haematuria. Acute kidney injury Acute kidney injury (AKI), previously referred to as acute renal failure, is not a diagnosis; rather it describes the situation where there is a sudden and often reversible loss of renal function, which develops over days or weeks and is often accompanied by a reduction in urine volume. Approximately 7% of all hospitalised patients and 20% of acutely ill patients develop AKI. In uncomplicated AKI mortality is low, even when RRT is required. In AKI associated with sepsis and multiple organ failure, mortality is 50–70% and the outcome is usually determined by the severity of the underlying disorder and other complications, rather than by kidney injury itself. Elderly patients are at higher risk of developing AKI and have a worse outcome (Box 15.25). Pathophysiology There are many causes of AKI and it is frequently multifactorial. It is helpful to classify it into three subtypes: • ‘pre-renal’, when perfusion to the kidney is reduced • ‘renal’, when the primary insult affects the kidney itself • ‘post-renal’, when there is obstruction to urine flow at any point from the tubule to the urethra (Fig. 15.18). In pre-renal AKI, a reduction in perfusion reduces GFR. If the insult is not corrected, this may lead to ‘renal’ injury: namely, acute tubular necrosis (ATN). Histologically, the kidney shows inflammatory changes, focal breaks in the tubular basement membrane and interstitial oedema (see Fig. 15.13B, p. 402). Dead tubular cells may also be shed into the tubular lumen, leading to tubular obstruction. Although tubular cell damage is the dominant feature under the microscope, there may also be profound alterations in the renal microcirculation. Renal AKI may be caused by nephrotoxic drugs (p. 426), which can cause ATN or allergic interstitial nephritis. The other common ‘renal’ cause is glomerulonephritis, in which there is direct inflammatory damage to the glomeruli (p. 416). Post-renal AKI occurs as the result of obstruction to the renal tract. This leads to elevation of intraluminal ureteral pressure transmitted to the nephrons after prolonged obstruction, with a subsequent fall in GFR. If the obstruction is not relieved, the low GFR is maintained by a drop in renal blood flow rate via thromboxane A2 and angiotensin II. This leads to chronic Fig. 15.18 Causes of acute kidney injury. RENAL Glomerulonephritis Small-vessel vasculitis Acute tubular necrosis • Drugs • Toxins • Prolonged hypotension Interstitial nephritis • Drugs • Toxins • Inflammatory disease • Infection PRE-RENAL Impaired perfusion: • Cardiac failure • Sepsis • Blood loss • Dehydration • Vascular occlusion POST-RENAL Urinary calculi (bilateral) Retroperitoneal fibrosis Benign prostatic enlargement Bladder cancer Prostate cancer Cervical cancer Urethral stricture/valves Meatal stenosis/phimosis

412 • NEPHROLOGY AND UROLOGY 15.25 Categorising acute kidney injury based on history, examination and investigations Type of AKI History Examination Investigations Pre-renal Volume depletion (vomiting, diarrhoea, burns, haemorrhage) Drugs (diuretics, ACE inhibitors, ARBs, NSAIDs, calcineurin inhibitors, iodinated contrast) Liver disease Cardiac failure Low BP (including postural drop) Tachycardia Weight decrease Dry mucous membranes and increased skin turgor JVP not visible even when lying down Urine Na < 20 mmol/L Fractional excretion Na < 1% High urea:creatinine ratio Urinalysis bland Renal ATN Prolonged pre-renal state Sepsis Toxic ATN: drugs (aminoglycosides, cisplatin, tenofovir, methotrexate, iodinated contrast) Other (rhabdomyolysis, snake bite, Amanita mushrooms) Vital signs Fluid assessment Limbs for compartment syndrome Urine Na > 40 mmol/L Fractional excretion Na ≥ 1% Dense granular ('muddy brown') casts Creatine kinase Glomerular Rash, weight loss, arthralgia Chest symptoms (pulmonary renal syndromes) IV drug use Hypertension Oedema Purpuric rash, uveitis, arthritis Proteinuria, haematuria Red cell casts, dysmorphic red cells ANCA, anti-GBM, ANA, C3 and C4 Viral hepatitis screen, HIV Renal biopsy Tubulo-interstitial Interstitial nephritis: drugs (PPIs, penicillins, NSAIDs) Sarcoidosis Fever Rash Leucocyturia Eosinophiluria (and a peripheral eosinophilia) White cell casts Minimal proteinuria Tubular obstruction:

1. Myeloma (cast nephropathy) Paraprotein Calcium (myeloma, sarcoidosis)
2. Tubular crystal nephropathy: Drugs (aciclovir, indinavir, triamterene, methotrexate) Oxalate (fat malabsorption, ethylene glycol) Urate (tumour lysis) Urine microscopy for crystals Serum urate Urine collection for oxalate Vascular (including renal infarction, renal vein thrombosis, cholesterol emboli, malignant hypertension) Flank pain, trauma Anticoagulation Recent angiography (cholesterol emboli) Nephrotic syndrome (renal vein thrombosis) Systemic sclerosis (renal crisis) Diarrhoea (HUS) BP (malignant hypertension) Fundoscopy Livedo reticularis (cholesterol emboli) Sclerodactyly Normal urinalysis or some haematuria C3 and C4 (cholesterol emboli, TMA) Doppler renal ultrasound CT angiography Platelets, haemolytic screen, LDH Consider ADAMTS13 and complement genetics (if TMA) Post-renal Prostate cancer history Neurogenic bladder Cervical carcinoma Retroperitoneal fibrosis Bladder outlet symptoms Rectal examination (prostate and anal tone) Distended bladder Pelvic mass Urinalysis frequently normal (may reveal haematuria depending on cause) Renal ultrasound (hydronephrosis) Isotope renogram (delayed excretion) if ultrasound inconclusive (ACE = angiotensin-converting enzyme; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; ARBs = angiotensin receptor blockers; BP = blood pressure; GBM = glomerular basement membrane; HIV = human immunodeficiency virus; HUS = haemolytic uraemic syndrome; JVP = jugular venous pulse; LDH = lactate dehydrogenase; Na = sodium; NSAIDs = non-

steroidal anti-inflammatory drugs; PPIs = proton pump inhibitors; TMA = thrombotic microangiopathy) initially present with poor peripheral perfusion, as mentioned above, but then show evidence of peripheral vasodilatation once they have undergone initial resuscitation with intravenous fluids. However, this is accompanied by relative underfilling of the arterial tree and the kidney responds as it would to absolute hypovolaemia, with renal vasoconstriction. It is important to note that pre-renal AKI may also occur without systemic hypotension, particularly in patients taking NSAIDs or ACE inhibitors (Fig. 15.19). The cause of hypotension is often obvious, but concealed blood loss can occur into the gastrointestinal tract, retroperitoneum, following trauma (particularly with pelvic and femoral fractures), and into the pregnant uterus. Large volumes of intravascular fluid may also be lost into tissues after crush injuries or burns, and in severe inflammatory skin diseases or sepsis. Uncorrected renal hypoperfusion causing pre-renal azotaemia may progress to ATN. Renal AKI Factors that can help differentiate the various causes of intrinsic renal AKI are summarised in Box 15.25. Patients with

glomerulonephritis demonstrate haematuria and proteinuria, and may have clinical manifestations of an underlying disease, such as SLE or systemic vasculitis. Although blood tests, including an immunological screen, should be performed to clarify the diagnosis in glomerulonephritis, a renal biopsy is usually required. Drug-induced acute interstitial nephritis is harder to spot but should be suspected in a previously well patient if there is an acute deterioration of renal function coinciding with introduction of a new drug treatment. Drugs that are commonly implicated include PPIs, NSAIDs and many antibiotics. Post-renal AKI Patients should be examined clinically to look for evidence of a distended bladder and should also undergo imaging with ultrasound to detect evidence of obstruction above the level of the bladder. Post-renal AKI is usually accompanied by hydronephrosis. Management Management options common to all forms of AKI are discussed in more detail below and summarised in Box 15.26. Haemodynamic status If hypovolaemia is present, it should be corrected by replacement of intravenous fluid or blood; excessive administration of fluid should be avoided, since this can provoke pulmonary oedema and worsen outcome in AKI. Monitoring of central venous pressure may be of value in determining the rate of administration of fluid in these circumstances. Balanced crystalloid solutions, such as Plasma-Lyte, Hartmann's or Ringer's lactate, may be preferable to isotonic saline (0.9% NaCl) when large volumes of fluid resuscitation are required, in order to avoid hyperchloraemic acidosis, but whether this substantially influences outcome remains unclear. Administration of hydroxyethyl starch solutions should be avoided, since they have been associated with higher rates of established AKI. Critically ill patients may require inotropic drugs to restore an effective blood pressure but clinical trials do not support a specific role for low-dose dopamine. Hyperkalaemia and acidosis Hyperkalaemia is common, particularly in patients with rhabdomyolysis, burns, haemolysis or metabolic acidosis Fig. 15.19 Renal haemodynamics and autoregulation of glomerular filtration rate (GFR). It is evident from this figure how angiotensinconverting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) may be associated with profound drops in GFR in the context of bilateral renal artery stenosis or intravascular volume depletion (which decrease perfusion to afferent arterioles). (NSAIDs = non-steroidal anti-inflammatory drugs) Afferent arteriole Prostaglandins maintain blood flow by vasodilating NSAIDs inhibit prostaglandins Angiotensin II vasoconstricts, maintaining intraglomerular pressure ACE inhibitors/ ARBs inhibit this Efferent arteriole (p. 362). If serum K^+

concentration is > 6.5 mmol/L, this should be treated immediately, as described in Box 14.17 (p. 363), to prevent life-threatening cardiac arrhythmias. Metabolic acidosis develops unless prevented by loss of hydrogen ions through vomiting. Severe acidosis can be ameliorated with sodium bicarbonate if volume status allows. Restoration of blood volume will correct acidosis by restoring kidney function. Infusions of isotonic sodium bicarbonate may also be used, if acidosis is severe, to reduce life-threatening hyperkalaemia (Box 15.26). Cardiopulmonary complications Pulmonary oedema (Fig. 15.20) may be caused by the administration of excessive amounts of fluids relative to urine 15.26 Management of acute kidney injury • Assess fluid status as this will determine fluid prescription: If hypovolaemic: optimise systemic haemodynamic status with fluid challenge and inotropic drugs if necessary Once euvolaemic, match fluid intake to urine output plus an additional 500 mL to cover insensible losses If fluid-overloaded, prescribe diuretics (loop diuretics at high dose will often be required); if the response is unsatisfactory, dialysis may be required • Administer calcium resonium to stabilise myocardium and glucose and insulin to correct hyperkalaemia if K^+ > 6.5 mmol/L (see Box 14.17, p. 363) as a holding measure until a definitive method of removing potassium is achieved (dialysis or restoration of renal function) • Consider administering sodium bicarbonate (100 mmol) to correct acidosis if H^+ is > 100 nmol/L (pH < 7.0) • Discontinue potentially nephrotoxic drugs and reduce doses of therapeutic drugs according to level of renal function • Ensure adequate nutritional support • Consider proton pump inhibitors to reduce the risk of upper gastrointestinal bleeding • Screen for intercurrent infections and treat promptly if present • In case of urinary tract obstruction, drain lower or upper urinary tract as necessary Fig. 15.20 Pulmonary oedema in acute kidney injury. The appearances are indistinguishable from left ventricular failure but the heart size is usually normal. Blood pressure is often high.

 challenge in unstable patients. Accordingly, the decision to institute RRT should be made on an individual basis, taking account of the potential risks and benefits, comorbidity and an assessment of whether early or delayed recovery is likely. Severe uraemia with pericarditis and neurological signs (uraemic encephalopathy) is uncommon in AKI but, when present, is a strong indication for RRT; other indications are given in Box 15.35 (p. 422). The two main options for RRT in AKI are intermittent haemodialysis and CRRT (see Box 15.38, p. 424). Peritoneal dialysis is also an option if haemodialysis is not available (p. 424). Recovery from AKI Most cases of AKI will recover after the insult resolves but recovery may be impaired in pre-existing CKD or a prolonged severe insult (Fig. 15.21). Recovery is heralded by a gradual return of urine output and a steady improvement in plasma biochemistry. Initially, there is often a diuretic phase in which urine output increases rapidly and remains excessive for several days before returning to normal. This may be due in part to tubular damage and to temporary loss of the medullary concentration gradient. After a few days, urine volume falls to normal as the concentrating output and by increased pulmonary capillary permeability. If pulmonary oedema is present and urine output cannot be rapidly restored, treatment with dialysis may be required to remove excess fluid. Temporary respiratory support may also be necessary using non-invasive ventilation. Once initial resuscitation has been performed, fluid intake should be matched to urine output plus 500 mL per day to cover insensible losses, unless diarrhoea is present, in which case additional fluids may be required. Electrolyte disturbances Electrolyte disturbances, such as dilutional hyponatraemia, may occur if the patient has continued to drink freely despite oliguria or has received inappropriate amounts of intravenous dextrose. They can be avoided by paying careful attention to fluid balance and by giving intravenous fluids slowly. Modest hypocalcaemia is common but rarely requires treatment. Serum phosphate levels are usually high but may fall in patients on daily or continuous renal replacement therapy (CRRT), necessitating phosphate replacement. Dietary measures Adequate nutritional support should be ensured and it is important to give sufficient amounts of energy and adequate amounts of protein; high protein intake should be avoided. This is particularly important in patients with sepsis and burns who are hypercatabolic. Enteral or parenteral nutrition may be required (p. 707). Infection Patients with AKI are at substantial risk of intercurrent infection because humoral and cellular immune mechanisms are depressed. Regular clinical examination, supplemented by microbiological investigation where appropriate, is required to diagnose infection. If infection is discovered, it should be treated promptly according to standard principles (Ch. 6). Medications Patients with drug-induced kidney injury (p. 402) should have the offending drug withdrawn. Additionally, vasoactive medications, such as NSAIDs and ACE inhibitors, should be discontinued, as they may prolong AKI (see Fig 15.19). H2-receptor antagonists or PPIs should be given to prevent gastrointestinal bleeding. Other drug treatments should be reviewed and the doses adjusted if necessary, to take account of renal function. Non-essential drug treatments should be stopped. Renal tract obstruction In post-renal AKI, the obstruction should be relieved as soon as possible. This may involve urinary catheterisation for bladder outflow obstruction, or correction of ureteric obstruction with a ureteric stent or percutaneous nephrostomy. Renal replacement therapy Conservative management can be successful in AKI with meticulous attention to fluid balance, electrolytes and nutrition, but RRT may be required in patients who are not showing signs of recovery with these measures (Box 15.26). No specific cut-off values for serum urea or creatinine have been identified at which RRT should be commenced, and clinical trials of earlier versus later RRT in unselected patients with AKI have not shown differences in outcome. Furthermore, RRT can be a risky intervention, since it requires the placement of central venous catheters that may become infected and it may represent a major haemodynamic Fig. 15.21 Recovery from acute kidney injury (AKI). Many patients make a full recovery of renal function (1). If the insult is prolonged or prior renal function not normal, however, patients may develop progressive chronic kidney disease (2) or, rarely, irreversible, complete loss of renal function (3). (ESRD = end-stage renal disease) AKI

Full recovery AKI to ESRD Time Renal function Acute on chronic kidney disease 15.27 Acute kidney injury in old age • Physiological change: nephrons decline in number with age and average GFR falls progressively, so many elderly patients will have established CKD and less functional reserve. Small acute declines in renal function may therefore have a significant impact. • Creatinine: as muscle mass falls with age, less creatinine is produced each day. Serum creatinine can be misleading as a guide to renal function. • Renal tubular function: declines with age, leading to loss of urinary concentrating ability. • Drugs: increased drug prescription in older people (diuretics, ACE inhibitors and NSAIDs) may contribute to the risk of AKI. • Causes: infection, renal vascular disease, prostatic obstruction, hypovolaemia and severe cardiac dysfunction are common. • Mortality: rises with age, primarily because of comorbid conditions.

