21.4 Clinical investigation of renal disease 4781

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ESSENTIALS An accurate history and careful examination will determine the sequence and spectrum of clinical investigations required to make a diagnosis or decide on prognosis or treatment. Examination of the urine Midstream urine (MSU) sample—this standard investigation requires consideration of (1) macroscopic appearance—this may be sug- gestive of a diagnosis (e.g. frothy urine suggests heavy proteinuria); (2) stick testing—including for pH (<5.3 in an early-morning spe- cimen makes a renal acidification defect unlikely), glycosuria, spe- cific gravity (should be >1.024 in an early-morning or concentrated sample), nitrite (>90% of common urinary pathogens produce nitrite), and leucocyte esterase; and (3) microscopy—for cellular elements (in particular red cells, with the presence of dysmorphic red cells de- tected by experienced observers indicative of glomerular bleeding), casts (cellular casts indicate renal inflammation), and crystals. Quantification of proteinuria—this is important because the risk for progression of underlying kidney disease to endstage renal failure is related to the amount of protein in the urine. Quantification by 24-h urinary collection is cumbersome and unreliable in many patients, and has been replaced by estimation of the urinary albumin:creatinine ratio (ACR; normal is <2.5 mg/mmol for men and <3.5 mg/mmol for women) or protein:creatinine ratio (PCR; normal is <13 mg/mmol) on a spot sample. An ACR of 100 mg/mmol ap- proximately corresponds to proteinuria of 1.5 g/day, and 350 mg/ mmol to nephrotic-range proteinuria. Low molecular weight proteinuria—is caused by proximal tubular injury and can be detected with markers including α-glutathione-S- transferase, α1-macroglobulin, and retinol-binding protein. Estimation of glomerular filtration rate Knowledge of the glomerular filtration rate (GFR) is of crucial import- ance in the management of patients, not only for detecting the pres- ence of renal impairment, but also in the monitoring of all patients with or at risk of renal impairment, and in determining appropriate dosing of those drugs cleared by the kidney. Measurement of plasma creatinine remains the standard biochemical test used to assess renal function. Estimating the glomerular filtration rate (eGFR)—from a measure- ment of plasma

creatinine concentration, the standard method uses the simplified Modification of Diet in Renal Disease (sMDRD) formula, which was based on a predominantly Caucasoid North American cohort with chronic kidney disease, and requires know- ledge of the patient's sex, age, and ethnicity (but not their weight or height). On the basis of the eGFR, stages of chronic kidney disease (CKD) are classified as follows: Limitations of the eGFR—this has not been validated in people below 18 years of age, hospitalized patients, or those with acute kidney injury, pregnancy, oedematous states, muscle-wasting dis- orders, amputations, or malnourishment. Similarly, it has not been validated for extremes of age or body weight, or for ethnic groups other than whites of northern European origin and African Americans. Because of the inaccuracy of the MDRD equation, par- ticularly for those with eGFRs greater than 60 ml/min, a revised ver- sion (CKD-EPI) has been introduced. Other methods of measuring GFR—isotopic methods can provide the most accurate determination of GFR, but are not often required in routine clinical practice. Estimation of creatinine clearance with a 24-h urinary collection remains a useful test, particularly when there is reason to doubt the validity of the eGFR. Investigation of tubular function Proximal tubule—analysis of excretion of the following substances can assist in the diagnosis of proximal tubular disorders: (1) glucose—the maximum reabsorption rate for glucose (TmG) in the proximal tubule can
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> 90, with other evidence of renal disease 2 60–89, with other evidence of renal disease 3A 45–59 3B 30–44 4 15–29 5 <15, or receiving renal replacement therapy a The suffix (p) can be used to denote the presence of proteinuria as defined by a spot urinary ACR of ≥30 mg/mmol, which is approximately equivalent to a PCR of ≥50 mg/mmol (≥0.5 g/24 h).

section 21 Disorders of the kidney and urinary tract 4782 be determined following infusion of 20% dextrose and is normally about 15 mmol/litre (TmG/GFR); (2) phosphate—the theoretical maximum tubular threshold of phosphate (TMP/GFR) can be estimated by formula from the plasma and urinary phosphate and creatinine concentra- tions, or can be measured directly following infusion of phosphate; and (3) amino acids—five types of renal aminoaciduria are distinguished: di- basic amino acids, neutral amino acids (monoaminomonocarboxylic acids), glycine and imino acids, dicarboxylic amino acids, and general- ized amino aciduria (Fanconi's syndrome). Distal tubule—a water-deprivation test can help to distinguish pa- tients with primary or secondary nephrogenic or cranial diabetes insipidus from those with primary polydipsia, who may all present with polyuria. Renal-induced electrolyte and acid–base imbalances—(1) estimation of urinary free-water clearance is useful in the analysis of patients with hyponatraemia (see Chapter 21.2.1);
(2) estimation of transtubular po- tassium gradient is advocated by some as useful in analysis of disorders of potassium homeostasis (see Chapter 21.2.2); (3) tests of urinary acidification are discussed in Chapter 21.15. Renal imaging Ultrasonography—this noninvasive, safe, versatile, and (relatively) in- expensive technique is the first-line method for imaging the kidney and urinary tract in many clinical circumstances. Ultrafast multislice CT scanning—this allows resolution of 2 to 3 mm or less and has become the mainstay of renal imaging. CT urography can be performed with a combination of unenhanced, nephrogenic- phase, and excretory-phase imaging: the unenhanced images are ideal for detecting urinary calculi; renal masses can be detected and characterized with

the combination of unenhanced, nephrogenic- phase, and excretory-phase imaging; the excretory phase provides imaging of the urothelium. CT angiography is the first-line investiga- tion in the evaluation of acute renal trauma, assessment of tumour blood supply in cases of nephron-sparing surgery, and for the diag- nosis of renal artery stenosis and/or aneurysms. MRI—this is an alternative to CT scanning in patients who are al- lergic to conventional iodine-based radiocontrast media and has particular value in the staging of renal carcinoma and assessment of complex renal cysts. Magnetic resonance angiography tends to over- emphasize the significance of stenoses. Gadolinium contrast scanning should be carefully considered in patients with eGFR below 30 ml/ min because of the risk of nephrogenic systemic fibrosis, which limits the utility of magnetic resonance techniques for many renal patients. Renal nuclear medicine scanning—(1) dimercaptosuccinic acid (DMSA), used in estimation of differential renal function and detection of scarring (usually associated with reflux); (2) mercaptoacetyltriglycine (MAG3), used in detection of functionally significant obstruction, esti- mation of differential renal function, screening for renal artery stenosis, and monitoring of renal transplants. Fluorodeoxyglucose positron emission tomography (FDG-PET) scanning combines the functional aspects of a nuclear medicine scan with the anatomical definition of CT scanning and is used to investi- gate renal tumours and to diagnose and monitor large vessel vasculitis. Invasive techniques—these can allow therapeutic intervention as well as diagnosis, including antegrade or retrograde ureteropyelography (insertion of stents to relieve urinary obstruction) and angiography (angioplasty or stenting of the renal artery).
Renal biopsy A renal biopsy should be considered in any patient with disease af- fecting the kidney when the clinical information and other laboratory investigations have failed to establish a definitive diagnosis or prog- nosis, or when there is doubt as to the optimal therapy. However, renal biopsy has the potential to cause morbidity and (on rare oc- casions) mortality, hence its risk must be outweighed by the poten- tial advantages of the result to the individual patient. Biopsies which would be ‘of interest’ but ‘not in the patient’s interest’ should not be performed. Introduction The key to making any correct diagnosis depends on a careful his- tory and thorough examination. In patients with kidney disease, the history and examination should attempt to differentiate acute from chronic kidney disease, single-organ system involvement from multisystem disease, and obstruction from intrinsic or prerenal dis- ease. Kidney disease may be associated with preceding infections and the ingestion of drugs or herbal remedies. An accurate history and careful examination will determine the sequence and spectrum of clinical investigations required to make a diagnosis or decide on prognosis or treatment. Examination of the urine Urine collection To minimize contamination, standard investigation is of a mid- stream urine (MSU) sample. Voiding from a full bladder containing at least 200 ml of urine should remove urethral organisms before the MSU is collected. Even so, in women, vaginal leucocytes and bacteria may contaminate the urine, and men should retract the foreskin to minimize contamination. Suprapubic aspiration is the technique of choice in babies and infants, and occasionally in adults who cannot cooperate to provide an MSU. The second urine of the morning is the best for microscopy as it is still acidic and concen- trated, but without the overnight stay in the bladder that results in the degeneration of casts and cells. Cell lysis can occur in both hypo- tonic and alkaline urine. Only the first 10 ml of the stream should be collected in cases of suspected urethritis. Macroscopic appearance Fresh urine usually has a yellow colour due to the presence of urochromes, but occasionally it will have a milky appearance due to pus, spermatozoa, insoluble phosphates in alkaline urine (sometimes seen following heavy meals), or occasionally in cases of chyluria, or urate crystals in acid urine. Foamy or frothy urine is typical of heavy proteinuria. Certain agents and conditions can discolour urine. Pink to red coloration Haematuria may result in a range of colours from smoky pink through to

port-wine red in cases of frank macroscopic haematuria. Other causes of a pink or red urine include eating sweets containing aniline dyes, beetroot, blackberries and rhubarb, or other foodstuffs containing anthocyanins; haemoglobin; myoglobin; some drugs including rifampicin, phenazopyridine, phenindione, phenol- phthalein, and senna-containing laxatives; chronic poisoning with lead or mercury; and (if the urine is left to stand) porphyrins in cases of acute intermittent porphyria. Blue or green coloration Blue or green coloration can be caused by pseudomonas urinary sepsis, methylene blue, biliverdin, triamterene, amitriptyline, chlorophyll-containing breath mints (Clorets), excessive use of mouthwash and deodorants, magnesium salicylate (Doan’s pills), phenyl salicylate, guaiacol (in cough remedies), thymol (in volatile oils and horesemint), iodochlorhydroxyquin, tolonium, Evans blue, methocarbamol, Diagnex blue, indigo blue, resorcinol, azuresin, bromoform, and occasionally propofol and indomethacin. Phenol and lysol can result in a green or black discolouration. Orange coloration Orange coloration can be caused by dehydration, and drugs including anthraquinone-containing laxatives, rifampicin, phenazopyridine, sulfasalazine, and some chemotherapeutic agents, and excess urobilinogen particularly in patients with obstructive jaundice. Yellow urine Yellow urine may be found in patients prescribed mepacrine or phenacetin, those taking excessive amounts of riboflavin, and icteric patients with conjugated hyperbilirubinaemia. Black or brown urine Alkaptonuria results in black or brown urine, whereas myoglobin and melanin only lead to black urine on standing. Other causes of brown urine include high dietary ingestion of fava beans, rhubarb and aloe, bilirubin, chloroquine, l-dopa, niridazole, furazolidone, laxatives containing senna or cascara, methocarbamol, metronida- zole, notrofurantoin, phenazopyridine, and primaquine—after standing—haemoglobin and myoglobin. As mentioned earlier, phenol and lysol can result in a black or green discolouration. Purple urine Patients with indwelling urinary catheters may present with the purple urine bag syndrome, when their urine becomes infected, typically with Gram negative Providencia stuartii and rettgeri, Klebsiella pneumoniae, Proteus mirabilis, Escherichia coli, Morganella morganii, and Pseudomonas aeruginosa, as these bac- teria may contain the enzyme indoxyl phosphatase which converts indoxyl sulphate to the red indirubin and blue indigo compounds. Stick testing The upper limit of normal for protein excretion in the urine is 128 mg/24 h. Although albumin is the largest single component, more than half of the protein content comprises low molecular weight proteins and protein fragments. Commercial sticks such as Albustix are very sensitive, detecting protein in urine starting at con- centrations around 100 mg/litre. Since these sticks detect protein on a concentration basis using bromocresol green as an indicator dye, the results they give are affected by urine flow rate and urine dilu- tion or concentration. The sticks are treated with a buffer to keep their pH constant: an elevated urinary protein concentration can erroneously be recorded if the buffer is washed off by leaving the stick in the urine for too long, and with very alkaline urine. Some antiseptics used to clean the skin, including cetrimide and chlor- hexidine, may also react and cause a false-positive result. More re- cently, antibody-based dipsticks have been developed for detecting microalbuminuria. pH Normal urine is slightly acidic, but can vary between pH 4.5 and 8.0. If an early-morning urine specimen is under pH 5.3, then there is unlikely to be a significant defect in urinary acidification. Alkaline pH is often found in urine infected with urea-splitting bacteria. In some cases of urinary stone disease, particularly in cystinuria and urate nephropathy, crystal solubility is greater in alkaline urine, and patients should regularly check their urine pH. Haemoglobin and myoglobin are also more soluble in alkaline urine, hence maintaining a forced alkaline diuresis is important in the manage- ment of patients following tumour lysis and those with rhabdo- myolysis or haemoglobinuria. Glycosuria The stick reaction is based on glucose oxidase, which releases hydrogen peroxide from glucose, so producing a graded colour change by oxidizing an indicator. This reaction is specific for glu- cose and does not detect other sugars. The reaction can be blocked by large doses of ascorbic acid. A positive stick test for glucose must be interpreted in light of the plasma glucose level as glycosuria may reflect a defect in renal tubular glucose absorption. Specific gravity Specific gravity is a measure of the number of particles dissolved in a litre, whereas osmolality is the number of particles per kilo- gram. Protein and glucose increase the specific gravity more than the osmolality as they are dense particles. In normal patients, the early-morning, or concentrated, urine sample should have a specific gravity of 1.024 or more. Nitrite stick test Nitrite sticks contain an aromatic amine that reacts with nitrites, which are produced by bacterial reduction of nitrate, to form a pink-coloured diazonium complex. More than 90% of the common urinary pathogens are nitrite-forming bacteria. However, pseudo- monas, Staphylococcus albus, S. saprophyticus, and Enterococcus faecalis may have minimal or no nitrite-producing capacity. Other false-negative results may be obtained in alkaline urine, in patients taking large doses of vitamin C, and with frequent voiding of dilute urine when the urinary nitrite concentration is too low. Leucocyte esterase stick test This stick test is based on the presence of a leucocyte esterase and is very specific for the presence of urinary leucocytes, both intact and lysed. This test may be more accurate than microscopy when the urine is alkaline or hypotonic. However, the test can be inhibited by high concentrations of glucose (20 g/litre or more), ketones, and antibiotics including cefalexin, cefalotin, nitrofurantoin, tetracyc- line, and tobramycin. The sensitivity of this test is also reduced when the specific gravity of the urine is high, for instance in the presence of a heavy proteinuria.

section 21 Disorders of the kidney and urinary tract 4784 Urine microscopy To obtain reproducible results, urine should be processed in a standard manner and examined under the microscope as soon as possible. In the author’s institution, a few drops of acetic acid (10% v/v) are added to ensure a pH of 6.0 or less; then 10 ml of urine is centrifuged for 5 min at 1500 rev/min (750 g), following which 9.5 ml of supernatant is removed and the deposit resuspended. One drop (50 µl) is placed on a microscope slide and covered with a standard coverslip (24 × 32 mm). Although phase-contrast micros- copy is an advantage in identifying red cells and casts, a standard microscope will suffice. A semiquantitative assessment of casts is made at low power (160×) and other elements at high power (400×), expressing the counts as numbers per field. Normal urine contains 1 or 2 leucocytes per high-power field (HPF), 1 erythrocyte per 2 or 3 HPF, 1 tubular cell per 10 HPF, and both hyaline casts (1 per low- power field, LPF) and granular casts (1 per LPF). Physical exercise can result in haematuria and cylindruria for several hours. Stains such as modified Sternheimer’s stain (Sedi-stain) can be used to help differentiate renal tubular cells from leucocytes. To improve the de- tection of casts, urine can be filtered through a 5-µm Millipore filter, and the retained casts stained with Papanicolaou’s stain. Cellular elements The morphology of the erythrocytes in the urine can give valuable information as to the source of bleeding. Those which have passed through the glomerulus and then along the renal tubule can become distorted or dysmorphic, whereas those originating from other sources within the urinary tract, such as the bladder, typically show much less evidence of damage so that they more closely resemble erythrocytes in the peripheral blood and are termed isomorphic. To establish a diagnosis of glomerular haematuria there should be a min- imum of three different forms of dysmorphic erythrocytes present. One particular type of dysmorphic erythrocyte, the acanthocyte, is reported to have 52% specificity and 98% sensitivity for glomerular haematuria when the acanthocyte count is 5% or more. However, not all workers have found erythrocyte morphology to be useful in discriminating glomerular from nonglomerular bleeding, and the physician who only occasionally examines urine under the micro- scope is unlikely to obtain clear, reproducible, and useful discrimin- ation between dysmorphic and isomorphic cells. Some centres use automated haematological cell counters (Coulter counter) to assess red cell morphology in both urine and peripheral blood. The distribution pattern for red cell size for lower urinary tract haematuria is similar to that of the peripheral blood, with a relatively narrow size range and a high frequency distribution curve, whereas the typical pattern for dysmorphic haematuria is one of a broader range of red cell sizes, with a lower frequency distribution. To have any reliability, urine samples must be processed rapidly by those who do it regularly. Microscopy may also reveal renal tubular epithelial cells. These cells are shed into the urine in acute tubular necrosis, in response to certain drugs (both nephrotoxic and ischaemic), and also in acute renal allograft rejection. In patients with nephrotic syndrome, these cells are seen as oval fat bodies, laden with lipid droplets. Squamous epithelial cells from the urethra and vagina and transitional cells from the ureter and bladder may also be present in normal urine. Urine cytology may reveal malignant transitional epithelial and/or metaplastic squamous cells from the bladder. During infection, the urine may contain large numbers of leuco- cytes and bacteria. When large numbers of leucocytes are present in the absence of bacteria (so-called sterile pyuria), then a variety of conditions should be considered: urinary stone disease, analgesic nephropathy, interstitial nephropathy, proliferative glomerulo- nephritis (rarely), renal tuberculosis, schistosomiasis, and partially treated bacterial urinary tract infection. Phase-contrast microscopy can distinguish lymphocytes from neutrophils, but eosinophils can only be identified with specific stains (Hansel’s stain). Urinary eo- sinophilia classically occurs in cases of acute interstitial nephritis, typically due to drugs, and also in cholesterol atheroembolic disease. Urinary casts Casts form from the transformation of Tamm–Horsfall glycopro- tein, secreted by the distal tubular cells, into a gel matrix. They typically assume a tubular structure. Hyaline casts only contain Tamm–Horsfall glycoprotein and are found in a variable amount in the urine of normal subjects (Fig. 21.4.1). Fever, cardiac failure, strenuous exercise, and some drugs, such as furosemide and ethacrynic acid, increase hyaline cast excretion. During pas- sage through the distal tubule and collecting duct, a variety of proteins, pigments, and cells can adhere to the Tamm–Horsfall protein, producing a wide variety of casts. Granular casts have deposits of either fine or coarse protein granules (Fig. 21.4.2). Although they may occur in normal subjects, or after exercise, they are typically found in cases of parenchymal renal disease. In patients with proteinuria, the protein deposited comes from the glomerulus, whereas in acute tubular necrosis, the protein comes from degenerate tubular cells. Broad waxy casts are much larger Fig. 21.4.1 Papanicolaou-stained urine showing a hyaline cast with both normal transitional and squamous cells and renal tubular cells. Courtesy of Dr Deery. Fig. 21.4.2 Unstained urine specimen showing a granular cast.