Many patients diagnosed at a late stage have bilateral small kidneys; renal biopsy is rarely undertaken in this group since it is more risky, less likely to provide a histological diagnosis because of the severity of damage, and unlikely to alter management. Clinical features The typical presentation is for a raised urea and creatinine to be found incidentally during routine blood tests, often during screening of high-risk patients, such as those with diabetes or hypertension. Most patients with slowly progressive disease are asymptomatic until GFR falls below 30 mL/min/1.73 m2 and some can remain asymptomatic with much lower GFR values than this. An early symptom is nocturia, due to the loss of concentrating ability and increased osmotic load per nephron, but this is non-specific. When GFR falls below 15–20 mL/min/1.73 m2, symptoms and signs are common and can affect almost all body systems (Fig. 15.22). They typically include tiredness or breathlessness, which may, in part, be related to renal anaemia or fluid overload. With further deterioration in renal function, patients may suffer pruritus, anorexia, weight loss, nausea, vomiting and hiccups. In very advanced renal failure, respiration may be particularly deep (Kussmaul breathing) due to profound metabolic acidosis, and patients may develop muscular twitching, fits, drowsiness and coma. Investigations The recommended investigations in patients with CKD are shown in Box 15.29. Their main aims are: • to exclude AKI requiring rapid investigation; in patients with unexpectedly high urea and creatinine (when there is an increase from previous results or no prior results are available), renal function should be retested within 2 weeks to avoid missing AKI • to identify the underlying cause where possible, since this may influence the treatment • to identify reversible factors that may worsen renal function, such as hypertension or urinary tract obstruction • to screen for complications of CKD, such as anaemia and renal osteodystrophy • to screen for cardiovascular risk factors. Referral to a nephrologist is appropriate for patients with potentially treatable underlying disease and those who are likely to progress to ESRD. Suggested referral criteria are listed in Box 15.30. Management The aims of management in CKD are to: • monitor renal function • prevent or slow further renal damage • limit complications of renal failure • treat risk factors for cardiovascular disease • prepare for RRT, if appropriate (p. 420). Monitoring of renal function The rate of change in renal function varies between patients and may vary over time in each individual. Renal function should therefore be monitored every 6 months in patients with stage 3 CKD, but more frequently in patients who are deteriorating rapidly or have stage 4 or 5 CKD. A plot of GFR against time (Fig. 15.23) can demonstrate whether therapy has been successful in slowing progression, detect any unexpected increase in the rate of decline that may warrant further investigation, and help mechanism and tubular reabsorption are restored. During the recovery phase of AKI, it may be necessary to provide temporary supplementation of bicarbonate, potassium and sometimes calcium, phosphate and magnesium. AKI in old age is described in Box 15.27. Chronic kidney disease Chronic kidney disease (CKD) refers to an irreversible deterioration in renal function that usually develops over a period of years (see Box 15.3, p. 388). Initially, it manifests only as a biochemical abnormality but, eventually, loss of the excretory, metabolic and endocrine functions of the kidney leads to the clinical symptoms and signs of renal failure, collectively referred to as uraemia. When death is likely without RRT (CKD stage 5), it is called end-stage renal disease (ESRD). Epidemiology The social and economic consequences of CKD are considerable. In many countries, estimates of the prevalence of CKD stages 3–5 (eGFR < 60 mL/min/1.73 m2) are around 5–7%, mostly affecting people aged 65 years and above (see Box 15.3). The prevalence of CKD in patients with hypertension, diabetes and vascular disease is substantially higher, and targeted screening for CKD should be considered in these and other high-risk groups. More than 25% of the population aged over 75 years have an eGFR of < 60 mL/min/1.73 m2, mostly stage 3A CKD, which in this context typically reflects an increased cardiovascular risk burden. In these patients, investigation and management should be focused on cardiovascular risk prevention, as very few will ever develop ESRD. Many primary renal diseases, however, are more common in the elderly, so investigation is warranted for those with declining renal function or with haematuria/proteinuria on dipstick. Pathophysiology Common causes of CKD are shown in Box 15.28. In many cases, the underlying diagnosis is unclear, especially among the large number of elderly patients with stage 3 CKD (see Box 15.3). 15.28 Common causes of chronic kidney disease Disease Proportion Comments Diabetes mellitus 20–40% Large racial and geographical differences Interstitial diseases 20–30% Often drug-induced Glomerular diseases 10–20% IgA nephropathy is most common Hypertension 5–20% Causality controversial, much may be secondary to another primary renal disease Systemic inflammatory diseases 5–10% Systemic lupus erythematosus, vasculitis Renovascular disease 5% Mostly atheromatous, may be more common Congenital and inherited 5% Polycystic kidney disease, Alport's syndrome Unknown 5–20%

416 • NEPHROLOGY AND UROLOGY be employed where possible; tight blood pressure control is applicable to CKD regardless of cause, however, and reducing proteinuria is a key target in those with glomerular disease. Antihypertensive therapy Lowering of blood pressure slows the rate at which renal function declines in CKD, independently of the agent used (apart from those with proteinuria; see below) and predict when ESRF will be reached to facilitate timely planning for RRT. Reduction of rate of progression Slowing the rate of progression of CKD may reduce complications and delay symptom onset and the need for RRT (Fig. 15.23). Therapies directed towards the primary cause of CKD should 15.29 Suggested investigations in chronic kidney disease Initial tests Interpretation Urea and creatinine To assess stability/progression: compare to previous results Urinalysis and quantification of proteinuria Haematuria and proteinuria may indicate glomerular disease and need for biopsy (p. 391). Proteinuria indicates risk of progressive CKD requiring preventive ACE inhibitor or ARB therapy Electrolytes To identify hyperkalaemia and acidosis Calcium, phosphate, parathyroid hormone and 25(OH)D Assessment of renal osteodystrophy Albumin Low albumin: consider malnutrition, inflammation, nephrotic syndrome Full blood count (± Fe, ferritin, folate, B12) If anaemic, exclude common non-renal explanations, then manage as renal anaemia Lipids, glucose ± HbA1c Cardiovascular risk high in CKD: treat risk factors aggressively Renal ultrasound Only if there are obstructive urinary symptoms, persistent haematuria, family history of polycystic kidney disease or progressive CKD. Small kidneys suggest chronicity. Asymmetric renal size suggests renovascular or developmental disease Hepatitis and HIV serology If dialysis or transplant is planned. Hepatitis B vaccination recommended if seronegative Other tests Consider relevant tests from Box 15.25, especially if the cause of CKD is unknown (ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; 25(OH)D = 25-hydroxyvitamin D) Fig. 15.22 Physical signs in advanced chronic kidney disease. (*Features of renal replacement therapy) Yellow complexion Pallor Dual-lumen central venous catheter for dialysis access (right or left)* Pericardial friction rub Arteriovenous fistulae for dialysis access* Transplanted kidney (right or left) with overlying scar* 'Brown line' pigmentation of nails Excoriation of pruritus Bruising easily Peripheral neuropathy

Absent reflexes

Reduced sensation

Paraesthesia

'Restless legs' Jugular venous pressure raised in fluid overload or pericardial tamponade Pulsus paradoxus in pericardial tamponade Tenckhoff catheter for peritoneal dialysis (right or left)* Increased respiratory rate and depth in metabolic acidosis patients with proteinuria (PCR > 50 mg/mmol or ACR > 30 mg/ mmol) through a reduction in glomerular perfusion pressure. In addition, ACE inhibitors have been shown to reduce the risk of cardiovascular events and all-cause mortality in CKD. Accordingly, ACE inhibitors and/or ARBs should be prescribed to all patients with diabetic nephropathy and patients with CKD and proteinuria, irrespective of whether or not hypertension is present. While ACE inhibitors and ARBs are excellent drugs for patients with diabetes or CKD and proteinuria, they need to be prescribed with care in certain circumstances. Initiation of treatment with ACE inhibitors and ARBs may be accompanied by an immediate reduction in GFR; patients should therefore have their renal function checked within 7–10 days of initiating or increasing the dose of an ACE inhibitor or ARB. Treatment can be continued so long as the reduction in GFR is not greater than 25% and is not progressive. Angiotensin II is critical for autoregulation of GFR in the context of low renal perfusion (see Fig. 15.1D, p. 385), and so ACE inhibitors or ARBs may exacerbate pre-renal failure (see Fig. 15.19). Patients on ACE inhibitors/ARBs should therefore be warned to stop taking the medication if they become unwell, such as with fever, vomiting or diarrhoea, restarting once they are better. This also applies to other common medications used in patients with CKD, such as diuretics, metformin and NSAIDs, and this advice may be reinforced by providing written information such as ‘sick-day rule’ cards (Box 15.31). ACE inhibitors and ARBs increase serum potassium and should not be commenced in patients with baseline potassium > 5.5 mmol/L. In patients with serum potassium > 6.0 mmol/L, the dose of ACE inhibitors or ARBs should be reduced or discontinued entirely, but only after all other measures to reduce potassium have been considered (see below). Combination therapy with ACE inhibitors and ARBs or direct renin inhibitors has not been shown to reduce progression of kidney disease but is associated with higher rates of hyperkalaemia and AKI, and is therefore to be avoided. Fig. 15.23 Plot of estimated glomerular filtration rate (eGFR) against time in a patient with type 1 diabetes mellitus. After approximately 6 years of monitoring (blue arrow), this patient entered an aggressive treatment programme aimed at optimising blood pressure (BP) and glycaemic control. The reduction in BP was accompanied by a fall in proteinuria (protein:creatinine ratio, PCR; shown in mg/mmol). At the previous rate of decline in renal function (dashed line), he was likely to reach the level of renal function at which dialysis therapy is typically required (eGFR = 10 mL/min/1.73 m2) within 18 months; however, the relative stabilisation in his renal function (dotted line) means that this has been deferred, potentially for several years. BP 162/88 PCR 284 BP 177/104 PCR 397 BP 146/77 PCR 170

eGFR mL/min/1.73 m2 BP 207/101 PCR 367 BP 122/68 PCR 107

Time (years)

15.30 Criteria for referral of chronic kidney disease patients to a nephrologist • eGFR < 30 mL/min/1.73 m2 • Rapid deterioration in renal function (> 25% from previous or

> 15 mL/min/1.73 m2/year) • Significant proteinuria (PCR > 100 mg/mmol or ACR > 70 mg/ mmol), unless known to be due to diabetes and patient is already on appropriate medications • ACR > 30 mg/mmol with non-visible haematuria •

> Hypertension that remains poorly controlled despite at least four antihypertensive medications • Suspicion of renal involvement in multisystem disease has additional benefits in lowering the risk of hypertensive heart failure, stroke and peripheral vascular disease. No threshold for beneficial effects has been identified and any reduction of blood pressure appears to be beneficial. Various targets have been suggested, such as 140/90 mmHg for patients with CKD and no albuminuria (ACR < 3 mg/mmol). A lower target of 130/80 mmHg should be considered for those who have moderately elevated albuminuria (ACR 3–3 mg/mmol), and is recommended for those with an ACR of more than 30 mg/mmol. Even lower targets, such as 125/75 mmHg, may be prudent in patients with CKD and heavy proteinuria (PCR > 100 mg/mmol or ACR > 70 mg/mmol). Achieving these blood pressure targets often requires multiple drugs, and therapeutic success may be limited by adverse effects and poor adherence. Reduction of proteinuria Patients with proteinuria are at higher risk of progression of renal disease, and there is strong evidence that reducing proteinuria reduces the risk of progression. ACE inhibitors and ARBs reduce proteinuria and retard the progression of CKD. These effects are partly due to the reduction in blood pressure but there is evidence for a specific beneficial effect in

 The inability of the failing kidney to excrete sodium and water loads commonly leads to their accumulation, which may manifest as oedema and may drive hypertension. Patients with evidence of volume expansion should be instructed to consume a low-sodium diet (< 100 mmol/24 hrs), and in severe cases fluid intake should also be restricted. Diuretics are commonly required, and as renal function deteriorates, increasing doses of potent loop diuretics or synergistic combinations of loop, thiazide and potassium-sparing diuretics may be necessary. Occasionally, some patients with tubulo-interstitial disease can develop ‘salt-wasting’ disease and may require a high sodium and water intake, including supplements of sodium salts, to prevent fluid depletion and worsening of renal function. Acid–base balance Reduced ability to excrete organic acids in patients with CKD may lead to an anion-gap metabolic acidosis. In addition, in patients with tubulo-interstitial disease or diabetic nephropathy, there may be specific defects in acid–base regulation within the kidney, causing a non-anion-gap renal tubular acidosis (p. 365). Although acidosis is usually asymptomatic, it may be associated with increased tissue catabolism and decreased protein synthesis, and may exacerbate bone disease and the rate of decline in renal function. Hence, plasma bicarbonate concentrations should be maintained above 22 mmol/L by prescribing sodium bicarbonate supplements (starting dose of 1 g 8-hourly, increasing as required). There is some evidence that correcting acidosis may reduce the rate of decline in renal function. Renal bone disease Disturbances of calcium and phosphate metabolism are almost universal in advanced CKD (Fig. 15.24). The sequence of events that leads to renal bone disease is complex, but two primary factors are impaired excretion of phosphate and failure of the renal tubular cells to convert 25-hydroxyvitamin D to its active metabolite, 1,25-dihydroxyvitamin D. A rise in serum phosphate levels promotes production of the hormone fibroblast growth factor 23 (FGF23) from osteocytes (Fig. 24.3, p. 986) and stimulates parathyroid hormone (PTH) release and hyperplasia of the parathyroid glands. The FGF23 and PTH promote tubular phosphate excretion, thereby partly compensating for the reduced glomerular filtration of phosphate. The reduced 1,25-dihydroxyvitamin D levels impair intestinal absorption of calcium. In addition, raised levels of serum phosphate complex with calcium in the extracellular space, leading to calcium phosphate deposition. Both the reduced absorption and increased deposition of calcium cause hypocalcaemia, which also stimulates PTH production by the parathyroid glands. Hence in many patients with CKD, compensatory responses initially maintain phosphate and calcium levels at the upper and lower ends of their respective normal ranges, at the expense of an elevated PTH level (secondary hyperparathyroidism). This is associated with a gradual transfer of calcium and phosphate from the bone to other tissues, leading to bone resorption (osteitis fibrosa cystica), and in severe cases this may result in bony pain and increased risk of fractures. Conversely there is increased deposition of calcium phosphate in many tissues, most notably blood vessels and heart valves, which may contribute to the increased risk of cardiovascular disease in patients with CKD (p. 420). In some cases, tertiary hyperparathyroidism supervenes, due to autonomous production of PTH by the enlarged parathyroid glands; this presents with hypercalcaemia. Additional problems in bone metabolism include low bone turnover (adynamic bone disease) in patients who have been over-treated with vitamin D metabolites, osteomalacia with over-treatment of Treatment of complications The kidneys have many functions in addition to excretion of waste (p. 384). Treatments that substitute for all of the normal roles of the kidneys must therefore be instigated to maintain normal body homeostasis and prevent complications. Maintenance of fluid and electrolyte balance The kidneys excrete waste and regulate many electrolytes, and so patients with CKD may accumulate waste products and develop electrolyte abnormalities. Urea is a key product of protein degradation and accumulates with progressive CKD. All patients with stages 4 and 5 CKD should be given dietetic advice aimed at preventing excessive consumption of protein. Severe protein restriction is not recommended, however; there is no evidence that this reduces the rate of decline in renal function but may lead to malnutrition. Potassium often accumulates in patients with advanced CKD, who should be provided with dietary advice to reduce daily potassium intake to below 70 mmol (Box 15.32). Potassiumbinding compounds limit absorption of potassium from the gut and may be a useful adjunctive therapy. Calcium resonium is not recommended other than as a very short-term measure, as it can be associated with bowel necrosis; however, newer agents, such as zirconium cyclosilicate and patiromer, appear promising for chronic use. Other measures that may help regulate potassium include diuretic therapy and control of acidosis with sodium bicarbonate (see below). Consideration should be given to stopping or reducing drugs that elevate potassium, such as potassium-sparing diuretics and ACE inhibitors/ARBs; however, this has to be balanced against the potential benefit that such drugs may have on retarding progression of renal and cardiovascular disease, and hence withdrawal should be reserved for when other measures have failed. 15.31 Exemplar medicine sick-day card When you are unwell with vomiting, diarrhoea or fever, stop taking the following medications: • ACE inhibitors: medicines ending in ‘-pril’, e.g. lisinopril, ramipril • Angiotensin receptor blockers: medicines ending in ‘-sartan’, e.g. irbesartan, losartan, candesartan • Non-steroidal anti-inflammatory painkillers: e.g. ibuprofen (Brufen), diclofenac (Voltarol) • Diuretics: e.g. furosemide, bendroflumethiazide, indapamide, spironolactone • Metformin: a medicine for diabetes. Restart when you are well again (after 24–48 hours of eating and drinking normally). 15.32 Foods high in potassium • Fruit: bananas, avocados, figs, rhubarb • Vegetables: tomatoes, spinach, parsnips, courgettes, sprouts, potatoes (including baked, fries, wedges; boiling vegetables reduces potassium content) • Sweets/snacks: crisps, chocolate, toffee, nuts (including peanut butter) • Drinks: beer, cider, wine (spirits contain less potassium), hot chocolate, fruit juice, milk, yoghurt • Salt substitutes, such as Lo-Salt: sodium chloride is substituted with potassium chloride

shortness of breath. Haemoglobin can be as low as 50–70 g/L in CKD stage 5, although it is often less severe or absent in patients with polycystic kidney disease. Several mechanisms are implicated, as summarised in Box 15.33. Iron deficiency is common in patients with CKD, and even more prevalent in those on haemodialysis as a result of haemolysis in the dialysis circuit. Hence many patients require iron supplements, which may be given intravenously for those with iron intolerance or in situations where adherence may be difficult. Once iron deficiency and other causes of anaemia have been excluded or corrected, recombinant human erythropoietin is very effective in correcting the anaemia of CKD and improving symptoms. Erythropoietin treatment does not influence mortality, however, and correcting haemoglobin to normal levels may carry some extra risk, including hypertension and thrombosis. The target haemoglobin is usually between 100 and 120 g/L. Erythropoietin is less effective in the presence of iron deficiency, active inflammation or malignancy, in particular myeloma. hyperphosphataemia (p. 369), and osteoporosis in patients with poor nutritional intake. The key focus in the management of renal bone disease should be directed towards the two main driving factors, hyperphosphataemia and inadequate activation of vitamin D. Hyperphosphataemia should be treated by dietary restriction of foods with high phosphate content (milk, cheese, eggs and protein-rich foods) and by the use of phosphate-binding drugs. Various drugs are available, including calcium carbonate, aluminium hydroxide, lanthanum carbonate and polymer-based phosphate binders such as sevelamer. The aim is to maintain serum phosphate values at or below 1.5 mmol/L (4.6 mg/dL) if possible, but many of these drugs are difficult to take and adherence can be a problem. Active vitamin D metabolites (either 1-α-hydroxyvitamin D or 1,25-dihydroxyvitamin D) should be administered in patients who are hypocalcaemic or have serum PTH levels more than twice the upper limit of normal. The dose should be adjusted to try to reduce PTH levels to between 2 and 4 times the upper limit of normal to limit hyperparathyroidism while avoiding over-suppression of bone turnover and adynamic bone disease, but care must be exercised in order to avoid hypercalcaemia. In patients with persistent hypercalcaemia (tertiary hyperparathyroidism), parathyroidectomy may be required. If parathyroidectomy is unsuccessful or not possible, calcimimetic agents, such as cinacalcet, may be used. These bind to the calcium-sensing receptor in the parathyroid glands and reduce PTH secretion. Anaemia Anaemia is common in patients with CKD and contributes to many of the non-specific symptoms, including fatigue and Fig. 15.24 Pathogenesis of renal osteodystrophy. Low 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) levels cause calcium malabsorption and this, combined with high phosphate levels, causes hypocalcaemia, which increases parathyroid hormone (PTH) production by the parathyroid glands. The raised level of PTH increases osteoclastic bone resorption. Although production of fibroblast growth factor 23 (FGF23) from osteocytes also increases, promoting phosphate excretion, this is insufficient to prevent hyperphosphataemia in advanced chronic kidney disease. Impaired renal function ↑Osteoclastic bone resorption Decreased conversion of 25(OH)D to $1,25(OH)_2D$ ↑PO_4 excretion ↓$1,25(OH)_2D$ FGF23 Stimulation of parathyroid glands leading to hyperplasia ↑PTH

↓PO_4 excretion ↑Plasma [PO_4] ↓Ca^{2+} absorption ↓Plasma [Ca^{2+}] Impaired mineralisation of bone 15.33 Causes of anaemia in chronic kidney disease • Deficiency of erythropoietin • Toxic effects of uraemia on marrow precursor cells • Reduced red cell survival • Blood loss due to capillary fragility and poor platelet function • Reduced intake, absorption and utilisation of dietary iron

420 • NEPHROLOGY AND UROLOGY Renal replacement therapy Renal replacement therapy (RRT) may be required on a temporary basis in patients with AKI or on a permanent basis for those with advanced CKD. Since the advent of long-term RRT in the 1960s, the numbers of patients with ESRD who are kept alive by dialysis and transplantation have increased considerably. By the end of 2014, almost 59 000 patients were on RRT in the UK, with a median age of 65 years. After a long period of expansion, the number of patients on dialysis in the UK and USA has begun to stabilise; however, the total number of patients on RRT continues to expand, due to an increasing proportion (53%) of patients with a functional transplant. The remaining patients were on haemodialysis (41%) and peritoneal dialysis (6%). There are variations in the numbers of patients receiving RRT in different countries because of differences in the incidence of predisposing disease, as well as differences in medical practice. For example, the incidence rate for RRT in the USA was about three times higher than in the UK (363 versus 115 patients per million population), and the prevalence rate was more than twice as high (2034 versus 913 per million population). Diabetic kidney disease is the most common cause of ESRD in many countries, accounting for 26% of all ESRD in the UK and almost 50% in the USA. The large increase in the prevalence of type 2 diabetes in developing countries is resulting in a predictable rise in cases of ESRD, which is challenging already stretched health-care resources. Survival on dialysis is strongly influenced by age and presence of complications such as diabetes (Fig. 15.26). For this reason, conservative care rather than RRT may be a more appropriate option for older patients or those with extensive comorbidities Although many young patients without extrarenal disease lead Treatment of risk factors for cardiovascular disease The risk of cardiovascular disease is substantially increased in patients with a GFR below 60 mL/min/1.73 m2 and in those with proteinuria, the combination of reduced eGFR and proteinuria being particularly unfavourable. Patients with CKD have a higher prevalence of traditional risk factors for atherosclerosis, such as hypertension, hyperlipidaemia and diabetes; however, additional mechanisms of cardiovascular disease may also be implicated. Left ventricular hypertrophy is commonly found in patients with CKD, secondary to hypertension or anaemia. Calcification of the media of blood vessels, heart valves, myocardium and the conduction system of the heart is also common and may be due, in part, to the high serum phosphate levels. Reflecting this fact, serum FGF23 levels, which increase in response to serum phosphate, are an independent predictor of mortality in CKD. Both left ventricular hypertrophy and cardiac calcification may increase the risk of arrhythmias and sudden cardiac death, which is a much more common mode of death in patients with CKD than in the general population, particularly in those with more advanced disease and those on dialysis. To reduce vascular risk, patients with CKD should be encouraged to adopt a healthy lifestyle, including regular exercise, and weight loss and smoking cessation where appropriate. Lipid-lowering drugs reduce cardiovascular events in patients with CKD, although their efficacy may be less once patients require dialysis. Preparing for renal replacement therapy It is crucial for patients who are known to have progressive CKD to be prepared well in advance for the institution of RRT. This involves ensuring that they are referred to a nephrologist in a timely manner, as those who are referred late, when they are either at the stage of or very close to requiring dialysis, tend to have poorer outcomes. Several decisions need to be taken in discussion with the patient and family. The first is to decide whether RRT is an appropriate choice or whether conservative treatment might be preferable (p. 421). This is especially relevant in patients with significant comorbidity. For those who decide to go ahead with RRT, there are further choices

between haemodialysis and peritoneal dialysis (Box 15.34), between hospital and home treatment, and on referral for renal transplantation. Since there is no evidence that early initiation of RRT improves outcome, the overall aim is to commence RRT when symptoms of CKD begin to impact on quality of life but before serious complications have occurred. While there is wide variation between patients, this typically occurs when the eGFR approaches 10 mL/ min/1.73 m2. This may be a useful marker to predict the timing of initiation of RRT by extrapolating from a plot of serial eGFR measurements over time (see Fig. 15.23). Preparations for starting RRT should begin at least 12 months before the predicted start date. This involves providing the patient with psychological and social support, assessing home circumstances and discussing the various choices of treatment (Fig. 15.25). Depression is common in patients who are on or approaching RRT, and support from the renal multidisciplinary team should be provided both for them and for their relatives, to explain and help them adapt to the changes to lifestyle that may be necessary once RRT starts; this may help to reduce their anxieties about these changes. Physical preparations include establishment of timely access for haemodialysis or peritoneal dialysis and vaccination against hepatitis B. 15.34 Comparison of haemodialysis and peritoneal dialysis Haemodialysis Peritoneal dialysis Efficient; 4 hrs three times per week is usually adequate Less efficient; four exchanges per day are usually required, each taking 30–60 mins (continuous ambulatory peritoneal dialysis) or 8–10 hrs each night (automated peritoneal dialysis) 2–3 days between treatments A few hours between treatments Requires visits to hospital (although home treatment is possible for some patients) Performed at home Requires adequate venous circulation for vascular access Requires an intact peritoneal cavity without major scarring from previous surgery Careful adherence to diet and fluid restrictions required between treatments Diet and fluid less restricted Fluid removal compressed into treatment periods; may cause symptoms and haemodynamic instability Slow continuous fluid removal, usually asymptomatic Infections related to vascular access may occur Peritonitis and catheter-related infections may occur Patients are usually dependent on others Patients can take full responsibility for their treatment

slightly shorter than that of patients who undergo RRT, but they avoid the hospitalisation and interventions associated with dialysis. Patients are offered full medical, psychological and social support to optimise and sustain their existing renal function and to treat complications, such as anaemia, for as long as possible, with appropriate palliative care in the terminal phase of their disease. Many of these patients enjoy a good quality of life for several years. When quality of life on dialysis is poor, it is appropriate to consider discontinuing it, following discussion with the patient and family, and to offer palliative care. Haemodialysis Haemodialysis is the most common form of RRT in ESRD and is also used in AKI. Haemodialysis involves gaining access to the circulation, either through a central venous catheter or an arteriovenous fistula or graft. The patient’s blood is pumped through a haemodialyser, which allows bidirectional diffusion of Fig. 15.25 Options for renal replacement therapy. A In haemodialysis, there is diffusion of solutes from blood to dialysate across a semipermeable membrane down a concentration gradient. B In haemofiltration, both water and solutes are filtered across a porous semipermeable membrane by a pressure gradient. Replacement fluid is added to the filtered blood before it is returned to the patient. C In peritoneal dialysis (PD), fluid is introduced into the abdominal cavity using a catheter. Solutes diffuse from blood across the peritoneal membrane to PD fluid down a concentration gradient, and water diffuses through osmosis (see text for details). D In transplantation, the blood supply of the transplanted kidney is generally anastomosed to the external iliac vessels and the ureter to the bladder. The transplanted kidney replaces all functions of the failed kidney. Haemodialysis Dialysate Haemofiltration Ultrafiltrate Replacement fluid Peritoneal dialysis Peritoneal cavity Transplantation External iliac artery Peritoneal membrane PD fluid Catheter Transplanted kidney External iliac vein Donor artery Donor vein Donor ureter Bladder Blood from patient Blood to patient Blood to patient Blood from patient A B C D normal and active lives on RRT, those aged 30–34 have a mortality rate 25 times higher than that of age-matched controls. The aim of RRT is to replace the excretory functions of the kidney and to maintain normal electrolyte concentrations and fluid balance. Various options are available, including haemodialysis, haemofiltration, haemodiafiltration, peritoneal dialysis and renal transplantation, and each of these is discussed in more detail below. Indications for starting RRT in both AKI and CKD may be found in Box 15.35. Conservative treatment In older patients with multiple comorbidities, conservative treatment of stage 5 CKD, aimed at limiting the adverse symptoms of ESRD without commencing RRT, is increasingly viewed as a positive choice (Box 15.36). Current evidence suggests that survival of these patients without dialysis can be similar or only

 In AKI, dialysis is performed through a large-bore, dual-lumen catheter inserted into the femoral or internal jugular vein (Fig. 15.27A). Subclavian lines are avoided where possible, largely due to bleeding risk. Also, thromboses or stenoses here will compromise the ability to form a functioning fistula in the arm if the patient fails to recover renal function and needs chronic dialysis. Haemodialysis in CKD In CKD, vascular access for haemodialysis is gained by formation of an arteriovenous fistula (AVF), usually in the forearm, up to a year before dialysis is contemplated (Fig. 15.27B). After 4–6 weeks, increased pressure transmitted from the artery to the vein leading from the fistula causes distension and thickening of the vessel wall (arterialisation). Large-bore needles can then be solutes between blood and the dialysate across a semipermeable membrane down a concentration gradient (Fig. 15.25A). The composition of the dialysate can be varied to achieve the desired gradient, and fluid can be removed by applying negative pressure to the dialysate side. Haemodialysis in AKI Haemodialysis offers the best rate of small solute clearance in AKI, compared with other techniques such as haemofiltration, but should be started gradually because of the risk of delirium and convulsions due to cerebral oedema (dialysis disequilibrium). Typically, 1–2 hours of dialysis is prescribed initially but, subsequently, patients with AKI who are haemodynamically stable can be treated by 4–5 hours of haemodialysis on alternate days, or 2–3 hours every day. During dialysis, it is standard practice to anticoagulate patients with heparin but the dose may be reduced if there is a bleeding risk. Epoprostenol can be used as an alternative but carries a risk of hypotension. In patients undergoing short treatments and in those with abnormal clotting, it may be possible to avoid anticoagulation altogether. Fig. 15.26 Percentage survival after commencing renal replacement therapy according to age group and presence of diabetes.