than normal casts and have clear-cut edges: they are formed in dilated hypertrophied tubules, as found in patients with chronic renal failure. Casts containing erythrocytes (red cell casts) indi- cate renal bleeding and are typically found when there is acute glomerular inflammation caused by glomerulonephritis or vascu- litis (Fig. 21.4.3). White cell casts (containing leucocytes) can be found in proliferative glomerulonephritis, acute interstitial neph- ritis, and acute pyelonephritis. Crystals Urine may contain several types of crystals, depending on the pH. The presence of a few crystals of uric acid, calcium oxalate, or cal- cium phosphate is usually not clinically relevant, although thin hexagonal crystals of cystine are a marker of cystinuria. In a few cases, crystalluria may be associated with intratubular obstruc- tion and acute kidney injury. Such cases would include acute uric acid nephropathy, ethylene glycol poisoning, and drugs including aciclovir, amoxicillin, indinavir, naftidrofuryl oxalate, sulfadiazine, and vitamin C. Urine cytology The importance of urine cytology in detecting urological malig- nancy is well established. However, exfoliated cells, particularly single cells, deteriorate rapidly and degenerative changes may be present with an hour. Collecting MSU samples in 5 ml of absolute alcohol helps slow down bacterial growth, and it is preferable to prepare the sample first and then stain the cells, rather than fix the cells and then prepare the sample. Standard preparation would in- clude centrifugation at 1500 rpm for 5 min, followed by a further cytocentrifugation at 1200 rpm for 5 min to prepare a cytospin preparation, which can then be spray fixed using a mixture of 80 ml polyethylene glycol, 690 ml isopropanol, 170 ml acetone, and 60 ml distilled water. Following a minimum of 5 min drying time, cytospin preparations can be stained using Papanicolaou's tech- nique with a Shandon Linistain GLX. In addition to examining the urine for dysplastic or malignant cells in cases of bladder, pros- tate, and kidney cancers, urine cytology may also be helpful in establishing viral infections following renal transplantation (cyto- megalovirus and BK virus inclusions in renal epithelial cells.), and in acute kidney injury necrotic tubular cells may be present following ischaemic renal injury, but may also be present fol- lowing administration of antibiotics (aminoglycosides and ceph- alosporins) and chemotherapeutic agents. Urine cytology may also act as an adjunct to urine microscopy in assessing cellular components of urine (red and white blood cells, eosinophils, casts, etc.) and bacteriuria. Measurement of proteinuria Quantification of proteinuria is important as the risk for progres- sion of underlying kidney disease to endstage renal failure is related to the amount of protein in the urine. Traditionally, proteinuria has been measured using 24-h urine collections and expressed as grams per day. This has the advantage that it averages out protein excre- tion and is not therefore affected by its normal diurnal variation (less overnight and first thing in the morning) or urine concentration. Several different methods are used to measure the protein content of 24-h urine collections, ranging from the biuret method, which uses a copper-based method to precipitate proteins, to dye-binding methods using Coomassie Brilliant Blue as the indicator. These are more accurate than the turbidimetric methods, which use trichloro- acetic or sulphosalicylic acid and measure turbidity with a densi- tometer. Radiocontrast media and some drugs (including penicillin, sulphonamides, and tolbutamide) may give false-positive results for proteinuria with the sulphosalicylic acid method. The biuret method measures total proteins, whereas the turbidimetric method provides different readings for albumin and globulins, as may do the dye- binding methods. However, because of the inherent problems of accuracy and reliability with 24-h urine collections, the assessment of protein in spot urine samples has become the standard method of as- sessing proteinuria in routine clinical practice. Urinary albumin concentration is measured by a variety of methods based on an antibody technique for detecting serum albumin, including radio- immunoassay, nephelometry, immunoturbidity, and enzyme- linked immunosorbent assay (ELISA). Under resting conditions, urinary creatinine excretion is relatively constant throughout the day, hence to overcome the problems of timing of urinary collections, proteinuria in spot urine samples is expressed as an albumin:creatinine ratio (ACR; normal is <2.5 mg/mmol for men and <3.5 mg/mmol for women in a daytime urine or 24-h col- lection, and <1.5 mg/mmol for an overnight or early-morning sample). An ACR of 100 mg/mmol approximately corresponds to 1.5 g/day, and 350 mg/mmol to nephrotic-range proteinuria. To improve the reliability of trends in serial samples over time, then as urinary protein has a diurnal variation, it is advisable to com- pare similar timed samples (morning or afternoon etc.) because of the diurnal variation of urinary protein excretion. However, albumin is not the only protein in urine and the rela- tionship between albumin and total urinary protein is not linear, with a ratio of 50% albumin with a urinary protein of 300 mg/litre increasing to 70% at 1000 mg/litre. As the measurement of protein in spot urine samples is cheaper than albumin, it has been suggested that, for patients with more than 1+ proteinuria on dipstick testing, the protein:creatinine ratio (PCR) should be used in routine clinical practice. The normal PCR is less than 13 mg/mmol, with a dipstick value of 1+ roughly equiva- lent to a PCR of 45 to 149 mg/mmol and ACR above 30 mg/mmol, a dipstick of 2+ to a PCR of 150 to 449 mg/mmol, and 3+ to 450 mg/ mmol or more. Aside from their use to replace 24-h urine collections, spot urine collections are particularly useful in the diagnosis of orthostatic Fig. 21.4.3 Papanicolaou-stained urine deposit showing a red cell cast.

section 21 Disorders of the kidney and urinary tract 4786 proteinuria, in other words where the patient has a normal urinary protein excretion when recumbent, or overnight, but has marginally increased proteinuria in the ambulant or daytime sample. The ACR should not be measured during acute illness, menstru- ation, or intercurrent illness as these will temporarily increase the degree of proteinuria. Microalbuminuria Various antibody-based assays for albumin can detect an increased urinary albumin excretion in patients with normal levels of protein- uria. High-performance liquid chromatography detects more urinary albumin than the radioimmunoassay and other serum antibody- based tests. Normoalbuminuria is defined as an excretion rate of 20 µg/min or less. Proteinuria is usually detectable on dipstick testing at rates of over 200 µg/min, hence microalbuminuria is defined as an excretion rate between 20 and 200 µg/min. The albumin excretion rate is some 25% higher during the day than the night. The classification of abnormal urinary albumin excretion is shown in Table 21.4.1. There is a good correlation between the morning albumin excretion rate and the ACR in the first urine sample of the morning. A further advantage of spot urines is that patients can provide a sample when they attend the clinic: provided these are taken at the same time and the patient’s dietary intake is relatively constant, they are very useful in assessing patients over time. A further advantage of measuring the ACR instead of albumin excretion rate is that the former, but not the latter, eliminates the need for timing of urinary samples. Microalbuminuria is not only an adverse factor for the progres- sion of diabetic renal disease, but is also predictive of cardiovas- cular events in both the diabetic and nondiabetic population. To grade this increased risk, then the United Kingdom (UK) National Institute for Clinical Excellence (NICE) guidelines proposed a grading system for ACR from grade A normal to mildly increased risk (< 3 mg/mmol), B moderately increased risk (3-30 mg/min) and C severe risk (>30 mg/min). In addition to those with diabetes, microalbuminuria may be found in patients with hypertension, car- diac failure, treatment with chemotherapeutic agents, and following a pyrexial or viral illness. Similarly, microalbuminuria may be pre- sent in healthy subjects after exercise and during normal pregnancy. Selectivity of proteinuria Patients with glomerular disease typically have a nonselective pro- teinuria, with a similar clearance of both high and low molecular weight plasma proteins. However, those with minimal change dis- ease may have selective proteinuria, with clearance of predominantly low molecular weight proteins, the demonstration of which is useful in paediatric practice where patients are often treated with steroids without a renal biopsy. Most laboratories compare the clearance of IgG as the large molecular weight protein (150 kDa) to that of albumin (or transferrin, 88 kDa) as the low molecular weight protein. Both plasma and spot urine samples are required. Protein concentrations are measured ei- ther by laser nephelometry or radial immunodiffusion. Nonselective proteinuria is taken as an ([IgG]urine/[IgG]plasma) × ([transferrin]plasma/ [transferrin]urine) ratio of 0.2 or more,

whereas selective proteinuria is taken as a ratio of 0.1 or less. Spill-over proteinuria Patients with myeloma, some types of amyloidosis, and those with reticuloendothelial disorders may have a spill-over proteinuria due to glomerular filtration of complete and incomplete κ and λ chains and immunoglobulin light chains. These low molecular weight pro- teins are not detected by simple urine stick testing, or by standard biochemical methods to determine urine protein concentration. Thus, when clinically appropriate, urine should specifically be sent for immunoelectrophoresis to exclude myeloma. However, light chains in particular may still not be detected, hence further inves- tigation with specific antisera may be required if their presence is suspected. Renal tubular proteinuria Interstitial renal disease can result in proteinuria, usually of less than 2 g/day. Proximal tubular injury leads to increased low molecular weight proteinuria, characterized by an excess of intestinal alkaline phosphatase, N-acetylglucosaminidase, retinol-binding protein, tissue-specific alkaline phosphatase, α-glutathione-S-transferase (α-GST), α1-macroglobulin, and β2-microglobulin. By contrast, Tamm–Horsfall glycoprotein and α-GST are increased in distal tubular injury. β2-Microglobulin is freely filtered at the glomerulus and then re- absorbed in the proximal tubule, such that less than 1% of the filtered load is excreted in the urine of normal subjects (normal is <370 μg/ 24 h). Thus urinary β2-microglobulin excretion has been used as a marker of proximal tubular damage. However, β2-microglobulin is unstable in urine, and its excretion can be affected both by an in- creased production rate (found in cases of myeloproliferative dis- ease, chronic inflammatory states, and acute liver disease) and by saturation of β2-microglobulin tubular uptake due to an excess of dibasic amino acids. Table 21.4.1 Classification of abnormal urinary albumin excretion 24-h urine albumin
(mg/24 h) Overnight albumin
(μg/min) Spot albumin
(mg/litre) Spot urine ACR (mg/mmol) PCR (mg/mmol) Normal <15 <10 <10 M <1.25 F <1.75 <13 Microalbuminuria 30 to <300 20 to <200 20 to <200 M 2.5 to <25 F 3.5 to <35 16 to <160 Macroalbuminuria

> 300 200 200 M >25 F >35 160 ACR, albumin:creatinine ratio; F, female; M, male; PCR, protein:creatinine ratio. The normal ACR ratio is lower in men than women due to higher urinary creatinine excretion.

21.4 Clinical investigation of renal disease 4787 More reliable markers of tubular proteinuria are now available. These include α-GST, α1-macroglobulin, and retinol-binding pro- tein. Turbidimetric or enzyme assays are now available. Results are expressed as either excretion rates (e.g. normal α-GST is <12.5 ng/min or <11.5 μg/litre) or as a ratio to urinary creatinine (e.g. normal reference range for retinol-binding protein:creatinine is <0.019 mg/mmol). Typically in cases of renal tubular protein- uria the ratio of retinol-binding protein:creatinine is equal to or greater than that of albumin:creatinine, whereas normally the ratio of urinary albumin:creatinine is twice that of retinol-binding protein:creatinine. These tests of renal tubular proteinuria are helpful in investigating patients with suspected Chinese herbal nephropathy, Asian subcon- tinent nephropathy, and Balkan nephropathy, and they may also be useful in monitoring progression of these diseases and other tubulointerstital diseases such as adult polycystic kidney disease. Industrial workers exposed to heavy metals and organic chemicals, such as those used in the dry-cleaning industry, may develop interstitial renal disease characterized by increased urinary low molecular weight proteinuria. Urinary biomarkers in acute renal injury Advances in urinary proteomics have led to the search for biomarkers of acute kidney injury and acute renal transplant rejection. Urinary biomarkers fall into three main categories: (1) markers of kidney function, similar to creatinine, typified by cystatin C; (2) markers of the severity of the inflammatory response made by the individual to the insult, including neutrophil gelatinase-associated lipocalin (NGAL), liver type fatty acid binding protein, and urinary IL-18; (3) markers of kidney damage, such as kidney injury molecule (KIM-1), urinary enzymes (α1-microglobulin, α1-acid glycoprotein, N-acetyl-β-d-glucosaminidase, γ-glutamyltranspeptidase, and alkaline phosphatase) and albumin; and (4) inducers of cell cycle G1 arrest, including urinary insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2). Whereas these biomarkers are associated with acute kidney injury, others such as urinary hepcidin-25 have been reported to be associated with a reduced risk of kidney injury, and urinary hepatocyte growth factor with an earlier renal recovery. Preliminary single-centre studies in children with pre-existing normal renal function have shown that urinary biomarkers are more effective in predicting both acute renal injury and severity than changes in serum creatinine, as creatine generation and conversion to creatinine typically falls during acute kidney injury. However, these encouraging findings have not always been replicated in multicentre studies that included patients with established chronic kidney disease, hence urinary biomarkers currently remain a research tool in acute kidney injury. However, whereas many of these biomarkers were originally only available as research assays, or required specialized techniques such as time of flight mass spectroscopy, commercial ELISA assays are now becoming available. Currently NGAL and KIM-1 appear the most promising as markers of the severity of acute kidney injury, and the inducers of cell cycle G1 arrest (IGFB7 and TIMP-2) as early biomarkers of acute renal injury, whereas urinary hepcidin-25 appears to have a negative predictive effect. Similarly, further studies are required to determine the role of urinary biomarkers such as granzyme in distinguishing renal transplant rejection from ischaemic renal injury. Studies evaluating the role of urinary biomarkers in assessing progression of chronic kidney disease are currently under way. Estimation of glomerular filtration rate Biochemical tests Knowledge of the glomerular filtration rate (GFR) is of crucial importance in the management of patients, not only for detecting the presence of renal impairment but also in the monitoring of all patients with or at risk of renal impairment, and in determining appropriate dosing of those drugs cleared by the kidney. Measurement of plasma creatinine remains the standard biochemical test used to assess renal function. Unfortunately, the plasma creatinine concentration is not linearly related to the GFR, hence some 30% of patients with significantly impaired renal function still have a plasma creatinine value within the normal range (<120 μmol/litre). Creatinine Creatine, which is endogenously synthesized in the liver or exogenously supplied by meat in the diet, is transported to muscle and converted to creatinine by nonenzymatic dehydration. Muscle mass represents some 98% of the total body creatine pool. Thus gender, racial, and age-related differences in body composition, physical training and exercise, muscle-wasting diseases, paralysis, and intercurrent illnesses will all affect the production rate of creatinine and therefore both the plasma creatinine concentration and urinary creatinine excretion (Table 21.4.2). Hence in young children there is a steady increase in the plasma creatinine level as their muscle mass increases. Dietary influences will affect plasma creatinine levels, with a reduction Table 21.4.2 Factors affecting creatinine generation Factor Effect on serum creatinine Ageing Decreased Female sex Decreased Race or ethnic group (compared with white) Black Increased Hispanic Decreased

Oriental Decreased South Asian Decreased Body habitus Muscular Increased Amputation Decreased Obesity Decreased Chronic illness Cirrhosis, malnutrition, chronic inflammation, cancer, severe cardiovascular or respiratory disease, hospitalized patients Decreased Neuromuscular diseases Decreased Hypothyroidism Increased Diet Vegetarian diet Decreased Ingestion of cooked meat Increased

in strict vegans and increased values in those with a high meat intake (particularly stewed meat: cooking leads to the conversion of creatine to creatinine) or those taking creatine supplements. For any individual, the plasma creatinine level is relatively constant throughout the day, although there is a tendency for it to increase slightly in the afternoon. Creatinine is not only freely filtered by the glomerulus but is also secreted into the renal tubule. Creatinine reabsorption may occur at low urinary flow rates, such as in congestive cardiac failure, and cir- rhosis. The relative proportion of renal tubular creatinine secretion to that filtered increases as renal function declines. In addition, in oedematous states such as nephrotic syndrome, calculated creatinine clearance exceeds inulin clearance, suggesting increased tubular cre- atinine secretion. Several drugs are known to block the tubular secre- tion of creatinine and thus cause an increase in the serum creatinine level: these include the diuretics amiloride, spironolactone, and triamterene; also cimetidine, aspirin, probenecid, and trimethoprim. The most accurate method of measuring plasma creatinine is by isotope dilution mass spectrometry (IDMS), followed by enzym- atic methods, but these are costly compared with the standard Jaffé assay. Most laboratories therefore measure plasma creatinine using standard automated analysers that assess the chromogenic product of creatinine and alkaline picrate (Jaffé reaction). Table 21.4.3 lists some substances which in high concentration can act directly or indirectly as chromogens, or affect the background control blanks, and so result in a spurious increase in the plasma creatinine level. In clinical practice, these may lead to an overestimation of creatinine in people with poorly controlled diabetes, and an underestimation in deeply jaundiced patients, such as those with primary biliary cir- rhosis. Blank and more recently compensated Jaffe rate reactions have been introduced in an attempt to overcome some of these tech- nical problems, but other enzymatic methods may provide greater accuracy, although at potentially greater cost. Reciprocal creatinine or logarithm of creatinine values As the plasma creatinine level roughly doubles for every 50% re- duction in GFR, expressing (transforming) the results as the reciprocal or logarithm is useful in assessing serial plasma values, which changes the graph from an exponential to a straight-line plot. The advantage of using a straight-line plot of plasma creatinine is that it allows the rate of renal decline to be calculated, which can then be used to predict the onset of endstage renal failure and the require- ment for dialysis treatment in many patients. The reciprocal cre- atinine plot assumes a constant rate of loss, whereas the logarithm a constant fractional loss of renal function. Patients with diabetic nephropathy tend to have a faster rate of decline in renal function than those with glomerular disease, who tend to have a faster rate than those with tubulointerstitial renal disease. In addition, it is easier to assess the effect of treatment interventions on the progression of renal disease by analysing transformed data, and also to recognize when there has been a sudden and unexpected deterioration in function that requires urgent investigation. Prediction of creatinine clearance from the plasma creatinine level and estimation of GFR (eGFR) Despite the potential inaccuracies in the determination of plasma creatinine, variations in endogenous creatinine production rates, and the relative increase in renal tubular and intestinal creatinine secretion with deteriorating renal function, formulas based on the plasma creatinine level are used in clinical practice to estimate cre- atinine clearance. The first commonly used equation, validated in adults, was the formula of Cockcroft and