Time (years) Survival (%) 18–44 years, no diabetes 18–44 years, with diabetes 44–64 years, no diabetes 44–64 years, with diabetes ≥ 65 years, no diabetes ≥ 65 years, with diabetes

15.36 Renal replacement therapy in old age • Quality of life: age itself is not a barrier to good quality of life on RRT. • Coexisting cardiovascular disease: older people are more sensitive to fluid balance changes, predisposing to hypotension during dialysis with rebound hypertension between dialysis sessions. A failing heart cannot cope with fluid overload, and pulmonary oedema develops easily. • Provision of treatment: often only hospital-provided haemodialysis is suitable and older patients require more medical and nursing time. • Survival on dialysis: difficult to predict for an individual patient, but old age plus substantial comorbidity are associated with poor median survival. Similar survival may be achieved through conservative care, without the complications associated with dialysis. • Withdrawal from dialysis: may be appropriate whenever quality of life deteriorates irreversibly, usually in the context of severe comorbidity. • Transplantation: relative risks of surgery and immunosuppression exclude most older people from transplantation. • Conservative therapy: without dialysis but with adequate support. This is an appropriate option for patients at high risk of complications from dialysis, who have a limited prognosis and little hope of functional recovery. 15.35 Indications for dialysis with examples for AKI and CKD Indication* Acute examples Chronic examples Fluid overload Acute pulmonary oedema Intractable dependent oedema resistant to diuretics Pulmonary oedema Severe hypertension Hyperkalaemia High potassium (generally > 6.5 mmol/L) with ECG changes (especially broad QRS) Potassium resistant to dietary control and medical intervention Uraemia Pericarditis Encephalopathy Uraemic syndrome including anorexia, nausea, lethargy etc. (generally not until eGFR < 10 mL/min/1.73 m2) Metabolic acidosis Severe acidosis (H+ > 79 nmol/L; pH < 7.1) Chronic acidosis resistant to bicarbonate therapy Other (often relative indications) Bleeding diathesis considered due to uraemia-induced platelet dysfunction Intractable anaemia despite erythropoietin and iron Hyperphosphataemia despite binders *The presence of anuria in AKI will modify the above indications, as these complications will not resolve if the patient is persistently anuric. Most indications to commence chronic dialysis are relative indications; a holistic approach is taken to making this decision. (ECG = electrocardiogram; eGFR = estimated glomerular filtration rate)

Fig. 15.27 Haemodialysis access. A A tunnelled cuffed dialysis catheter. B An arteriovenous fistula. C An arteriovenous graft. Right internal jugular vein Catheter Right atrium of heart Mixed arteriovenous blood Artery Artery Vein Arteriovenous graft Vein, expanded due to increased blood pressure Arteriovenous fistula Blood from dialysis machine Blood to dialysis machine Blood from dialysis machine Blood to dialysis machine A B C inserted into the vein to provide access for each haemodialysis treatment. Preservation of arm veins is thus very important in patients with progressive renal disease who may require haemodialysis in the future. If creation of an AVF is not possible, synthetic polytetrafluoroethylene (PTFE) grafts may be fashioned between an artery and a vein, or central venous catheters may be used for short-term access (Fig. 15.27C). These are tunnelled under the skin to reduce infection risk. All patients must be screened in advance for hepatitis B, hepatitis C and HIV, and vaccinated against hepatitis B if they are not immune. All dialysis units should have segregation facilities for hepatitis B-positive patients, given its easy transmissibility. Patients with hepatitis C and HIV are less infectious and can be treated satisfactorily using machine segregation and standard infection control measures. Haemodialysis is usually carried out for 3–5 hours three times weekly, either at home or in an outpatient dialysis unit. The intensity and frequency of dialysis should be adjusted to achieve a reduction in urea during dialysis (urea reduction ratio) of over 65%; below this level there is an associated increase in mortality. Most patients notice an improvement in symptoms during the first 6 weeks of treatment. The intensity of dialysis can be increased by: • escalating the number of standard sessions to four or more per week • performing short, frequent dialysis sessions of 2–3 hours 5–7 times per week • performing nocturnal haemodialysis, when low bloodpump speeds and single-needle dialysis are used for approximately 8 hours overnight 5–6 times per week. More frequent dialysis and nocturnal dialysis can achieve better fluid balance and phosphate control, improve left ventricular mass and possibly improve mortality, although the latter has not yet been robustly demonstrated. Box 15.37 summarises some of the problems related to haemodialysis. Haemofiltration This technique is principally used in the treatment of AKI as CRRT (Box 15.38). Large volumes of water are filtered from blood across a porous semipermeable membrane under a pressure gradient. Solutes are removed via ‘solvent drag’. Replacement fluid of a suitable electrolyte composition is added to the blood after it exits the haemofilter. If removal of fluid is required, then less fluid is added back than is removed (see Fig. 15.25B). Haemofiltration may be either intermittent or continuous, and typically 1–2 L of filtrate is replaced per hour (equivalent to a GFR of 15–30 mL/ min/1.73 m2); higher rates of filtration may be of benefit in patients with sepsis and multi-organ failure. In continuous arteriovenous haemofiltration (CAVH), the extracorporeal blood circuit is driven by the arteriovenous pressure difference, but poor filtration rates and clotting of the filter are common and this treatment has fallen out of favour. Continuous venovenous haemofiltration (CVVH) is pump-driven, providing a reliable extracorporeal circulation. Issues concerning anticoagulation are similar to those for haemodialysis, but may be more problematic because longer or continuous anticoagulation is necessary. Haemodiafiltration This technique combines haemodialysis with approximately 20–30 L of ultrafiltration (with replacement of filtrate) over a 3–5-hour treatment. It uses a large-pore membrane and combines the improved clearance of medium-sized molecules observed in haemofiltration with the higher small-solute clearance of haemodialysis. It is sometimes used in the treatment of AKI, often as continuous therapy (Box 15.38). It is increasingly favoured in the treatment of CKD but is more expensive than haemodialysis and the long-term benefits are not yet established.

 Renal transplantation Renal transplantation offers the best chance of long-term survival in ESRD and is the most cost-effective treatment. All patients with ESRD should be considered for transplantation but many are not suitable due to a combination of comorbidity and advanced age (although no absolute age limit applies). Active malignancy, vasculitis, cardiovascular disease and a high risk of recurrence of renal disease (generally glomerulonephritides) are common contraindications to transplantation. Kidney grafts may be taken from a deceased donor in the UK after brain death (40%) or circulatory death (24%), or from a living donor (36%). As described on page 88, matching of a donor to a specific recipient is strongly influenced by immunological factors, since graft rejection is the major cause of transplant failure. Compatibility of ABO blood group between donor and recipient is usually required and the degree of matching for major histocompatibility (MHC) antigens, particularly human leucocyte antigen DR (HLA-DR), influences the incidence of rejection. Immediately prior to transplantation, cross-matching should be performed for anti-HLA antibodies (traditionally mixing of recipient serum with donor lymphocytes) (p. 88). Positive tests predict early rejection and worse graft survival. Although some ABO- and HLA-incompatible transplants are now possible, this involves appropriate preparation with pre-transplant plasma exchange and/or immunosuppression, so that recipient antibodies to the donor’s tissue are reduced to acceptably low levels. This option is generally only available for living donor transplants because of the preparation required. Paired exchanges, in which a donor–recipient pair who are incompatible, either in blood group or HLA, are computer-matched with another pair to overcome the mismatch, are also used to help increase the number of successful transplants that can be performed. During the transplant operation, the kidney is placed in the pelvis; the donor vessels are usually anastomosed to the recipient’s external iliac artery and vein, and the donor ureter to the bladder (see Fig. 15.25D). The native kidneys are usually left in place but may be removed pre-transplant if they are a source of repeated sepsis or to make room for a transplant in patients with very large kidneys due to adult polycystic kidney disease. Peritoneal dialysis Peritoneal dialysis is principally used in the treatment of CKD, though it may occasionally be employed in AKI. It requires the insertion of a permanent Silastic catheter into the peritoneal cavity (see Fig. 15.25C). Two types are in common use. In continuous ambulatory peritoneal dialysis (CAPD), about 2 L of sterile, isotonic dialysis fluid are introduced and left in place for approximately 4–6 hours. Metabolic waste products diffuse from peritoneal capillaries into the dialysis fluid down a concentration gradient. The fluid is then drained and fresh dialysis fluid introduced, in a continuous four-times-daily cycle. The inflow fluid is rendered hyperosmolar by the addition of glucose or glucose polymer; this results in net removal of fluid from the patient during each cycle, due to diffusion of water from the blood through the peritoneal membrane down an osmotic gradient (ultrafiltration). The patient is mobile and able to undertake normal daily activities. Automated peritoneal dialysis (APD) is similar to CAPD but uses a mechanical device to perform the fluid exchanges during the night, leaving the patient free, or with only a single exchange to perform, during the day. CAPD is particularly useful in children, as a first treatment in adults with residual renal function, and as a treatment for elderly patients with cardiovascular instability. The long-term use of peritoneal dialysis may be limited by episodes of bacterial peritonitis and damage to the peritoneal membrane, including encapsulating peritoneal sclerosis, but some patients have been treated successfully for more than 10 years. Box 15.39 summarises some of the problems related to CAPD treatment. 15.37 Problems with haemodialysis Problem Clinical features Cause Treatment During treatments Hypotension Sudden ↓BP; often leg cramps; sometimes chest pain Fluid removal and hypovolaemia Saline infusion; exclude cardiac ischaemia; quinine may help cramp Cardiac arrhythmias Hypotension; sometimes chest pain Potassium and acid–base shifts Check K^+ and arterial blood gases; review dialysis prescription; stop dialysis Haemorrhage Blood loss (overt or occult); hypotension Anticoagulation Venous needle disconnection Stop dialysis; seek source; consider heparin-free treatment Air embolism Circulatory collapse; cardiac arrest Disconnected or faulty lines and equipment malfunction Stop dialysis Dialyser hypersensitivity Acute circulatory collapse Allergic reaction to dialysis membrane or sterilisant Stop dialysis; change to different artificial kidney Between treatments Pulmonary oedema Breathlessness Fluid overload Ultrafiltration ± dialysis Systemic sepsis Rigors; fever; ↓BP Usually involves vascular access devices (catheter or fistula) Blood cultures; antibiotics (BP = blood pressure) 15.38 Types of continuous renal replacement therapy (CRRT) used in AKI management* • CVVH: continuous venovenous haemofiltration • CVVHD: continuous venovenous haemodialysis • CVVHDF: continuous venovenous haemodiafiltration *Most CRRT machines may perform all of these treatments. Continuous arteriovenous treatments (i.e. continuous arteriovenous haemofiltration) have fallen out of favour.

used initially due to impaired wound healing. Antibodies to deplete or modulate specific lymphocyte populations are increasingly used for induction and for treatment of glucocorticoid-resistant acute rejection. Basiliximab, an interleukin (IL)-2 receptor antagonist, is frequently used at induction to lower rates of rejection. Acute cellular rejection is usually treated, in the first instance, by short courses of high-dose glucocorticoids, such as intravenous methylprednisolone on three consecutive days. Anti-lymphocyte preparations (e.g. anti-thymocyte globulin, ATG) are used for glucocorticoid-resistant rejection. Antibody-mediated rejection is more difficult to treat and usually requires plasma exchange All transplant patients require regular life-long follow-up to monitor renal function and complications of immunosuppression. Allograft dysfunction is often asymptomatic and picked up during routine surveillance blood tests. The common causes at different time points post transplant are summarised in Box 15.40. Immunosuppressive therapy (see Box 4.26, p. 89) is required to prevent rejection and is more intensive in the early post-transplantation period, when rejection risk is highest. A common regimen is triple therapy with prednisolone; ciclosporin or tacrolimus; and azathioprine or mycophenolate mofetil. Sirolimus is an alternative that can be introduced later but is generally not 15.39 Problems with continuous ambulatory peritoneal dialysis Problem Clinical features Cause Treatment Peritonitis Cloudy drainage fluid; abdominal pain and systemic sepsis are variable Usually entry of skin contaminants via catheter; bowel organisms less common Culture of peritoneal dialysis fluid Intraperitoneal antibiotics, tobramycin, vancomycin Catheter removal sometimes required Catheter exit site infection Erythema and pus around exit site Usually skin organisms Antibiotics; sometimes surgical drainage Ultrafiltration failure Fluid overload Damage to peritoneal membrane, leading to rapid transport of glucose and loss of osmotic gradient Replacement of glucose with synthetic, poorly absorbed polymers for some exchanges (icodextrin) Peritoneal membrane failure Inadequate clearance of urea etc. Scarring/damage to peritoneal membrane Increase in exchange volumes; consideration of automated peritoneal dialysis or switch to haemodialysis Sclerosing peritonitis Intermittent bowel obstruction Malnutrition Unknown; typically occurs after many years Switch to haemodialysis (may still progress) Surgery and tamoxifen may be used 15.40 Common causes of renal allograft dysfunction Time post transplant Cause Risk factors Hours to days Renal artery/vein thrombosis Technically difficult surgery Thrombophilia/SLE Ureteric leak Small bladder/anuria pre-transplant Delayed graft function (i.e. transplant does not start working immediately) Prolonged cold ischaemia time* Donation after circulatory death Older, hypertensive donor with stroke as cause of death, high tacrolimus level Hyperacute rejection Pre-formed anti-HLA antibodies HLA mismatch Previous transplant Weeks Acute rejection (especially < 3 months; can occur later with non-adherence/insufficient immunosuppression) Pre-formed anti-HLA antibodies HLA mismatch Previous transplant Months BK virus nephropathy Intensive immunosuppression Ureteric stent use Renal artery stenosis Donor disease Injury at organ retrieval Years Chronic allograft injury (often antibody-mediated) Previous acute rejections Non-adherence/insufficient immunosuppression Any time Tacrolimus/ciclosporin toxicity High doses/serum levels Concurrent use of drugs that inhibit cytochrome P450 system Sepsis (opportunistic and conventional) Recurrence of disease: Early (FSGS/MCGN) Later (IgA nephropathy/membranous glomerulonephritis) Primary FSGS and MCGN Previous transplant recurrence *Time from organ retrieval in the donor, with cold perfusion occurring ex vivo, until implantation into the recipient. (FSGS = focal segmental glomerulosclerosis; HLA = human leucocyte antigen; IgA = immunoglobulin A; MCGN = mesangiocapillary glomerulonephritis; SLE = systemic lupus erythematosus)

 drugs and their metabolites. Some may reach high concentrations in the renal cortex as a result of proximal tubular transport mechanisms. Others are concentrated in the medulla by the operation of the countercurrent system. The same applies to certain toxins. Toxic renal damage may occur by a variety of mechanisms (Box 15.43). Very commonly, drugs contribute to the development of acute tubular necrosis as one of multiple insults. Numerically, reactions to NSAIDs and ACE inhibitors are the most important. Haemodynamic renal impairment, acute tubular necrosis and allergic reactions are usually reversible if recognised early enough. Other types, however, especially those associated with extensive fibrosis, are less likely to be reversible. Non-steroidal anti-inflammatory drugs Impairment of renal function may develop in patients on NSAIDs, since prostaglandins play an important role in regulating renal blood flow by vasodilating afferent arterioles (see Fig. 15.19, p. 413). This is particularly likely in patients with other disorders, such as volume depletion, heart failure, cirrhosis, sepsis and pre-existing renal impairment. In addition, idiosyncratic immune reactions may occur, causing minimal change nephrotic syndrome, membranous nephropathy (p. 400) and acute interstitial nephritis (p. 402). Analgesic nephropathy (p. 403) is now a rare complication of long-term use. ACE inhibitors These abolish the compensatory angiotensin II-mediated vasoconstriction of the glomerular efferent arteriole that takes place in order to maintain glomerular perfusion pressure distal to a renal artery stenosis and in renal hypoperfusion (see Figs 15.1 and 15.19, pp. 385 and 413). Monitoring of renal function before and after initiation of therapy is essential and an expected rise in creatinine of about 20% is frequently observed. Prescribing in renal disease Many drugs and drug metabolites are excreted by the kidney and so the presence of renal impairment alters the required dose and frequency (p. 31). Infections of the urinary tract In health, bacterial colonisation is confined to the lower end of the urethra and the remainder of the urinary tract is sterile (see Ch. 6). The urinary tract can become infected with various bacteria but the most common is E. coli derived from the gastrointestinal tract. The most common presenting problem is cystitis with urethritis (generally referred to as urinary tract infection). Urinary tract infection Urinary tract infection (UTI) is the term used to describe acute urethritis and cystitis caused by a microorganism. It is a common disorder, accounting for 1–3% of consultations in general medical practice. The prevalence of UTI in women is about 3% at the age of 20, increasing by about 1% in each subsequent decade. In males, UTI is uncommon, except in the first year of life and in men over 60, when it may complicate bladder outflow obstruction. and intravenous immunoglobulin (p. 89). Complications of immunosuppression include infections and malignancy (p. 89). Approximately 50% of white patients develop skin malignancy by 15 years after transplantation. The prognosis after kidney transplantation is good. Recent UK statistics for transplants from cadaver donors indicate 96% patient survival and 93% graft survival at 1 year, and 88% patient survival and 84% graft survival at 5 years. Even better figures are obtained with living donor transplantation (91% graft survival at 5 years). Renal disease in pregnancy Pregnancy has important physiological effects on the renal system. Some diseases are more common in pregnancy (Box 15.41), the manifestations of others are modified during pregnancy, and a few diseases, such as pre-eclampsia (see Box 30.8, p. 1276), are unique to pregnancy. These are discussed in detail in Chapter 30. 15.41 Renal diseases in pregnancy • Eclampsia: severe hypertension, encephalopathy and fits • Disseminated intravascular coagulation • Thrombotic microangiopathy: may also occur post-partum (post-partum thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome) • Acute fatty liver of pregnancy • ‘HELLP’ syndrome: haemolysis, elevated liver enzymes, low platelets (thrombotic microangiopathy with abnormal liver function) 15.42 Kidney disease in adolescence • Adherence: young adults moving from parental supervision may become disengaged. There may also be reduced adherence to prophylactic and therapeutic treatment. • Adverse events: there is an increased risk of transplant loss and other adverse events in young adults on renal replacement therapy. • Management: joint transition clinics should be established with the paediatric team to facilitate transfer to adult specialist clinics. Renal disease in adolescence Many causes of renal failure present during infancy or childhood, such as congenital urological malformations and inherited disorders like cystinosis and autosomal recessive polycystic kidney disease. The consequences continue throughout the patient’s life and the situation often arises whereby patients transition from paediatric to adult nephrology services. Some of the issues and challenges surrounding this transition are summarised in Box 15.42. Drugs and the kidney Drug-induced renal disease The kidney is susceptible to damage by drugs because it is the route of excretion of many water-soluble compounds, including