Gault, later modified by Gault: Creatinine clearance (140 age) weight(kg) 72 plasma creatini

− × × ne concentration(mg/dl) Or Creatinine clearance (ml/min) 1.2 weight(kg) 72 plasma creat

× × inine concentration(mol/litre) µ In the original formula there was a different equation for women, with a factor of 0.85 (instead of 1.2) to allow for the lower rate of cre- atinine production in women due to differences in their body com- position. As creatinine turnover is affected by muscle mass and body size, Salazar and Corcoran modified the Cockcroft–Gault equation to correct for size by using an estimate of fat free weight: Male: 137 age yr 0.285 wt kg 12.1 ht m /51 seru (( )) ([( )] [( )]) 2 − × × + × × m creatinine mg/dl ( ) Female: 148 age yr 0.257 wt kg 9.74 ht m /60 seru (( )) ([( )] [ ]) 2 − × × + × × m creatinine mg/dl ( ) (To convert creatinine µmol/litre to mg/dl, divide by 88.4.) Similar equations were developed for children:

Schwartzequation: GFR ml/min/1.73 m 0.55 ht m /serum cre ( ) [( )] 2 = × atinine mg/dl ( ) Counahan Barratt equation: GFR ml/min/1.73 m 0.43 ht m ( ) [( )] 2 −

× /serum creatinine mg/dl ( ) Although these formulas may be helpful in clinical practice to provide an estimation of renal function (eGFR), they are not al- ways accurate, particularly in people with diabetes and in African Americans (due to differences in body composition). Another equation was developed in 1999 following the Modification of Diet in Renal Disease (MDRD) trial, based on 1628 adult, predominantly Caucasoid patients in the United States of Table 21.4.3 Compounds that can affect the measurement of plasma or urinary creatinine concentration Endogenous compounds Exogenous compounds Protein Acetohexamide Ketones Cephalosporins Ketoacids 5-Fluorocytosine Glucose Methanol metabolites Fatty acids Phenylacetylurea Urate Dopamine Urea Bilirubin

America with chronic kidney

disease, and this was further revised in 2005 as the simplified MDRD equation (sMDRD): eGFR ml per m serumcreatinine mg dl ( ) [( )] (/min . / . 1 73 175 2 1 154

× × − age inyears if female if black) ( ) ( ) . . . − × × 0 203 0 742 1 212 eGFR ml per m serumcreatinine mol litre ( ) ([( )/ . /min . / 1 73 175 1 2 = × µ 004 0 011312 1 154 1 212] .) ( ) ( ) . . × × − − age inyears if black The sMDRD equation has the advantage over the Cockcroft–Gault and many other formulas in being easier to calculate as it does not require knowledge of the patient’s weight, and their sex and age are routine demographics collected for sample identification. Use of the sMDRD equation has now been introduced into standard clinical practice in the United States of America, the United Kingdom, and Australia to define stages of chronic kidney disease, the intention being to encourage recognition of renal impairment at an early stage in the population at large, and therefore allow management of risk factors to reduce both renal progression and cardiovascular risk (Table 21.4.4). The Kidney Disease Improving Global Outcomes (KDIGO) group suggested combining both CKD grade and urinary proteinuria to risk assess patients for adverse events. Because of the inaccuracy of the MDRD equation for patients with an eGFR of 60 ml/min per 1.73 m2 or greater, a further modi- fication has been published, termed CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration): For men with serum creatinine <0.9 mg/dl: GFR ml/min per 1.73 m2 = 141 × (serum creatinine/0.9)−0.411

= 0.993age = 1.159 (if black) For men with serum creatinine >0.9 mg/dl: GFR ml/min per 1.73 m2 = 141 × (serum creatinine/0.9)−1.209

= 0.993age = 1.159 (if black) For women with serum creatinine <0.7 mg/dl: GFR ml/min per 1.73 m2 = 144 × (serum creatinine/0.7)−0.329

= 0.993age = 1.159 (if black) For women with serum creatinine >0.7 mg/dl:
GFR ml/min per 1.73 m2 = 144 × (serum creatinine/0.7)−1.209

= 0.993age = 1.159 (if black) (Divide by 88.4 to convert serum creatinine µmol/litre to mg/dl.) However, these equations have not been validated for elderly pa- tients or those from ethnic minorities. Furthermore, they were derived based on iothalamate urinary clearances, which themselves have inherent inaccuracies, both because of the requirement for urinary collections, and also the relative importance of nonrenal ex- cretion at low levels of GFR. Further refinements to the predictive equations will probably be developed. The first problem in rolling out such a programme of population screening was to standardize the measurement of plasma creatinine. For example, in the United Kingdom alone there were 31 different modifications of the standard Jaffé reaction used in routine clinical practice. Rather than each laboratory changing its method/analyser, each individual laboratory had to develop correction factors from the IDMS-traceable version of the MDRD equation. Thus in the United Kingdom the following equation is employed using an IDMS-based national external quality assessment service: eGFR (ml/min per 1.73 m2) = 175 × (([creatinine (μmol/litre) − intercept]/slope) × 0.011312)−1.154 × (age in years)−0.203 × 0.742 (if female) × 1.212

(if black) where intercept and slope are the individual laboratory correction factors for the IDMS method. The eGFR has not been formally validated in people younger than 18 years, hospitalized patients, or those with acute kidney in- jury, pregnancy, oedematous states, muscle-wasting disorders, amputations, or malnourishment. Similarly, it has not been validated for extremes of age or body weight, or for ethnic groups other than whites of northern European origin and African Americans. In the United Kingdom, the value of the eGFR falls within 30% of the true GFR in 90% of patients. Typically, the eGFR under- estimates true renal function in patients with hyperfiltration, with its accuracy improving as renal function deteriorates. In the United States of America, Australia, and Scotland, laboratories were initially instructed to report all eGFR values higher than 60 ml/min per 1.73 m2 simply as ‘greater than 60’ because of in- creased inaccuracy at higher eGFR, whereas in the United Kingdom the advice to laboratories is to report values up to 90 ml/min per 1.73 m2, and then ‘greater than 90’. Although the eGFR, however estimated, has inherent inaccuracies, it is now universally employed, may prove useful in assessing stability or progression of renal function over time in the general population, and can allow a rational basis for referral to specialist renal physicians. Creatinine clearance In clinical practice, creatinine clearance is now being replaced by the eGFR, as the accuracy of the creatinine clearance method depends on patient compliance to provide an accurate 24-h urine collection. Even when patients are in a steady state, urinary creatinine excre- tion varies from day to day, and reliability can be increased by per- forming consecutive daily clearances. Creatinine clearance is calculated as follows: Creatinine clearance (ml/min) urinevolume(ml/24h) urinecrea

× tinine concentration(mol/litre) plasmacreatinineconcentrat µ ion(mol/litre) 24 60 µ × × Table 21.4.4 The stages of chronic kidney disease (CKD) CKD stagea eGFR (ml/min per 1.73 m2 body surface area) 1

> 90, with other evidence of renal disease 2 60–89, with other evidence of renal disease 3A 45–59 3B 30–44 4 15–29 5 <15, or receiving renal replacement therapy a The suffix (p) can be used to denote the presence of proteinuria as defined by a spot urinary ACR of ≥30 mg/mmol, which is approximately equivalent to a PCR of ≥50 mg/mmol (≥0.5 g/24 h). Patients with CKD stages 3A, 3B, 4, and 5 may or may not have any other evidence of renal disease.

With regard to the use of the creatinine clearance measurement as an estimate of GFR, two errors tend to balance each other out. The chromogenic assay tends to overestimate the plasma, but not urinary, creatinine concentration, leading to an underestimation of GFR. By contrast, creatinine is not only excreted by glomerular filtration: some is secreted by the renal tubules, leading to an overestimation of the GFR. However, in patients with impaired renal function these contrasting effects are not balanced, and the relative increase in tubular creatinine secretion results in creatinine clearance exceeding GFR. This problem can be overcome by the administration of 400 mg of cimetidine to block renal tubular creatinine secretion, but this manoeuvre is rarely (if ever) performed in clinical practice solely for this purpose. By convention, creatinine clearance values are commonly corrected for body surface area to adjust for differences in muscle mass, assuming a fixed mathematical relationship between body surface area and the relative proportions of fat to muscle. However, body composition is not only age and gender dependent, but also varies from race to race, and other inaccuracies occur in oedematous and obese states. Cystatin C Cystatin C is a low molecular weight basic protein (13.26 kDa) from the cystatin superfamily of cysteine proteinase inhibitors that is produced by all nucleated cells. It is freely filtered by the glomerulus and initially was thought not reabsorbed, secreted or catabolized by the renal tubules during its passage into the urine. The generation of cystatin C appears to be less variable from person to person than creatinine and is not affected by dietary protein intake, hence it has been advocated as a better marker for GFR than creatinine. However, it is now realized that cystatin C generation varies more than creatinine and is increased in inflammatory states, including cardiac failure, but appears to be reduced in acute kidney injury. Rapid and fully automated immunonephelometric assays are now available, but there is assay variation between different manufacturers, also with different assay platforms, and as such there has been a recent move to standardize commercially available assays. Currently cystatin C assays are more costly than those of creatinine. As with creatinine, several equations have been proposed to allow estimation of GFR (ml/min per 1.73 m2) based on serum cystatin C measurements (mg/litre): • Larsson equation: GFR = 77.329 × cystatin C−1.2623 • Hoek equation: GFR = −4.32 + 80.34 × 1/cystatin C • Le Bricon equation: GFR = 78 × (1/cystatin C) + 4 • Rule equation: GFR = 76.6 × cystatin C−1.16 • Filler–Lepage equation: GFR = 1.962 + [1.123 × log (1/cystatin C)] • Grubb equation: GFR = 84.69 × cystatin C−1.68 • Grubb equation (children): GFR = 84.69 × cystatin C−1.68 × 1.34 (if <14 years old) • Stevens equation (children): GFR = 76.7 × cystatin C−1.19 CKD- EPI GFR= 133 × min(cystatin C/0.8, or 1)−0.499 × max(cystatin C/0.8, or 1)−1.328 × 0.999age × 0.932(if female) In addition there are combined serum creatinine and cystatin C equations: • Berlin Initiative Study: GFR = 767 × cystatin C−0.4 × creatinine−0.4 × age−0.57 × 0.87 (if female) • CKD-EPI: GFR = 135 × min(creatinine/k, 1)a × max(creatinine/ k, 1)–0.601 × min(cystatin/0.8, 1)–0.375 × max(cystatin/0.8, 1)–0.711 × 0.995age × 0.969 (if female) × 1.08 (if black) in which k is 0.7 for women and 0.9 for men, a is –0.248 for women and –0.207 for men, min indicates the minimum of serum creatinine/k or 1, and max indicates the maximum of serum creatinine/k or 1 In most studies, the accuracy of cystatin C assessment of GFR is superior to that of creatinine-based eGFR (using the sMDRD formula) in those patients in the crucial chronic kidney disease stage 3 and 4 groups, both in children and adults. However, evidence is accumulating that the serum concentration of cystatin C is influenced by many factors, including corticosteroid use, sex, age, weight, height, smoking status, proteinuric states, chronic liver disease, heart failure, malignancy, and the level of C-reactive protein, even after adjustment for creatinine clearance. Cystatin C has also been reported to be reduced in renal transplant recipients, with some drugs (including valsartan), in bone marrow

transplant pa- tients, following myeloablative chemotherapy, and in hypothyroid states, and to be increased in thyrotoxicosis. These factors coupled with the variation between different assays accounts for the number of different equations proposed to equate cystatin C concentrations with GFR. For these reasons, amongst others, cystatin C has failed to replace creatinine as a biomarker of renal function in routine clinical practice. Combined serum creatinine and cystatin C equa- tions have been developed and may have an advantage for elderly patients, and those with early chronic kidney disease stages without proteinuria. In addition, these equations may be applicable to different racial groups. Carbamylation Urea accumulates with deteriorating renal function and in plasma can spontaneously dissociate to form a reactive cyanate species that can react with the terminal valine of haemoglobin α and β chains (and also similar valine molecules in other proteins). This reaction is termed ‘carbamylation’ and the product ‘carbamylated haemoglobin’ (or other protein). Whereas glycosylated haemo- globin has proved useful in clinical practice for assessing time-averaged diabetic control, carbamylated haemoglobin or carbamyl-lysine adducts have not been shown to be superior to simple serum creatinine measurements in determining stable renal function. However, they are useful in helping to differen- tiate acute from chronic renal failure, because of the time course of the carbamylation reaction, and also in the assessment of time-averaged urea levels in the dialysis patient with endstage renal failure. However, until the relevant assays are commercially avail- able, their use will remain experimental. Other methods
Isotopic methods The GFR can be determined by the clearance of a compound which is freely filtered by the glomerulus and then passes through the nephron without tubular reabsorption or secretion. Traditionally, inulin—a naturally occurring polyfructose—was given as a con- stant infusion to achieve a constant plasma concentration, and

21.4 Clinical investigation of renal disease 4791 then clearance determined from timed urinary collections. This was a laborious technique. Furthermore, the biochemical esti- mation of inulin was initially tedious and difficult, with signifi- cant interassay variation, and accurate timed urine collections are unreliable in patients with urinary tract anomalies. To overcome these and other difficulties, compounds other than inulin are gen- erally used to estimate GFR, and methods other than constant infusion. Following a single bolus injection, depending on the compound used, the fall in plasma concentration follows either a single- or two-compartment model related to renal clearance. Chromium- labelled ethylenediaminetetraacetic acid ([51Cr]EDTA) is the most commonly used isotope. After the single injection, three timed plasma samples are taken to calculate the plasma decay rate and the GFR is then calculated by taking the linear decay slope back to the abscissa and estimating the area under the curve. More recently it has been showed that only a single blood sample at 4 h is required for a GFR over 30 ml/min. At GFRs above 30 ml/min there is a very good correlation between inulin and [51Cr]EDTA clearance, but below 30 ml/min the accuracy of the isotope tech- nique is reduced, there being some renal tubular reabsorption. Accuracy can be improved in this situation by taking a delayed (24-h) plasma sample, especially in patients with peripheral oe- dema and ascites. Other isotopes that have been used to estimate GFR include [125I] iothalamate, which when given as a subcutaneous injection results in a constant plasma concentration equivalent to the infusion tech- nique, and 99Tcm-diethylenetriaminepentaacetic acid (DTPA), which is less accurate because of its short half-life (6 h) and dissoci- ation of DTPA from the radionuclide. With all the isotopic methods, it is conventional for the GFR to be corrected for the size of the patient. This correction as- sumes a fixed relationship between the weight and height of an individual: hence serial estimations to detect a change in renal function are more likely to be accurate than single estimations. However, the normal relationship between body surface area and muscle mass may well be lost in patients with chronic kidney disease who may have protein energy wasting, or volume over- loaded, and similarly patients at the extremes of body habitus, and those with cancer cachexia, so introducing an error in GFR when scaling to body surface area. Other errors arise as single bolus iso- topic determinations are determined by the area under the curve, and as such will overestimate the GFR in patients who are fluid overloaded, and also by affecting the decay slope in those with ascites, such as patients with cirrhosis, due to initial redistribu- tion of the tracer into the ascitic fluid followed by return into the plasma. This redistribution and return error can be overcome by using a continuous infusion technique to establish equilibrium, which may require significant time (8–10 h), or by taking delayed samples at 24 h. Radiological methods Iohexol is a nonionic, low-osmolality radiocontrast dye. It can be used to estimate GFR following a single bolus injection of between 2 and 5 ml. In patients with a clearance of over 30 ml/min, a single plasma sample taken 3 h after injection provides an accurate esti- mation, whereas additional later samples are required to improve the accuracy in those with severely impaired renal function. Iohexol should not be used in patients with known iodine sensitivity, and has the same errors as single bolus isotopic methods. Summary Because of the difficulty in interpreting plasma creatinine concen- trations below 150 µmol/litre as an assessment of renal function, the eGFR was initially introduced into clinical practice in the United States of America, Australia, and the United Kingdom to detect pa- tients with early stages of chronic kidney disease, and is now be- coming widespread. It is an appropriate and adequate technique for most clinical purposes. When more precise estimation of GFR is required, an isotopic assessment is the most accurate method of determination, otherwise two 24-h urine collections with corres- ponding plasma samples should be used to calculate the GFR by cre- atinine clearance. Cystatin C has failed to replace serum creatinine in clinical practice as yet and predominantly remains a research tool. To examine changes in renal function, where eGFR measurements are not available, plasma creatinine concentrations should be trans- formed to either the reciprocal or the logarithm to assess trends in serial results. Estimation of renal blood flow Renal blood flow can be estimated noninvasively using Doppler flow probes, provided there is a single renal artery and adequate imaging is possible. This is technically easier for a transplanted kidney than a native kidney. The recent development of contrast agents for ultrasonography may increase the reliability of these estimations. Alternatively, renal blood flow can be estimated from the measure- ment of the renal plasma flow and the haematocrit. However, the haematocrit of peripheral venous blood may not be the same as that entering the renal artery. More recently, the development of positron emission tomography (PET) coupled with CT has allowed assess- ment of renal blood flow using 15O-labelled water, 82Rb, and other tracers. Renal plasma flow Ideally, any compound used to assess renal plasma flow should have 100% uptake by the kidney, with any fraction not filtered by the glom- erulus being extracted by the tubules and secreted. p-Aminohippurate is the most commonly used compound, but is only 85% extracted during a single passage through the kidney, and thus at best only provides an estimate of renal plasma flow. Continuous infusion of p-aminohippurate provides a more accurate estimation of renal plasma flow than single-injection techniques. Renal blood flow varies in normal subjects with pain, stress, physical exercise, and normal pregnancy, and following a high-protein meal. In patients with impaired renal function, the decline in renal plasma flow generally corresponds to the decrease in GFR. However, in some con- ditions where there may be renal tubular hypoxia or toxicity, such as in patients with severe heart disease or those with ciclosporin nephro- toxicity, the reduction in estimated renal plasma flow is greater than that expected for the change in GFR, due to a reduction in the renal tubular uptake of p-aminohippurate. Similarly, p-aminohippurate uptake is reduced in small children. [125I]o-Iodohippurate has also been used to estimate renal plasma flow, but this has a lower extraction than p-aminohippurate (75%), and is less reliable.