15.43 Mechanisms and examples of drug-induced renal disease/dysfunction Mechanism Drug or toxin Comments Haemodynamic NSAIDs Reduce renal blood flow due to inhibition of prostaglandin synthesis causing afferent arteriolar vasoconstriction ACE inhibitors Reduce efferent glomerular arteriolar tone, so especially problematic in the presence of renal artery stenosis and other causes of renal hypoperfusion (e.g. NSAIDs) Radiographic contrast media Multifactorial aetiology may include intense vasoconstriction Acute tubular necrosis Aminoglycosides, amphotericin In most examples there is evidence of direct tubular toxicity but haemodynamic and other factors probably contribute Paracetamol overdose May occur with or without serious hepatotoxicity Radiographic contrast media Directly toxic to proximal tubular cells Loss of tubular/collecting duct function Lithium Cisplatin Aminoglycosides, amphotericin Dose-related, partially reversible loss of concentrating ability Occurs at lower exposures than cause acute tubular necrosis Glomerulonephritis (immune-mediated) Penicillamine, gold Membranous nephropathy Penicillamine, propylthiouracil, hydralazine Crescentic or focal necrotising glomerulonephritis in association with ANCA and systemic small-vessel vasculitis NSAIDs Minimal change nephropathy, membranous nephropathy Interstitial nephritis (immune-mediated) NSAIDs, penicillins, proton pump inhibitors, many others Acute interstitial nephritis Interstitial nephritis (toxicity) Lithium As a consequence of acute toxicity Chronic interstitial nephritis Ciclosporin, tacrolimus Interstitial nephritis (with papillary necrosis) Various NSAIDs (p. 403) Ischaemic damage secondary to NSAID effects on renal blood flow Tubular obstruction (crystal formation) Aciclovir Crystals of the drug form in tubules Aciclovir is now more common than the original example of sulphonamides Chemotherapy Uric acid crystals form as a consequence of tumour lysis (typically, a first-dose effect in haematological malignancy) Nephrocalcinosis Oral sodium phosphate-containing bowel cleansing agents Precipitation of calcium phosphate occurring in 1–4% and exacerbated by volume depletion Usually mild but damage can be irreversible Retroperitoneal fibrosis Ergolinic dopamine agonists (cabergoline), methysergide*, practolol* Idiopathic retroperitoneal fibrosis is more common (p. 434) *These drugs are no longer in use in the UK. (ACE = angiotensin-converting enzyme; ANCA = antineutrophil cytoplasmic antibody; NSAIDs = non-steroidal anti-inflammatory drugs) Pathophysiology Urine is an excellent culture medium for bacteria; in addition, the urothelium of susceptible persons may have more receptors, to which virulent strains of E. coli become adherent. In women, the ascent of organisms into the bladder is easier than in men; the urethra is shorter and the absence of bactericidal prostatic secretions may be relevant. Sexual intercourse may cause minor urethral trauma and transfer bacteria from the perineum into the bladder. Instrumentation of the bladder may also introduce organisms. Multiplication of organisms then depends on a number of factors, including the size of the inoculum and virulence of the bacteria. Conditions that predispose to UTI are shown in Box 15.44. Clinical features Typical features of cystitis and urethritis include: • abrupt onset of frequency of micturition and urgency • burning pain in the urethra during micturition (dysuria) • suprapubic pain during and after voiding • intense desire to pass more urine after micturition, due to spasm of the inflamed bladder wall (strangury) • urine that may appear cloudy and have an unpleasant odour • non-visible or visible haematuria. Systemic symptoms are usually slight or absent. However, infection in the lower urinary tract can spread to cause acute pyelonephritis. This is suggested by prominent systemic symptoms with fever, rigors, vomiting, hypotension and loin pain, guarding or tenderness, and may be an indication for hospitalisation. Only about 30% of patients with acute pyelonephritis have associated symptoms of cystitis or urethritis. Prostatitis is suggested by perineal or suprapubic pain, pain on ejaculation and prostatic tenderness on rectal examination. The differential diagnosis of lower urinary tract symptoms includes urethritis due to sexually transmitted disease, notably chlamydia (p. 340) and urethritis associated with reactive arthritis (p. 1031). Some patients, usually female, have symptoms suggestive of urethritis and cystitis but no bacteria are cultured from the urine (the ‘urethral syndrome’). Possible explanations include infection with organisms not readily cultured by ordinary

 of typical clinical features and abnormalities on urinalysis. Most urinary pathogens can reduce nitrate to nitrite, and neutrophils and nitrites can usually be detected in symptomatic infections by urine dipstick tests for leucocyte esterase and nitrite, respectively. The absence of both nitrites and leucocyte esterase in the urine makes UTI unlikely. Interpretation of bacterial counts in the urine, and of what is a ‘significant’ culture result, is based on probabilities. Urine taken by suprapubic aspiration should be sterile, so the presence of any organisms is significant. If the patient has symptoms and there are neutrophils in the urine, a small number of organisms is significant. In asymptomatic patients, more than 105 organisms/mL is usually regarded as significant (asymptomatic bacteriuria; see below). Typical organisms causing UTI in the community include E. coli derived from the gastrointestinal tract (about 75% of infections), Proteus spp., Pseudomonas spp., streptococci and Staphylococcus epidermidis. In hospital, E. coli still predominates but Klebsiella and streptococci are becoming more common. Certain strains of E. coli have a particular propensity to invade the urinary tract. Investigations to detect underlying predisposing factors for UTI are used selectively, most commonly in children, men or patients with recurrent infections (see Box 15.45). Management Antibiotics are recommended in all cases of proven UTI (Box 15.47). If urine culture has been performed, treatment may be started while awaiting the result. For infection of the lower urinary tract, treatment for 3 days is the norm and is less likely to induce significant alterations in bowel flora than more prolonged therapy. Trimethoprim or nitrofurantoin is the usual first choice of drug for initial treatment; however, between 10% and 40% of organisms causing UTI are resistant to trimethoprim, the lower rates being seen in community-based practice. Trimethoprim and nitrofurantoin are not recommended if eGFR is <30 mL/ min/1.73m2 due to reduced efficacy/increased risk of toxicity. In addition, trimethoprim may increase serum potassium and creatinine levels and lead to artefactual reductions in eGFR, which resolve once the drug is discontinued. Quinolone antibiotics such as ciprofloxacin and norfloxacin, and cefalexin are also generally effective. Co-amoxiclav and amoxicillin are no longer recommended as blind therapy, as up to 30% of organisms are resistant. They may be used once cultures confirm that the organism is sensitive. Penicillins and cephalosporins are safe to use in pregnancy but trimethoprim, sulphonamides, quinolones and tetracyclines should be avoided. methods (such as Chlamydia and certain anaerobes), intermittent or low-count bacteriuria, reaction to toiletries or disinfectants, symptoms related to sexual intercourse, or post-menopausal atrophic vaginitis. The differential diagnosis of acute pyelonephritis includes pyelonephrosis, acute appendicitis, diverticulitis, cholecystitis, salpingitis, ruptured ovarian cyst or ectopic pregnancy. In pyelonephrosis due to upper urinary tract obstruction, patients may become extremely ill, with fever, leucocytosis and positive blood cultures. With a perinephric abscess, there is marked pain and tenderness, and often bulging of the loin on the affected side. Urinary symptoms may be absent in this situation and urine testing negative, containing neither pus cells nor organisms. Investigations An approach to investigation is shown in Box 15.45. In an otherwise healthy woman with a single lower urinary tract infection, urine culture prior to treatment is not mandatory. Investigation is necessary, however, in patients with recurrent infection or after failure of initial treatment, during pregnancy, or in patients susceptible to serious infection, such as the immunocompromised, those with diabetes or an indwelling catheter, and older people (Box 15.46). The diagnosis can be made from the combination 15.44 Risk factors for urinary tract infection Bladder outflow obstruction • Benign prostatic enlargement • Prostate cancer • Urethral stricture Anatomical abnormalities • Vesico-ureteric reflux • Uterine prolapse • Bladder fistula Neurological problems • Multiple sclerosis • Spina bifida • Diabetic neuropathy Foreign bodies • Urethral suprapubic catheter • Ureteric stent • Nephrostomy tube • Urolithiasis Loss of host defences • Atrophic urethritis and vaginitis in post-menopausal women • Diabetes mellitus 15.45 Investigation of patients with urinary tract infection All patients • Dipstick* estimation of nitrite, leucocyte esterase and glucose • Microscopy/cytometry of urine for white blood cells, organisms • Urine culture Infants, children, and anyone with fever or complicated infection • Full blood count; urea, electrolytes, creatinine • Blood cultures Pyelonephritis: men; children; women with recurrent infections • Renal tract ultrasound or CT • Pelvic examination in women, rectal examination in men Continuing haematuria or other suspicion of bladder lesion • Cystoscopy *May substitute for microscopy and culture in simple uncomplicated infection. 15.46 Urinary infection in old age • Prevalence of asymptomatic bacteriuria: rises with age. Among the most frail in institutional care it rises to 40% in women and 30% in men. • Decision to treat: treating asymptomatic bacteriuria does not improve chronic incontinence or decrease mortality or morbidity from symptomatic urinary infection. It risks adverse effects from the antibiotic and promotion of the emergence of resistant organisms. Bacteriuria should not be treated in the absence of urinary symptoms. • Source of infection: the urinary tract is the most frequent source of bacteraemia in older patients admitted to hospital. • Incontinence: new or increased incontinence is a common presentation of UTI in older women. • Treatment: post-menopausal women with acute lower urinary tract symptoms may require longer than 3 days’ therapy.

} Scenario Drug Regimen Duration Comment Cystitis First choices Trimethoprim 200 mg twice daily 3 days 7–10 days in men Second choices1 Nitrofurantoin 50 mg 4 times daily Cefalexin 250 mg 4 times daily Ciprofloxacin 250 mg twice daily Pivmecillinam 400 mg 3 times daily In pregnancy Nitrofurantoin 50 mg 4 times daily 7 days Avoid trimethoprim and quinolones during pregnancy; avoid nitrofurantoin at term Cefalexin 250 mg 4 times daily Prophylactic therapy First choice Trimethoprim 100 mg at night Continuous Second choice1 Nitrofurantoin 50 mg at night Pyelonephritis First choice Cefalexin 1 g 4 times daily 14 days Admit to hospital if no response within 24 hrs Ciprofloxacin 500 mg twice daily 7 days Second choice Gentamicin2 Adjust dose according to renal function and serum levels 14 days Switch to appropriate oral agent as soon as possible Cefuroxime 750–1500 mg 3 times daily Epididymo-orchitis First choice Ciprofloxacin 500 mg twice daily 14 days Refer young men to genito-urinary department to check for Neisseria gonorrhoeae, which requires addition of a single dose of ceftriaxone 500 mg IM Young men Doxycycline 100 mg twice daily Older men Ciprofloxacin 500 mg twice daily Acute prostatitis First choice Trimethoprim 200 mg twice daily 28 days Second choice Ciprofloxacin 500 mg twice daily } 15.47 Antibiotic regimens for urinary tract infection in adults1 1In all cases, the choice of drug should take locally determined antibiotic resistance patterns into account. 2See Hartford nomogram (Fig. 6.18, p. 122). (IM = intramuscular) In more severe infection, antibiotics should be continued for 7–14 days. Seriously ill patients may require intravenous therapy with gentamicin for a few days (Box 15.47), later switching to an oral agent. A fluid intake of at least 2 L/day is usually recommended, although this is not based on evidence and may make symptoms of dysuria worse. Persistent or recurrent UTI If the causative organism persists on repeat culture despite treatment, or if there is reinfection with any organism after an interval, then an underlying cause is more likely to be present (see Box 15.44) and more detailed investigation is justified (see Box 15.45). In women, recurrent infections are common and investigation is justified only if infections are frequent (three or more per year) or unusually severe. Recurrent UTI, particularly in the presence of an underlying cause, may result in permanent renal damage, whereas uncomplicated infections rarely (if ever) do so (see chronic reflux nephropathy, p. 430). If an underlying cause cannot be treated, suppressive antibiotic therapy (see Box 15.47) can be used to prevent recurrence and reduce the risk of sepsis and renal damage. Urine should be cultured at regular intervals; a regimen of two or three antibiotics in sequence, rotating every 6 months, is often used in an attempt to reduce the emergence of resistant organisms. Other simple measures may help to prevent recurrence (Box 15.48). Trimethoprim or nitrofurantion is recommended for prophylaxis. Alternative antibiotics include cefalexin, co-amoxiclav and ciprofloxacin, but these should be avoided if possible because of adverse effects and the generation of resistance. Asymptomatic bacteriuria This is defined as more than 105 organisms/mL in the urine of apparently healthy asymptomatic patients. Approximately 1% of children under the age of 1 year, 1% of schoolgirls, 0.03% of schoolboys and men, 3% of non-pregnant adult women and 5% of pregnant women have asymptomatic bacteriuria. It is increasingly common in those aged over 65. There is no evidence that this condition causes renal scarring in adults who are not pregnant and have a normal urinary tract, and, in general, treatment is not indicated. Up to 30% will develop symptomatic infection within 1 year, however. Treatment is required in infants, pregnant women and those with urinary tract abnormalities. Catheter-related bacteriuria In patients with a urinary catheter, bacteriuria increases the risk of Gram-negative bacteraemia five-fold. Bacteriuria is common, 15.48 Prophylactic measures to be adopted by women with recurrent urinary infections • Fluid intake of at least 2 L/day • Regular complete emptying of bladder • Good personal hygiene • Emptying of bladder before and after sexual intercourse • Cranberry juice/tablets may be effective