section 21 Disorders of the kidney and urinary tract 4792 Investigation of tubular function In a normal subject, some 180 litres of glomerular filtrate is produced each day and less than 3% of this is excreted, due to reabsorption by the tubules. The proximal and distal tubules have different functions, and traditionally

each is considered separately. Proximal tubular function Defects in proximal tubular function may be isolated or generalized, as in Fanconi’s syndrome. Glucose, phosphate, amino acids, and organic ions are reabsorbed by the apical border of proximal renal tubular cells by sodium-dependent cotransporters, and are then transported across the basolateral membrane by different, sodium-independent, cotransporters. Glucose There is a maximum reabsorption rate for glucose (TmG) in the prox- imal tubule of 15.1 ± 2.5 mmol/litre (TmG/GFR), above which glyco- suria will be present. To determine TmG/GFR, a 20% dextrose infusion is administered at increasing rates to produce a slow rise in the plasma glucose up to a maximum of 30 mmol/litre, which is maintained for a minimum of 1 h. Plasma and urine samples are collected every 30 min. Renal function is determined by [51Cr]EDTA-GFR. The glucose absorption rate is calculated as the difference between the filtered load in urine (urine volume × [glucose]urine) and the filtered load in plasma (GFR × [glucose]plasma). Patients with type A renal glycosuria typically have a reduced threshold of around 5 mmol/litre. Phosphate Phosphate is normally filtered at the glomerulus and reabsorbed in the proximal tubule, with only 10 to 20% of the filtered load being excreted. The normal tubular reabsorption of phosphate (TRP) is above 85% and can be calculated from: %TRP (1 [ ]) 100 phosphate clearance/eGFR

− × If renal function is normal, then this can be simplified by collecting an early-morning specimen of urine, and: %TRP 1 [phosphate] [creatinine]

[creatinine] urine plasma urin

− × e plasma [phosphate]

100 × × □ □□ □ □□

Alternatively, the theoretical maximum tubular threshold of phosphate (TmP) can be estimated from: Tm plasma urine plasm P GFR phosphate phosphate creatinine

× [ ] [ ] [ ] a urine creatinine [ ] or measured directly as for TmG, following an infusion of phosphate (1.0 litre of 0.1 mol/litre sodium phosphate at pH 7.4) with a corres- ponding [51Cr]EDTA-GFR. Renal tubular epithelial cell phosphate transport is regulated by phosphatonins, and several genetic conditions (X-linked hypophosphataemic rickets, autosomal dominant and autosomal recessive hypophosphataemic rickets) and other diseases have now been described with excessive phosphate losses due to phosphatonins, including tumour-associated osteomalacia. Excessive urinary phos- phate losses occur in proximal tubular disorders such as Fanconi’s syndrome, primary and secondary hyperparathyroidism, and mito- chondrial disorders, both primary and secondary, including those due to antiretroviral therapy, particularly the nucleotide analogue reverse transcriptase inhibitors, such as tenofovir. In the various forms of hypophosphataemic rickets, phosphaturia occurs with a characteristically reduced TmP/GFR of less than 0.56 mmol/litre. Amino acids Apart from the reabsorption of histidine (90–95%), that of other amino acids is almost complete (97–99%). Although amidoaciduria can occur as a result of overflow when the plasma concentra- tion exceeds the tubular transport maximum, this is very rarely the cause of aminoaciduria in adults. In general, five types of renal aminoaciduria are distinguished: dibasic amino acids, neutral amino acids (monoaminomonocarboxylic acids), glycine and imino acids, dicarboxylic amino acids, and generalized aminoaciduria in the case of Fanconi’s syndrome. Generalized and specific aminoacidurias can be detected and quantified by thin-layer chromatography. In Fanconi’s syndrome, amino acids from all four groups are present, whereas in glycinuria there is only excess glycine. Classic cases of cystinuria have increased urinary arginine, ornithine, lysine, and cystine; and patients with Hartnup’s disease have an excess of neutral amino acids. For more detailed discussion of other aspects of proximal tubular function and their diseases, see Chapter 21.16. Distal tubular function Patients with primary or secondary nephrogenic or cranial diabetes insipidus and those with primary polydipsia may present with polyuria. A water-deprivation test can help to differentiate between these conditions, and can be performed as follows. The patient should be ad- mitted to a metabolic ward on the evening prior to the test, be weighed, and have samples taken for baseline plasma osmolality, chemistries, and arginine vasopressin (AVP) measurement. An osmolality above 295 mOsm/kg and a sodium concentration above 143 mmol/litre ex- clude a diagnosis of primary polydipsia. After midnight, no oral fluids are allowed until completion of the test. The early-morning urine osmolality is measured, and if it is above 800 mOsm/kg (normal re- sponse) the test is abandoned. Thereafter, the patient’s weight, plasma and urine osmolality, and plasma AVP concentration should be re- corded regularly. If weight loss exceeds 5%, then the test should be abandoned to prevent dangerous dehydration. Once urine osmolality reaches a plateau (an hourly increase of less than 30 mOsm/kg for 3 consecutive hours), then five units of aqueous vasopressin is adminis- tered subcutaneously and urine and plasma osmolality measured after a further 30 min, and then at hourly intervals. Comparison of the last urine osmolality reading prior to the admin- istration of vasopressin with the maximum osmolality following vaso- pressin is used to categorize patients. Those with nephrogenic diabetes insipidus will produce a urine osmolality under 300 mOsm/kg, with no response to exogenous vasopressin, and they will have high AVP levels. Those with severe cranial diabetes insipidus will have dilute urine, again less than 300 mOsm/kg, but they will respond to exogenous vaso- pressin by increasing urine osmolality by 50% or more, accompanied by low endogenous AVP levels. Both cranial and nephrogenic diabetes insipidus can occur as partial forms, which show some response to dehydration, but they can be discriminated by analysing the relative changes in endogenous AVP and the urinary and plasma osmolalities. Patients with primary polydipsia do not show pituitary suppression, and have little or no response to exogenous vasopressin.

Renally induced electrolyte imbalances Sodium and water There are many causes of hyponatraemia, as discussed in Chapter 21.2.1. Patients with cardiac failure, chronic liver disease, nephrotic syndrome, and prerenal acute renal failure will have a fractional excretion of sodium (FENa) of less than 1% (normal is 1–2%), where: %FE sodium creatinine sodium crea Na urine plasma plasma

× × [ ] [ ] [ ] [tinine urine] ×100 A reduced effective circulating volume stimulates antidiuretic hormone release, increasing distal sodium and water reabsorp- tion. Hence a reduced fractional excretion of urea (<35%) is more sensitive and specific than reduction in FENa in differentiating be- tween prerenal and renal causes of acute kidney injury, especially when diuretics have been given, and also in hepatorenal syndrome. However, values of both FENa and FEUrea are not always reliable in making a clear distinction between different forms of acute kidney injury, and most nephrologists do not use them routinely. Patients with the syndrome of inappropriate diuresis preferen- tially retain water and have a normal FENa, indeed the diagnosis cannot be made if FENa is low, but when interpreting measurements of FENa it must be remembered that this is increased by diuretic ad- ministration and in chronic renal failure. Both those with reduced effective circulating plasma volume and those with the syndrome of inappropriate diuresis have impaired free-water excretion, which can be tested by giving the patient 20 ml/kg body weight of water to drink after voiding. More than 75%

of the water load should be excreted within 3 h, and the urine osmolality should fall to under 100 mOsm/kg (specific gravity <1.003), although this test can be affected by gastrointestinal dis- ease, smoking, and emotional factors. The free-water clearance (Ch2o) can be quantitated from: CH O urine volume in ml min osmolality osmolality ur urine plasma 2

− × inevolume in ml min / A positive free-water clearance occurs when the urine is more di- lute than plasma, and a negative free-water clearance when the urine is more concentrated. For further discussion of these issues, and the clinical approach to disorders of sodium and water homeostasis, see Chapter 21.2.1.

A water loading test may also be useful in investigating patients with cyclical or idiopathic oedema. Diuretics should be avoided for at least 10 days, and then—after an overnight fast—20 ml/kg of water is consumed in 30 min, the bladder emp- tied, and all urine collected over the following 4 h. In normal individuals, more than 70% of the ingested water should be recovered when the test is performed with the patient in the supine position, and also when they are ambulant, whereas in cases of idiopathic cyclical oedema, the urinary volume and sodium excretion are reduced in the ambulant test, typically with a urinary sodium con- centration of less than 33% in the ambulant compared to the supine position. Renal salt wasting It has been recognized for many years that patients with acute subarachnoid haemorrhage and after pituitary surgery can develop an acute renal sodium wasting condition, previously termed cerebral salt wasting. It is now realized that this condition may also occur with other illnesses, including pneumonia. In severe cases, patients can lose more than 600 mmol sodium/day and suffer depletion of intravascular volume and dehydration. However, in less severe forms clinical dehydration may not be obvious and there can be some biochemical similarities to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) (Table 21.4.5). Renal salt wasting is associated with a proximal tubular defect, leading to increased distal delivery of sodium that blunts the otherwise anticipated rise in plasma renin, and also with increased fractional excretion of urate and sometimes phosphate. Although fractional excretion of urate is also initially raised in SIADH, this typically corrects once the serum sodium rises, whereas that in renal salt wasting persists. Potassium To determine whether there is a renal tubular cause for potassium disturbances, the transtubular potassium gradient (TTKG) can be calculated. This attempts to estimate the potassium

concentration in the cortical collecting duct as follows: TTKG potassium potassium osmolality osm urine plasma plasma