 however, and almost universal during long-term catheterisation. Treatment is usually avoided in asymptomatic patients, as this may promote antibiotic resistance. Careful sterile insertion technique is important and the catheter should be removed as soon as it is not required. Acute pyelonephritis The kidneys are infected in a minority of patients with UTI. Acute renal infection (pyelonephritis) presents as a classic triad of loin pain, fever and tenderness over the kidneys. The renal pelvis is inflamed and small abscesses are often evident in the renal parenchyma (see Fig. 15.13C, p. 402). Renal infection is almost always caused by organisms ascending from the bladder, and the bacterial profile is the same as for lower urinary tract infection (p. 428). Rarely, bacteraemia may give rise to renal or perinephric abscesses, most commonly due to staphylococci. Predisposing factors, such as cysts or renal scarring, facilitate infection. Rarely, acute pyelonephritis is associated with papillary necrosis. Fragments of renal papillary tissue are passed per urethra and can be identified histologically. They may cause ureteric obstruction and, if this occurs bilaterally or in a single kidney, it may lead to AKI. Predisposing factors include diabetes mellitus, chronic urinary obstruction, analgesic nephropathy and sickle-cell disease. A necrotising form of pyelonephritis with gas formation, 'emphysematous pyelonephritis', is occasionally seen in patients with diabetes mellitus. Xanthogranulomatous pyelonephritis is a chronic infection that can resemble renal cell cancer. It is usually associated with obstruction, is characterised by accumulation of foamy macrophages and generally requires nephrectomy. Infection of cysts in polycystic kidney disease (p. 405) calls for prolonged antibiotic treatment. Appropriate investigations are shown in Box 15.45 and management is described above and in Box 15.47. Intravenous rehydration may be needed in severe cases. If complicated infection is suspected or response to treatment is not prompt, urine should be re-cultured and renal tract ultrasound performed to exclude urinary tract obstruction or a perinephric collection. If obstruction is present, drainage by a percutaneous nephrostomy or ureteric stent should be considered. Tuberculosis Tuberculosis of the kidney and renal tract is secondary to tuberculosis elsewhere (p. 588) and is the result of blood-borne infection. Initially, lesions develop in the renal cortex; these may ulcerate into the renal pelvis and involve the ureters, bladder, epididymis, seminal vesicles and prostate. Calcification in the kidney and stricture formation in the ureter are typical. Clinical features may include symptoms of bladder involvement (frequency, dysuria); haematuria (sometimes macroscopic); malaise, fever, night sweats, lassitude and weight loss; loin pain; associated genital disease; and chronic renal failure as a result of urinary tract obstruction or destruction of kidney tissue. Neutrophils are present in the urine but routine urine culture may be negative ('sterile pyuria'). Special techniques of microscopy and culture may be required to identify tubercle bacilli and are most usefully performed on early morning urine specimens. Bladder involvement should be assessed by cystoscopy. Radiology of the urinary tract and a chest X-ray to look for pulmonary tuberculosis are mandatory. Anti-tuberculous chemotherapy follows standard regimens (p. 592). Surgery to relieve urinary tract obstruction or to remove a very severely infected kidney may be required. Reflux nephropathy This condition, which was previously known as chronic pyelonephritis, is a specific type of chronic interstitial nephritis associated with vesico-ureteric reflux (VUR) in early life and with the appearance of scars in the kidney, as demonstrated by various imaging techniques. About 12% of patients in Europe requiring treatment for ESRD may have this disorder but diagnostic criteria are imprecise. Pathophysiology Reflux nephropathy is thought to be due to chronic reflux of urine from the bladder into the ureters, in association with recurrent UTI in childhood. It was previously assumed that ascending infection was necessary for progressive renal damage in patients with VUR but there is evidence to suggest that renal scars can occur, even in the absence of infection. Furthermore, epidemiological surveys and controlled trials have found that efforts to correct VUR by using surgical or other means are ineffective in halting progression of the disease. Susceptibility to VUR has a genetic component and may be associated with renal dysplasia and other congenital abnormalities of the urinary tract. It can be connected with outflow obstruction, usually caused by urethral valves, but usually occurs with an apparently normal bladder. Clinical features Usually, the renal scarring and dilatation are asymptomatic and the patient may present at any age with hypertension (sometimes severe), proteinuria or features of CKD. There may be no history of overt UTI. However, symptoms arising from the urinary tract may be present and include frequency of micturition, dysuria and aching lumbar pain. VUR may occur in children but diminishes as the child grows, and usually has disappeared by adulthood. Urinalysis often shows the presence of leucocytes and moderate proteinuria (usually < 1 g/24 hrs) but these are not invariable. The risk of renal stone formation is increased. A number of women first present with hypertension and/or proteinuria in pregnancy.

Children and adults with small or unilateral renal scars have a good prognosis, provided renal growth is normal. With significant unilateral scars there is usually compensatory hypertrophy of the contralateral kidney. In patients with more severe bilateral disease, prognosis is related to the severity of renal dysfunction, hypertension and proteinuria. If the serum creatinine is normal and hypertension and proteinuria are absent, then the long-term prognosis is usually good. Investigations Renal scarring can be detected by ultrasound but it has poor sensitivity and is only capable of detecting major defects and excluding significant obstruction. Radionuclide DMSA scans are more sensitive (see Fig. 15.6, p. 390), and serial imaging by MRI or CT may be useful in assessing progression. Abnormalities may be unilateral or bilateral and of any grade of severity. Gross scarring of the kidneys, commonly at the poles, is seen, with reduced kidney size and narrowing of the cortex and medulla. Renal scars may be juxtaposed to dilated calyces. In patients who develop heavy proteinuria and hypertension, renal biopsies show glomerulomegaly and focal glomerulosclerosis, probably as a secondary response to reduced nephron numbers. Radionuclide

proteins and glycoproteins. The most common types are summarised in Box 15.49. A number of risk factors have been identified for renal stone formation (Box 15.50). In developed countries, however, most calculi occur in healthy young men, in whom investigations reveal no clear predisposing cause. Renal stones vary greatly in size, from sand-like particles anywhere in the urinary tract to large, round stones in the bladder. In developing countries, bladder stones are common, particularly in children. In developed countries, the incidence of childhood bladder stones is low; renal stones in adults are more common. Staghorn calculi fill the whole renal pelvis and branch into the calyces (Fig. 15.29); they are usually associated with infection and composed largely of struvite. Deposits of calcium may be present throughout the renal parenchyma, giving rise to fine calcification within it (nephrocalcinosis), especially in patients with renal tubular acidosis, hyperparathyroidism, vitamin D intoxication and healed renal tuberculosis. Cortical nephrocalcinosis may occur in areas of cortical necrosis, typically after AKI in pregnancy or other severe AKI. Clinical features The clinical presentation is highly variable. Many patients with renal stone disease are asymptomatic, whereas others present with pain, haematuria, UTI or urinary tract obstruction. A common presentation is with acute loin pain radiating to the anterior techniques can also be used to demonstrate VUR as a noninvasive alternative to micturating cystourethrography (MCUG; the bladder is filled with contrast media through a urinary catheter and images are taken during and after micturition; Fig. 15.28). As surgical intervention for VUR has declined in popularity (see below), however, this type of imaging is used less often. Management Infection, if present, should be treated; if recurrent, it should be prevented with prophylactic therapy, as described for UTI (p. 429). If recurrent pyelonephritis occurs in an abnormal kidney with minimal function, nephrectomy may be indicated. Occasionally, hypertension is cured by the removal of a diseased kidney when the disease is predominantly or entirely unilateral. As most childhood reflux tends to disappear spontaneously and trials have shown small or no benefits from anti-reflux surgery, such intervention is now less common. Severe reflux may be managed by ureteric reimplantation or subtrigonal injection of Teflon or polysaccharide (STING) beneath the ureteric orifice. Urolithiasis Renal stone disease is common, affecting people of all countries and ethnic groups. In the UK, the prevalence is about 1.2%, with a lifetime risk of developing a renal stone by age 60–70 of approximately 7% in men. In some regions, the risk is higher, most notably in countries such as Saudi Arabia, where the lifetime risk of developing a renal stone in men aged

60–70 is just over 20%. Pathophysiology Urinary calculi consist of aggregates of crystals, usually containing calcium or phosphate in combination with small amounts of Fig. 15.28 Vesico-ureteric reflux (grade IV) shown by micturating cystogram. The bladder has been filled with contrast medium through a urinary catheter. After micturition, there was gross vesico-ureteric reflux into widely distended ureters and pelvicalyceal systems. Courtesy of Dr A.P. Bayliss and Dr P. Thorpe, Aberdeen Royal Infirmary. 15.49 Composition of renal stones Composition Percentage Calcium oxalate1 60% Calcium phosphate 15% Uric acid 10% Magnesium ammonium phosphate (struvite)2 15% Cystine and others 1% 1Stones often contain small amounts of calcium phosphate. 2Associated with urine infection. 15.50 Predisposing factors for kidney stones Environmental and dietary causes • Low urine volumes: high ambient temperatures, low fluid intake • Diet: high protein, high sodium, low calcium • High sodium excretion • High oxalate excretion • High urate excretion • Low citrate excretion Acquired causes • Hypercalcaemia of any cause (p. 661) • Ileal disease or resection (increases oxalate absorption and urinary excretion) • Renal tubular acidosis type I (distal, p. 365) Congenital and inherited causes • Familial hypercalciuria • Medullary sponge kidney • Cystinuria • Renal tubular acidosis type I (distal) • Primary hyperoxaluria

 Fig. 15.29 Computed tomogram of the kidneys, ureters and bladder (CTKUB): coronal view showing a staghorn calculus in the left kidney. Courtesy of Dr I. Mendichovszky, University of Cambridge. 15.51 Investigations for renal stones Sample Test First stone Recurrent stone Stone Chemical composition1 □ Blood Calcium □ □ Phosphate □ □ Uric acid □ □ Urea and electrolytes □ □ Bicarbonate □ □ Parathyroid hormone2 (□) Urine Dipstick test for protein, blood, glucose □ □ Amino acids □ 24-hr urine Urea □ Creatinine clearance □ Sodium □ Calcium □ Oxalate □ Uric acid □ 1The most valuable test if a stone can be obtained. 2Only if serum calcium or urinary calcium excretion is high. abdominal wall, together with haematuria: a symptom complex termed renal or ureteric colic. This is most commonly caused by ureteric obstruction by a calculus but the same symptoms can occur in association with a sloughed renal papilla, tumour or blood clot. The patient is suddenly aware of pain in the loin, which radiates round the flank to the groin and often into the testis or labium, in the sensory distribution of the first lumbar nerve. The pain steadily increases in intensity to reach a peak in a few minutes. The patient is restless and generally tries unsuccessfully to obtain relief by changing position or pacing the room. There is pallor, sweating and often vomiting. Frequency, dysuria and haematuria may occur. The intense pain usually subsides within 2 hours but may continue unabated for hours or days. It is usually constant during attacks, although slight fluctuations in severity may be seen. Subsequent to an attack of renal colic, intermittent dull pain in the loin or back may persist for several hours. Investigations Patients with symptoms of renal colic should be investigated to determine whether or not a stone is present, to identify its location and to assess whether it is causing obstruction. About 90% of stones contain calcium and these can be visualised on plain abdominal X-ray (radio-opaque stones) but non-contrast CTKUB (Fig. 15.29) is the gold standard for diagnosing a stone within the kidney or ureter, as 99% are visible using this method. Ultrasound can show stones within the kidney and dilatation of the renal pelvis and ureter if the stone is obstructing urine flow; it is useful in unstable patients or young women, in whom exposure to ionising radiation is undesirable. A minimum set of investigations (Box 15.51) should be performed in patients with a first renal stone. The yield of more detailed investigation is low, and hence usually reserved for young patients, those with recurrent or multiple stones, or those with complicated or unexpected presentations. Chemical analysis of stones is often helpful in defining the underlying cause. Since most stones pass spontaneously through the urinary tract, ideally the urine should be sieved for a few days after an episode of colic in order to collect the calculus for analysis. Management The immediate treatment of renal colic is with analgesia and antiemetics. Renal colic is often unbearably painful and demands powerful analgesia; diclofenac orally or as a suppository (100 mg) is often very effective, followed by morphine (10–20 mg) or pethidine (100 mg) intramuscularly. Around 90% of stones of less than 4 mm diameter pass spontaneously, but this applies to only 10% of stones bigger than 6 mm, and these may require intervention (see below). Patients with renal or ureteric stones are at high risk of infection; if surgery is contemplated, the patient should be covered with appropriate antibiotics. Immediate action is required if infection occurs in the stagnant urine proximal to the stone (pyonephrosis), and in patients with a solitary kidney who develop anuria in association with a stone in the ureter. Stones that do not pass spontaneously through the urinary tract may need to be removed surgically, using ureteroscopy and stone fragmentation usually with a laser, or percutaneous nephrolithotomy (PCNL) and fragmentation with an ultrasonic disaggregator. Alternatively, stones can be fragmented by extracorporeal shock wave lithotripsy (ESWL), in which shock waves generated outside the body are focused on the stone, breaking it into small pieces that can pass easily down the ureter. The indications for intervention to manage or remove stones from the renal tract are summarised in Box 15.52. Procedures vary, depending on the site (Fig. 15.30). Measures to prevent further stone formation are guided by the investigations in Box 15.51. Some general principles apply to almost every patient with calcium-containing stones (Box 15.53). More specific measures apply to some types. Urate stones can be prevented by allopurinol but its role in patients with calcium

stones and high urate excretion is uncertain. Stones formed in cystinuria can be reduced by penicillamine therapy. It may also be helpful to attempt to alkalinise the urine with sodium bicarbonate, as a high pH discourages urate and cystine stone formation. Diseases of the collecting system and ureters Congenital abnormalities Various congenital anomalies of the urinary tract can occur (Fig. 15.31); they affect more than 10% of infants. If not immediately lethal, they can lead to complications in later life, including obstructive nephropathy and CKD. Single kidneys About 1 in 500 infants is born with only one kidney. Although this is usually compatible with normal life, it may be associated with other abnormalities. Medullary sponge kidney disease Medullary sponge kidney is a congenital disorder characterised by malformation of the papillary collecting ducts in the pericalyceal region of the renal pyramids. This leads to the formation of microscopic and large medullary cysts. Patients often present as adults with renal stones but the prognosis is generally good. The diagnosis is made by ultrasound, CT or intravenous urography, where contrast medium is seen to fill dilated or cystic tubules, which are sometimes calcified. Fig. 15.30 Options for removal of urinary stones. A A patient undergoing extracorporeal shock wave lithotripsy (ESWL). B The procedures that are used for removal of stones in the urinary tract, shown in relation to the site of the stone. (PCNL = percutaneous nephrolithotomy) A B Renal pelvis or kidney ESWL PCNL Ureteroscopy Upper ureter ESWL Ureteroscopy Bladder Cystoscopic removal or destruction Percutaneous endoscopic removal or destruction Open surgery removal or destruction Lower ureter ESWL Ureteroscopy 15.52 Indications for intervention to manage and remove stones from the urinary tract Clinical presentation Procedure Obstruction and/or anuria Emergency nephrostomy or stent Pyonephrosis associated with stone Emergency nephrostomy or stent Stone in a patient with solitary kidney Urgent PCNL, stent, ESWL or ureteroscopy* Severe pain and persistence of stone in renal tract Urgent PCNL, stent, ESWL or ureteroscopy* Pain and persistence of stone in renal tract Elective PCNL, ESWL or ureteroscopy* *Procedure depends on site of stone; see Fig. 15.30. (ESWL = extracorporeal shock wave lithotripsy; PCNL = percutaneous nephrolithotomy) 15.53 Measures to prevent calcium stone formation Diet Fluid • At least 2 L output per day (intake 3–4 L): check with 24-hr urine collections • Intake distributed throughout the day (especially before bed) Sodium • Restrict intake Protein • Moderate, not high Calcium • Maintain good calcium intake (calcium forms an insoluble salt with dietary oxalate, lowering oxalate absorption and excretion) • Avoid calcium supplements separate from meals (increase calcium excretion without reducing oxalate excretion) Oxalate • Avoid foods that are rich in oxalate (spinach, rhubarb) Drugs Thiazide diuretics • Reduce calcium excretion • Valuable in recurrent stone-formers and hypercalciuria Allopurinol • If urate excretion high (unproven except for urate stones) Avoid • Vitamin D supplements (increase calcium absorption and excretion) • Vitamin C supplementation (increases oxalate excretion)

 Pelvi-ureteric junction obstruction Pelvi-ureteric junction obstruction (PUJO) causes idiopathic hydronephrosis and results from a functional obstruction at the junction of the ureter and renal pelvis. The abnormality is likely to be congenital and is often bilateral. It can be seen in very young children but gross hydronephrosis may present at any age. The common presentation is ill-defined renal pain or ache, exacerbated by drinking large volumes of liquid (Dietl's crisis). Rarely, it is asymptomatic. The diagnosis is often suspected after ultrasound or CT scan, and can be confirmed with a 99mTc-MAG3 renogram followed by diuretic. In a PUJO, the MAG3 renogram shows a pathognomonic 'rising curve' as the radioisotope accumulates in the renal pelvis and still does not drain following the diuretic injection. Treatment is surgical excision of the pelvi-ureteric junction and reanastomosis (pyeloplasty), which can now be performed laparoscopically. Less invasive alternatives are also possible, including balloon dilatation and endoscopic pyelotomy, but are generally less effective. Retroperitoneal fibrosis Fibrosis of the retroperitoneal connective tissues may encircle and compress the ureter(s), causing obstruction. The fibrosis is most commonly idiopathic but can represent a reaction to infection, radiation or aortic aneurysm, or be caused by metastatic cancer. It is recognised as part of the spectrum of disorders associated with elevated IgG4 levels (p. 890). Rarely, it can be associated with inflammatory bowel disease. Patients usually present with ill-defined symptoms of ureteric obstruction. Typically, there is an acute phase response (high CRP and ESR, and polyclonal hypergammaglobulinaemia). Imaging with CT or IVU shows ureteric obstruction with medial deviation of the ureters. Idiopathic retroperitoneal fibrosis may respond well to glucocorticoids (with a reduction in inflammatory marker levels) but ureteric stenting is often necessary to relieve obstruction and preserve renal function. Failure to improve indicates the need for surgery (ureterolysis), both to relieve obstruction and to exclude malignancy. Tumours of the kidney and urinary tract Several malignant tumours can affect the kidney and urinary tract, including renal cell cancer, upper urinary tract urothelial cancers, bladder carcinoma, prostate carcinoma, and cancers of the testis and penis. The urogenital tract can also be affected by benign tumours and secondary tumour deposits, which can cause obstructive uropathy. Renal cell cancer and bladder carcinoma are described here, while prostate cancer (p. 438) and testicular tumours (p. 439) are covered later in this chapter. Renal cell cancer Renal cell cancer (RCC) is by far the most common malignant tumour of the kidney in adults, making up 2.5% of all adult cancers, with a prevalence of 16 cases per 100 000 population. It is twice as common in males. The peak incidence is between 65 and 75 years of age and it is uncommon before 40. The tumour arises from renal tubular cells. Haemorrhage and necrosis give the cut surface a characteristic mixed golden-yellow and red appearance (Fig. 15.32B). Microscopically, clear cell RCCs are the most common histological subtype (85%), with papillary, Fig. 15.31 Congenital abnormalities of the urinary tract. (PUJ = pelvi-ureteric junction) Renal agenesis/ dysplasia Ectopic kidney Single kidney PUJ obstruction Horseshoe kidney Duplex ureter Ectopic ureter Megaureter Ureterocele Urethral valves Vesico-ureteric reflux Ureterocele A ureterocele occurs behind a pin-hole ureteric orifice when the intramural part of the ureter dilates and bulges into the bladder. It can become very large and cause lower urinary tract obstruction. Incision of the pin-hole opening relieves the obstruction. Ectopic ureters and duplex kidneys Ectopic ureters occur with congenital duplication of one or both kidneys (duplex kidneys). Developmentally, the ureter has two main branches and, if this arrangement persists, the two ureters of the duplex kidneys may drain separately into the bladder. The lower pole moiety enters the bladder superiorly and laterally, while the upper pole moiety enters the bladder inferomedially to the lower pole moiety ureter or, more rarely, enters the vagina or seminal vesicle. The lower pole moiety has an ineffective valve mechanism, so that urine passes up the ureter on voiding (vesico-ureteric reflux, p. 430), whereas the upper pole moiety is often associated with a ureterocele. Megaureter A megaureter is a ureter dilated to more than 5 mm in diameter. It may be obstructed or non-obstructed and refluxing or nonrefluxing. Some 50% of cases are asymptomatic but patients may present with pain, haematuria or infection. Radiographic and pressure/flow studies may be needed to determine whether there is obstruction to urine flow. Patients with symptoms or reduced renal function are treated. Ideally, treatment is expectant with antibiotic prophylaxis. Surgery (narrowing of the ureter and/or reimplantation) may, however, be needed for recurrent symptoms, reduction of more than 10% in renal function or complications (i.e. stones).

renal-related morbidity. Patients at high operative risk who have small tumours may also be treated percutaneously by cryotherapy or radiofrequency ablation. There is an evolving role for active surveillance with serial imaging in selected patients with small renal masses of less than 4 cm. Surgery may also play a role in the treatment of solitary metastases, since these can remain single for long periods and excision may be curative. RCC is resistant to most chemotherapeutic agents. For many years, cytokine therapy with interferon and interleukin-2 was used in metastatic renal cancer but, in recent years, two new classes of targeted drugs have been introduced and are now the mainstay of therapy. These are the tyrosine kinase inhibitors sunitinib and pazopanib, and the mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus. In previous years, patients who presented with distant metastases were treated with cytoreductive nephrectomy, in which nephrectomy was coupled with systemic cytokine treatment, since this was shown to improve survival as compared with either treatment in isolation. It is, at present, unclear whether this survival benefit still prevails with the newer agents mentioned above. Studies that antedate the introduction of these new agents show that, if the tumour is confined to the kidney, 5-year survival is 75%, but this falls to 5% when there are distant metastases. Urothelial tumours Tumours arising from the transitional epithelium of the renal tract can affect the renal pelvis, ureter, bladder or urethra. They are rare under the age of 40, affect men 3–4 times more often than women, and account for about 3% of all malignant tumours. The bladder is by far the most frequently affected site. Although almost all tumours are transitional cell carcinomas (otherwise known as urothelial cancers), squamous carcinoma may occur in urothelium that has undergone metaplasia, usually following chronic inflammation due to stones or schistosomiasis. The appearance of a transitional cell tumour ranges from a delicate papillary structure with a relatively good prognosis to a solid ulcerating mass in more aggressive disease. chromophobe and collecting duct tumours comprising the remainder. In RCC, there is potentially spread along the renal vein and the inferior vena cava. Direct invasion of perinephric tissues is common. Lymphatic spread occurs to para-aortic nodes, while blood-borne metastases (which may be solitary) most commonly develop in the lungs, bone and brain. Clinical features In 50% of patients, asymptomatic renal tumours are identified as an incidental finding during imaging investigations carried out for other reasons. Among symptomatic patients, about 60% present with haematuria, 40% with loin pain and 25% with a palpable mass. About 10% present with a triad of pain, haematuria and a mass; this usually represents advanced disease. A remarkable range of systemic effects may be present, including fever, raised ESR, polycythaemia, disorders of coagulation, hypercalcaemia, and abnormalities of plasma proteins and liver function tests. The patient may present with pyrexia of unknown origin (PUO) or, rarely, with neuropathy. Some of these systemic effects are caused by secretion of products by the tumour, such as renin, erythropoietin, parathyroid hormone-related protein (PTHrP) and gonadotrophins. The effects disappear when the tumour is removed but may reappear when metastases develop. Investigations Ultrasound is often the initial investigation and allows differentiation between solid tumour and simple renal cysts. If the results are suggestive of a tumour, contrast-enhanced CT of the abdomen and chest should be performed for staging (Fig. 15.32A). For tumours with no evidence of metastatic spread and when the nature of the lesion is uncertain, ultrasound or CT-guided biopsy may be used to avoid nephrectomy for benign disease. Management Radical nephrectomy that includes the perirenal fascial envelope is the treatment of choice. Nephrectomy is commonly performed laparoscopically, with equivalent outcomes to open surgery. Partial nephrectomy, which may be carried out by open or minimally invasive surgery, is recommended for tumours of 4 cm or less, as there is a lower incidence of long-term cardiac- and Fig. 15.32 Renal cell cancer. A In this CT, the right kidney is expanded by a low-density tumour, which fails to take up contrast material. Tumour is shown extending into the renal vein and inferior vena cava (arrow). B Pathology specimen showing typical necrosis of a renal cell cancer. (A, B) Courtesy of Dr A.P. Bayliss and Dr P. Thorpe, Aberdeen Royal Infirmary. A B

 multiple angiomyolipomas (tubers) may occasionally cause renal failure in adults; they may also bleed, requiring embolisation. The von Hippel–Lindau syndrome (p. 1132) is associated with multiple renal cysts, renal adenomas and clear cell renal cell cancers. Other organs affected include the central nervous system (haemangioblastomas), pancreas and adrenals (phaeochromocytoma). Urinary incontinence Urinary incontinence is defined as any involuntary leakage of urine. It may occur in patients with a normal urinary tract, as the result of dementia or poor mobility, or transiently during an acute illness or hospitalisation, especially in older people (Box 15.54). The prevalence of any form of incontinence in all females is 25–45%, with a concomitant socioeconomic burden. Childbirth, hysterectomy, obesity, recurrent UTI, smoking, caffeine and constipation are risk factors for incontinence. Pathophysiology As urine accumulates in the bladder during the storage phase, the sphincter tone gradually increases, but there are no significant changes in vesical pressure, detrusor pressure or intra-abdominal pressure. During voiding, intravesical pressure increases as a result of detrusor contraction and the sphincter relaxes, allowing urine to flow from the bladder until it is empty. Clinical disorders associated with incontinence are connected with various abnormalities in this cycle and these are discussed in more detail below. Stress incontinence This occurs because passive bladder pressure exceeds the urethral pressure, due either to poor pelvic floor support or a weak urethral sphincter. Usually there is an element of both these factors. Stress incontinence is very common in women and seen most frequently following childbirth. It is rare in men and usually follows surgery to the prostate. The presentation is with incontinence during coughing, sneezing or exertion. In women, perineal inspection may reveal leakage of urine when the patient coughs. Urge incontinence This usually occurs because of detrusor over-activity, which produces an increased bladder pressure that overcomes the urethral sphincter. Urgency with or without incontinence may also be driven by a hypersensitive bladder resulting from UTI or a bladder stone. Detrusor over-activity is usually idiopathic, Pathophysiology Risk factors include cigarette smoking and exposure to industrial carcinogens such as aromatic amines, aniline dyes and aldehydes. Clinical features More than 80% of patients present with painless, visible haematuria. It should be assumed that such bleeding is from a tumour until proven otherwise (p. 391). Tumours of the ureter or bladder may also cause symptoms of obstruction, depending on the site of involvement, and tumours of the bladder present with dysuria or storage symptoms. Physical examination is usually unremarkable, except in patients with very advanced disease, when bimanual examination may reveal a palpable mass. Investigations Cystoscopy (usually flexible cystoscopy under a local anaesthetic) is mandatory to evaluate the bladder in cases of haematuria or suspected bladder cancer. Imaging of the upper urinary tract (CT urogram is the gold standard but IVU combined with renal ultrasound is also acceptable) is also important to rule out abnormalities of the kidney, ureters and renal pelvis in patients with haematuria. If a suspicious defect is seen on CT urography or IVU in the ureter or renal pelvis, a retrograde ureteropyelogram, ureteroscopy and biopsy are required. If evidence of a solid invasive urothelial tumour is found, CT of the abdomen, pelvis and chest should be performed to define tumour stage. Management Most bladder tumours are low-grade superficial lesions that can be successfully treated endoscopically by transurethral resection of the tumour. Intravesical chemotherapy with mitomycin C is usually administered as a one-off treatment post resection to prevent tumour recurrence, or may be given as a prolonged course to treat multiple low-grade bladder tumours. Patients with carcinoma in situ have a high risk of progression to invasive cancer. These patients often respond well to intravesical bacille Calmette–Guérin (BCG) treatment but more radical treatment may also be needed if this is unsuccessful. Following initial treatment and endoscopic clearance of bladder tumours, regular check cystoscopies are required to look for evidence of recurrence. Patients with recurrences of superficial disease can usually be treated by further resection and diathermy, but if this is unsuccessful, a cystectomy may be needed. The management of invasive bladder tumours involves radical cystectomy with urinary diversion into an incontinent ileal conduit or a continent catheterisable bowel pouch; the latter is usually reserved for patients under the age of 70 years. The prognosis of bladder tumours depends on tumour stage and grade. About 5% of patients with low-grade superficial bladder cancer progress to develop invasion of the bladder muscle, compared with about 50% of those with high-grade superficial bladder cancers. Overall, the 5-year survival for patients with muscle-invasive bladder cancer of either grade is 50–70%. Urothelial cell carcinoma of the renal pelvis and ureter is usually treated by open or laparoscopic nephro-ureterectomy, but if the tumour is solitary and low-grade, it can be treated endoscopically. Inherited tumour syndromes affecting the renal tract Some uncommon autosomal dominantly inherited conditions are associated with multiple renal tumours in adult life. In tuberous sclerosis (p. 1264), replacement of renal tissue by 15.54 Incontinence in old age • Prevalence: urinary incontinence affects 15% of women and 10% of men aged over 65 years. • Cause: incontinence may be transient and due to delirium, urinary infection, medication (such as diuretics), faecal impaction or restricted mobility, and these should be treated before embarking on further specific investigation. • Detrusor over-activity: established incontinence in old age is most commonly due to detrusor over-activity, which may be caused by damage to central inhibitory centres or local detrusor muscle abnormalities. • Catheterisation: poor manual dexterity or cognitive impairment may necessitate the help of a carer to assist with intermittent catheterisation.

other than in patients with neurological conditions such as spina bifida or multiple sclerosis, in whom it is neurogenic (p. 1093). The incidence of urge incontinence increases with age, occurring in 10–15% of the population aged over 65 years and in approximately 50% of patients requiring nursing home care. It is also seen in men with lower urinary tract obstruction and most often remits after the obstruction is relieved. Continual incontinence This is suggestive of a fistula, usually between the bladder and vagina (vesicovaginal), or the ureter and vagina (ureterovaginal). It is most common following gynaecological surgery but is also seen in patients with gynaecological malignancy or post radiotherapy. In parts of the world where obstetric services are scarce, prolonged obstructed labour can be a common cause of vesicovaginal fistulae. Continual incontinence may also be seen in infants with congenital ectopic ureters. Occasionally, stress incontinence is so severe that the patient leaks continuously. Overflow incontinence This occurs when the bladder becomes chronically over-distended and may lead to AKI (high-pressure chronic urinary retention). It is most commonly seen in men with benign prostatic enlargement or bladder neck obstruction (see below) but may arise in either sex as a result of failure of the detrusor muscle (atonic bladder). The latter may be idiopathic but more commonly is the result of damage to the pelvic nerves, either from surgery (commonly, hysterectomy or rectal excision), trauma or infection, or from compression of the cauda equina by disc prolapse, trauma or tumour. Incontinence due to prostatic enlargement can be regarded as a type of overflow incontinence. Post-micturition dribble This is very common in men, even in the relatively young. It is due to a small amount of urine becoming trapped in the U-bend of the bulbar urethra, which leaks out when the patient moves. Post-micturition dribble is more pronounced if associated with a urethral diverticulum or urethral stricture. It may occur in women with a urethral diverticulum and may mimic stress incontinence. Clinical features Patients should be encouraged to keep a voiding diary, including the measured volume voided, frequency of voiding, a note of incontinence pad usage, precipitating factors and associated features, such as urgency, since this can be of diagnostic value. Structured questionnaires may help objectively quantify symptoms. The patient should be assessed for evidence of cognitive impairment and impaired mobility. A neurological assessment should be performed to detect disorders such as multiple sclerosis that may affect the nervous supply of the bladder, and the lumbar spine should be inspected for features of spina bifida occulta. Perineal sensation and anal sphincter tone should be assessed. Rectal examination is needed to assess the prostate in men and to exclude faecal impaction as a cause of incontinence. Genital examination should be done to identify phimosis or paraphimosis in men, and vaginal mucosal atrophy, cystoceles or rectoceles in women. Investigations Urinalysis and culture should be performed in all patients. Ultrasound examination can be helpful in identifying patients with overflow incontinence who have incomplete bladder emptying, as they may reveal a significant amount of fluid in the bladder (> 100 mL) post micturition. Urine flow rates and full urodynamic assessment by cystometrography may be required to diagnose the type of incontinence and are indicated in selected cases when the diagnosis is unclear on clinical grounds. A CT scan and cystoscopy should be performed in patients with continual incontinence who are suspected of having a fistula. Imaging with MRI is indicated when a urethral diverticulum is suspected.

Management Weight reduction in obese patients will aid resolution of incontinence. Women with stress incontinence respond well to physiotherapy. The mainstay of treatment for urge incontinence is bladder retraining, which involves teaching patients to hold more urine voluntarily in their bladder, assisted by anticholinergic medication. Surgery may be required in patients who have severe daytime incontinence despite conservative treatment. The treatment of incontinence secondary to fistula formation is surgical. Patients with overflow incontinence due to bladder obstruction should be treated surgically or with long-term catheterisation (intermittent or continuous). Incontinence secondary to neurological diseases can be managed by intermittent self-catheterisation. Prostate disease Prostatitis This results from inflammation of the prostate gland. Acute or chronic bacterial prostatitis can be caused by infection with the same bacteria that are associated with UTI (p. 426) but prostatitis can also be ‘non-bacterial’, in which case no organism can be cultured from the urine. This is also known as chronic pelvic pain syndrome. Clinical features of prostatitis include frequency, dysuria, painful ejaculation, perineal or groin pain, difficulty passing urine and, in acute disease, considerable systemic disturbance. The prostate is enlarged and tender. Bacterial prostatitis is confirmed by a positive culture from urine or from urethral discharge obtained after prostatic massage, and the treatment of choice is a quinolone antibiotic. A 4–6-week course of antibiotics is required (see Box 15.47, p. 429). Treatment of chronic pelvic pain syndrome is challenging but some patients respond to a combination of α-blockers, NSAIDs and amitriptyline. Benign prostatic enlargement Benign prostatic enlargement (BPE) is extremely common. It has been estimated that about half of all men aged 80 years and over will have lower urinary tract symptoms associated with bladder outlet obstruction (BOO) due to BPE. Benign prostatic hyperplasia (BPH) is the histological abnormality that underlies BPE. Pathophysiology The prostate gland increases in volume by 2.4 cm3 per year on average from 40 years of age. The process begins in the periurethral (transitional) zone and involves both glandular and stromal tissue to a variable degree. The cause is unknown, although BPE does not occur in patients with hypogonadism, suggesting that hormonal factors may be important. Clinical features The primary symptoms of BPE arise because of difficulty in voiding urine due to obstruction of the urethra by the prostate; these voiding symptoms consist of hesitancy, poor urinary flow and a sensation of incomplete emptying. Other storage

 post-void residual volume of urine assessed with ultrasound, and prostate volume by transrectal ultrasound scan (TRUS). Objective assessment of obstruction is possible by urodynamics but this is seldom required. If symptoms or signs, such as a palpable bladder, nocturnal enuresis, recurrent UTI or a history of renal stones, are present, renal function should be assessed; if it is abnormal, screening should be conducted for evidence of obstructive uropathy by ultrasound examination. Management Patients who present with acute retention require urgent treatment and should undergo immediate catheterisation to relieve the obstruction. Those with mild to moderate symptoms can be treated by medication (Box 15.56). The first-line treatments are α1A-adrenoceptor blockers such as tamsulosin, which reduce the tone of smooth muscle cells in the prostate and bladder neck, thereby reducing the obstruction. The 5α-reductase inhibitors finasteride and dutasteride inhibit conversion of testosterone to the nine times more potent dihydrotestosterone in the prostate and so cause the prostate to reduce in size. This class of drugs is indicated in patients with an estimated prostate size of more than 30 g or a prostate-specific antigen (PSA) level of more than 1.4 ng/mL. Patients who fail to respond to a single drug may be treated with a combination of α-blockers and 5α-reductase inhibitors, since this is more efficacious than either agent alone. Symptoms that are resistant to medical therapy require surgical treatment to remove some of the prostate tissue that is causing urethral obstruction. This is usually achieved by transurethral resection of the prostate (TURP) but enucleation of the prostate by holmium laser or vaporisation by potassium-titanyl-phosphate (KTP) laser (Greenlight laser) is equally effective and has potentially fewer complications. Open surgery is rarely needed, unless the gland is very large. Prostate cancer Prostate cancer is the most common malignancy in men in the UK, with a prevalence of 105 per 100 000 population. It is also common in northern Europe and the USA (particularly in the African American population) but is rare in China and Japan. It is uncommon in India but the incidence is increasing. Prostate cancer rarely occurs before the age of 50 and has a mean age at presentation of 70 years. Pathophysiology Prostate cancers tend to arise within the peripheral zone of the prostate and almost all are adenocarcinomas. Metastatic spread to pelvic lymph nodes occurs early and metastases to bone, mainly the lumbar spine and pelvis, are common. Genetic factors are known to play an important role in pathogenesis, symptoms include urinary frequency, urgency of micturition and urge incontinence, although these are not specific to BPE. Some patients present suddenly with acute urinary retention, when they are unable to micturate and develop a painful, distended bladder. This is often precipitated by excessive alcohol intake, constipation or prostatic infection. Severity of symptoms can be ascertained by using the International Prostate Symptom Score (IPSS) questionnaire (Box 15.55), which serves as a valuable starting point for assessment of the patient. Once a baseline value is established, any improvement or deterioration may be monitored on subsequent visits. The IPSS may be combined with a quality-of-life score, in which patients are asked the following question: ‘If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?’ Responses range from 0 (delighted) to 6 (terrible). Patients may also present with chronic urinary retention. Here, the bladder slowly distends due to inadequate emptying over a long period of time. Patients with chronic retention can also develop acute retention: so-called acute-on-chronic retention. This condition is characterised by pain-free bladder distension, which may result in hydroureter, hydronephrosis and renal failure (high-pressure chronic retention, of which nocturnal incontinence is a pathognomonic symptom). On digital rectal examination (DRE), patients with BPE have evidence of prostatic enlargement with a smooth prostate gland. Abdominal examination may also reveal evidence of bladder enlargement in patients with urinary retention. Investigations The diagnosis of BOO secondary to BPE is a clinical one but flow rates can be accurately measured with a flow meter, 15.55 The International Prostate Symptom Score (IPSS) Symptom Question Example score Straining How often have you had to push or strain to begin urination?

Urgency How often have you found it difficult to postpone urination?

Hesitancy How often have you found that you stopped and started again several times when you urinated?

Incomplete emptying How often have you had a sensation of not emptying your bladder completely after you finished urinating?

Frequency How often have you had to urinate again less than 2 hours after you finished urinating?

Weak stream How often have you had a weak urinary stream?

Nocturia How many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

Total score

0 = not at all; 1 = less than one-fifth of the time; 2 = less than half the time; 3 = about half of the time; 4 = more than half of the time; 5 = almost always. A score of 0–7 indicates mild symptoms, 8–19 moderate symptoms and 20–35 severe symptoms. In the example shown, the patient had moderate symptoms. 15.56 Treatment for benign prostatic enlargement Medical • Prostate < 30 g: α-adrenoceptor blockers • Prostate > 30 g: 5α-reductase inhibitors ± α-adrenoceptor blockers Surgical • Transurethral resection of the prostate (TURP) • Laser enucleation • Laser vaporisation • Open prostatectomy

the presence and extent of local involvement. An isotope bone scan should be carried out if distant metastases are suspected (rare if the PSA is below 20 ng/mL); very high levels of serum PSA (> 100 ng/mL) almost always indicate distant bone metastases. Following diagnosis, serial assessment of PSA levels is useful for monitoring response to treatment and disease progression. Management Tumour confined to the prostate is potentially curable by radical prostatectomy, radical radiotherapy or brachytherapy (implantation of small radioactive particles into the prostate). These options should be considered only in patients with more than 10 years' life expectancy. Patients who are found to have small-volume, low-grade disease do not appear to require specific treatment but should be followed up periodically with PSA testing, DRE and a schedule of biopsies; this is known as active surveillance. Prostatic cancer, like breast cancer, is sensitive to steroid hormones; metastatic prostate cancer is treated by androgen depletion, involving either surgery (orchidectomy) or, more commonly, androgen-suppressing drugs. Androgen receptor blockers, such as bicalutamide or cyproterone acetate, may also prevent tumour cell growth. Gonadotrophin-releasing hormone (GnRH) analogues, such as goserelin, continuously occupy pituitary receptors, preventing them from responding to the GnRH pulses that normally stimulate luteinising hormone (LH) and follicle-stimulating hormone (FSH) release. This initially causes an increase in testosterone before producing a prolonged reduction, and for this reason the initial dose must be covered with an androgen receptor blocker to prevent a tumour flare. A small proportion of patients fail to respond to endocrine treatment. A larger number respond for a year or two but then the disease progresses. Chemotherapy with docetaxel can then be effective and provide a modest (around 3 months) survival advantage. Radiotherapy is useful for localised bone pain but the basis of treatment remains pain control by analgesia (p. 1331). Provided that patients do not die of another cause, the 10-year survival rate of patients with tumours localised to the prostate is 95%, but if metastases are present, this falls to 10%. Life expectancy is not reduced in patients with small foci of tumour. Testicular tumours Testicular tumours are uncommon, with a prevalence of 5 cases per 100 000 population. They occur mainly in young men aged between 20 and 40 years. They often secrete α-fetoprotein (AFP) and β-human chorionic gonadotrophin (β-hCG), which are useful biochemical markers for both diagnosis and prognosis. Seminoma and teratoma account for 85% of all tumours of the testis. Leydig cell tumours are less common. Seminomas arise from seminiferous tubules and represent a relatively low-grade malignancy. Metastases can occur through lymphatic spread, however, and typically involve the lungs. Teratomas arise from primitive germinal cells and tend to occur at a younger age than seminomas. They may contain cartilage, bone, muscle, fat and a variety of other tissues, and are classified according to the degree of differentiation. Welldifferentiated tumours are the least aggressive; at the other extreme, trophoblastic teratoma is highly malignant. Occasionally, teratoma and seminoma occur together. Leydig cell tumours are usually small and benign but secrete oestrogens, leading to presentation with gynaecomastia (p. 657). and multiple genetic loci have been found to predispose to the disease in genome-wide association studies. A family history of prostate cancer greatly increases a man's chances of developing the disease. Clinical features Most patients either are asymptomatic or present with lower urinary tract symptoms indistinguishable from BPE. On DRE the prostate may feel nodular and stony-hard, and the median sulcus may be lost, but up to 45% of tumours are impalpable. Symptoms and signs due to metastases are much less common at the initial presentation but may include back pain, weight loss, anaemia and obstruction of the ureters. Investigations Measurement of PSA levels in a peripheral blood sample, together with DRE, is the cornerstone of diagnosis. Prior to a PSA test, men should be given careful counselling about the limitations of the test: namely, a normal level does not exclude prostate cancer, while a high value does not confirm the diagnosis but will open a discussion about biopsy and possible future treatments with potential side-effects (Box 15.57). The need for radical treatment of localised prostate cancer is still not established; radical treatments have significant potential morbidity and mortality, yet early identification and treatment of prostate cancer may save lives. Current evidence suggests that population-based screening for prostate cancer with PSA is of limited value, due in part to the fact that over 700 patients would need to be screened to cure 1 man of prostate cancer. Individuals suspected of having prostate cancer, based on an elevated PSA and/or abnormal DRE, should undergo transrectal ultrasound-guided prostate biopsies. About 40% of patients with a serum PSA of 4.0–10 ng/mL or more will have prostate cancer on biopsy, although 25% of patients with a PSA of less than 4 ng/mL may also have prostate cancer. Occasionally, a small focus of tumour is found incidentally in patients undergoing TURP for benign hyperplasia. If the diagnosis of prostate cancer is confirmed, staging should be performed by pelvic MRI to assess 15.57 Advantages and disadvantages of prostate-specific antigen (PSA) testing in order to identify men with prostate cancer Advantages • Identification of prostate cancer at a treatable stage, which otherwise may not have been identified* Disadvantages • High false-positive rate: 50–60% of men with an elevated PSA will not have prostate cancer • High false-negative rate: 25% of men with a normal PSA have prostate cancer • Leads to further invasive tests (biopsy) with morbidity (e.g. sepsis or bleeding) • May lead to diagnosis of prostate cancer, which is often over-treated by surgery or radiotherapy with associated side-effects (e.g. impotence or incontinence) • If PSA is elevated but biopsy is normal, there is a potential need for further testing and associated anxiety *The advantages of identifying prostate cancer earlier than would be the case if the man developed symptomatic disease must be considered against the limitations of PSA testing.

 discuss matters frankly with the patient, and to establish whether there are associated features of hypogonadism (p. 655) and if erections occur at any other time. If the patient has erections on wakening, vascular and neuropathic causes are much less likely and a psychological cause should be suspected. Investigations Blood should be taken for glucose, lipids, thyroid function tests, prolactin, testosterone, LH and FSH. A number of further tests are available but are rarely employed because they do not usually influence management. These include nocturnal tumescence monitoring (using a plethysmograph placed around the shaft of the penis overnight) to establish whether blood supply and nerve function are sufficient to allow erections to occur during sleep; intracavernosal injection of prostaglandin E1 to test the adequacy of blood supply; internal pudendal artery angiography; and tests of autonomic and peripheral sensory nerve conduction. Management First-line therapy is usually with oral phosphodiesterase type 5 inhibitors, such as sildenafil, which elevate cyclic guanosine monophosphate (cGMP) levels in vascular smooth muscle cells of the corpus cavernosum, causing vasodilatation and penile erection. Co-administration of these drugs with nitric oxide donors, such as glycerol trinitrate, is contraindicated because of the risk of severe hypotension. Other treatments for impotence include self-administered intracavernosal injection or urethral administration of prostaglandin E1; vacuum devices that achieve an erection maintained by a tourniquet around the base of the penis; and prosthetic implants, either of a fixed rod or an inflatable reservoir. Psychotherapy involving the patient and sexual partner may be helpful for psychological problems. Erectile dysfunction associated with peripheral neuropathy and vascular disease is difficult to treat. If hypogonadism is detected, it should be managed as described on page 655. Further information Websites edren.org Renal Unit, Royal Infirmary of Edinburgh; information about individual diseases, protocols for immediate in-hospital management and more. edrep.org/resources Educational resources. nephron.com The links under ‘Physicians’ include useful urology pages, eGFR and other calculators, and other resources. renal.org/ckd UK Renal Association; current UK guidelines on the detection, referral and management of CKD. renalfellow.blogspot.co.uk/ Educational blog written by renal trainees for trainees. uroweb.org/guidelines European Association of Urology guidelines; current European guidelines on the management of all common urological conditions. Clinical features and investigations The common presentation is incidental discovery of a painless testicular lump, although some patients complain of a testicular ache. All suspicious scrotal lumps should be imaged by ultrasound. Serum levels of AFP and β-hCG are elevated in extensive disease. Oestradiol may be elevated, suppressing LH, FSH and testosterone. Accurate staging is based on CT of the lungs, liver and retroperitoneal area. Management and prognosis The primary treatment is surgical orchidectomy. Subsequent treatment depends on the histological type and stage. Radiotherapy is the treatment of choice for early-stage seminoma. Teratoma confined to the testes may be managed conservatively, but more advanced cancers are treated with chemotherapy, usually the combination of bleomycin, etoposide and cisplatin. Follow-up is by CT and assessment of AFP and β-hCG. Retroperitoneal lymph node dissection is now performed only for residual or recurrent nodal masses. The 5-year survival rate for patients with seminoma is 90–95%. For teratomas, the 5-year survival varies between 60% and 95%, depending on tumour type, stage and volume. Erectile dysfunction Causes of erectile failure are shown in Box 15.58. Vascular, neuropathic and psychological causes are most common. Exclusion of previously unrecognised cardiovascular disease is important in men presenting with erectile dysfunction. With the exception of diabetes mellitus, endocrine causes are relatively uncommon and are characterised by loss of libido, as well as erectile dysfunction. Erectile dysfunction and reduced libido occur in over 50% of men with advanced CKD or those on dialysis, and is a markedly under-diagnosed problem. It is important to 15.58 Causes of erectile dysfunction With reduced libido • Hypogonadism • Depression With intact libido • Psychological problems, including anxiety • Vascular insufficiency (atheroma) • Neuropathic causes (diabetes mellitus, alcohol excess, multiple sclerosis) • Drugs (β-blockers, thiazide diuretics)

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