× [ ] [ ] olality urine In a patient with hypokalaemia, a TTKG of less than 2 suggests a nonrenal cause, whereas a high TTKG (>10) is associated with mineralocorticoid excess, Liddle's syndrome, or drugs such as acetazolamide, fludrocortisone, and amphotericin. In a patient with hyperkalaemia, a TTKG above 10 implies a nonrenal cause and a low TTKG (<2) would be found in cases of potassium-sparing diuretics, hypoaldosteronism, and pseudohypoaldosteronism. However, while having some theoretical attraction, it is doubtful whether such analysis helps greatly in the diagnosis or management of patients with hypokal- aemia or hyperkalaemia. Bartter's and Gitelman's syndromes are the classic renal tubular de- fects presenting with hypokalaemia, hypomagnesaemia, metabolic alkalosis, hyperreninaemic hyperaldosteronism, and normotension. Each syndrome contains a number of different channelopathies, thus in Bartter's syndrome most children have hypercalciuria, in- creased urinary prostaglandins, and hypomagnesaemic, but not all. Table 21.4.5 Biochemical differences and similarities between renal salt wasting and the syndrome of inappropriate antidiuretic hormone (SIADH) Renal salt wasting SIADH Serum sodium (mmol/litre) <135 <135 Serum osmolality (mOsmol/kg) <285 <285 Urine osmolality (mOsmol/kg)

> 200 200 Urine sodium (mmol/litre) 25 25 Serum renin ±↑ ±↓ Serum aldosterone ↑ ±↓ Serum urate ↓↓ Normal or ↓ Fractional excretion urate ↑↑ Normal or ↑ Fractional excretion phosphate ±↑ Normal

section 21 Disorders of the kidney and urinary tract 4794 Similarly in Gitelman's syndrome, children or adults have the classic phenotype of hypokalaemia, hypomagnesaemia, and hypocalciuria, with normal urinary prostaglandins. For further discussion of these issues, and the clinical approach to disorders of potassium homeostasis, see Chapter 21.2.2. Renal tubular acidosis Renal tubular acidosis should be considered in cases of metabolic acidosis with a normal anion gap (serum sodium + potassium – chloride – bicarbonate = 12–16 mmol/litre, corrected for albumin to exclude dehydration), and no evidence of intestinal bicarbonate losses. Arterial blood gases are required to confirm metabolic acid- osis with a reduced bicarbonate, as serum bicarbonate may appear to be reduced due to sample analysis delay, and failure to fill sample tube correctly. Serum potassium is typically reduced in classic distal tubular acidosis (DTA) and may also be reduced in proximal tubular acidosis (PTA), whereas it is increased in hyperkalaemic DTA and in hyporeninaemic states or hypoaldosteronism. Spot urine pH testing of the first urine of the morning is persistently greater than 5.5 in DTA. If the urinary pH is alkaline, then urinary ammonia determination can help diagnose mixed forms of DTA from classic DTA, which has reduced urinary ammonia (normal 100 mmol/litre). If laboratories cannot directly measure urinary ammonia, then the ammonia can be calculated by measuring the urine osmolar gap and subtracting the calculated urine osmolality, provided renal and hepatic function are normal: Urinary ammo- nium mmol/litre = 0.5 × (measured UOsmo – UOsmo calculated as (2 UNa + 2 UK) + UGlucose +UUrea). Milder forms of renal tubular acidosis may have low normal serum bicarbonate and further testing may be required, including the furosemide and fludrocortisone test, which is now the screening test for DTA. On arrival in the morning, the patient produces a fresh urine sample as a baseline for testing with a pH electrode meter, after which 40 mg furosemide and 1 mg of Fludrocortisone are administered orally, with hourly urine sam- ples tested thereafter for 6 h. The test is negative if the urine pH falls below 5.5, although it should continue to the full 6 h to fully characterize urinary acidification. If this test is inconclusive, then a formal ammonium chloride test is required. Following a base- line venous bicarbonate estimation, the patient is requested to drink ammonium chloride (100 mg/kg body weight) with water over a period of up to 1 h. In the author’s hospital, the ammo- nium chloride tablets are specially prepared by in-house phar- macy to disguise the taste. Urine samples are collected every hour (or when passed), checking volume and pH, and stored at 4°C, whilst the patient drinks regularly to maintain an adequate urine flow. Further venous bicarbonate measurements are made after 3 h and then at the end of the test at 6 h to ensure an adequate fall in serum bicarbonate of 4 to 5 mmol/litre. Urine samples are stored at −20°C and then checked for pH, ammonia, and chloride. If urine pH falls below 5.5 with an adequate fall in serum bicar- bonate, then the test is negative. Urinary citrate is reduced in DTA, whereas in cases of PTA pa- tients may have increased urinary phosphate losses, glycosuria, renal tubular and microalbuminuria, and hypouricaemia. For more detailed discussion of other aspects of distal tubular function and their diseases, including tests of urinary acidification, see Chapter 21.15. Biochemical screening investigations for patients with renal calculi Renal stones are common in patients from developed countries, with an estimated prevalence of 5% in North Americans. Most stones contain calcium, and stones that are passed should be sent for chemical analysis whenever possible. Routine screening would include serum calcium, magnesium, uric acid, bicarbonate, chloride, parathyroid hormone and 1,25 vitamin D. Spot urine samples should be tested for pH (calcium salts are less soluble at pH >6.5, whereas urate and cystine are more insoluble at lower pH), specific gravity, microbacteriology, and dibasic amino acids. Twenty-four-hour urine collections are helpful in assessing volume of urine passed, and also biochemical analysis, with urine col- lected in plain containers to exclude increased excretion of calcium (normal upper limit for males 7.5 mmol/day and females 6.0 mmol/ day, but risk is increased if >6.25 and 4.25 mmol/day, respectively), magnesium (0.6–4.8 mmol/day), sodium (normal 50–125 mmol/ litre or 100–250 mmol/day), creatinine (normal 7–18 mmol/day), urate (normal excretion 500–800 mg/day or 3.0–4.8 mmol/day, with increased risk of uric acid stones >750 mg uric acid/day for men and >800 mg/day for women), and cystine (normal 30 g/day or 0.13 mmol/day, with increased risk with >75 g cystine/litre). In addition, acid-washed urine containers are required for collection of oxalate (normal 0.1–0.46 mmol/day, with values found in cases of primary hyperoxaluria typically being 9–30 mmol/day) and citrate to exclude hypocitraturia (<350 mg/day for males, and <500 mg/day for females). Imaging of patients with renal disease There are a number of techniques that can be used to image the kidney: a simple comparison of some of these is given in Table 21.4.6. Plain radiography Plain abdominal radiographs may demonstrate opaque urinary stones, nephrocalcinosis, and the renal outlines. Ultrafast, noncontrast CT scanning with three-dimensional reconstruction has generally replaced nephrotomograms for detecting low-opacity renal stones. Chest radiography may be helpful in the diagnosis of pulmonary oedema, and also in demonstrating the cardiac silhouette and lung pathology sometimes associated with renal disease, such as pulmonary haemorrhage and cavitation. Multiple rib fractures may suggest multiple myeloma. Intravenous urography Intravenous urography (IVU) is no longer the standard investigation in nephrology, but still has an important place in the investigation of patients with suspected obstruction, particularly of the upper urinary tract. As with all radiographic procedures, potential fetal irradiation should be avoided. Bowel preparation is no longer standard, due to the risks of dehydration in older people and of gaseous distension of the bowel obscuring the urinary tract. Even the newer nonionic lower-oncotic contrast media can cause nephrotoxicity in some patients, and care should be taken to ensure that those at risk (older people, and those with diabetes, myeloma, or pre-existing renal impairment) are adequately hydrated. Normal renal length is between three and four lumbar vertebrae, with a width approximately half that of the length. The calyces and papillae are well demonstrated by IVU, which may be diagnostic in cases of medullary sponge kidney, papillary necrosis, and sloughed papillae. Similarly, intraluminal radiolucent foreign bodies may be demonstrated surrounded by contrast, typified by radiolucent stones, blood clots, fungal ball, tumour, or sloughed papillae. Abnormalities of the ureteric wall such as localized thickening are found in cases of transitional cell carcinoma, oedema, tuberculosis, and parasitic granuloma. The IVU may also demonstrate external compression: this can be due to aberrant blood vessels in the upper tract, retroperitoneal fibrosis affecting the middle ureter, or prostatic pathology in the lower tract. The IVU may provide valuable information about renal size and possible intrarenal masses. It retains a role for investigation of upper tract pathology to detect intraluminal tumours and blood clot, but has been replaced by other techniques, such as ultrasonography and ultrafast CT scanning, to investigate renal colic. Other conventional uroradiological techniques Further information about the site and nature of any obstruction can be obtained by ureteropyelography. An antegrade study involves percutaneous puncture of the renal pelvis, with immediate relief of the obstruction by nephrostomy, and allows demonstration of the site of obstruction following an injection of contrast media (antegrade ureteropyelography) (Fig. 21.4.4). A retrograde study requires cystoscopy, allowing direct visualization of the distal ureter and the possibility of removing an obstructing stone, with injection of contrast media from below demonstrating the site of obstruction (retrograde ureteropyelography). Passage of a double JJ stent from above (antegrade) or below (retrograde) can relieve obstruction by allowing internal drainage into the bladder (Fig. 21.4.5). By definition, vesicoureteric reflux is diagnosed by a micturating cystourtherogram (MCUG), staged according to the severity of calyceal dilatation and hydronephrosis (stages I–V), and subdivided into active, with reflux demonstrated during micturition, and passive, with no reflux on micturition. As a MCUG has a high radiation dose, it is usually restricted to infants less than 6 months, and ultrasonography is the screening test of choice. Antegrade techniques are usually more successful in relieving obstruction, particularly in those with pelvic malignancy or obstruction of a renal transplant. In cases when renal obstruction is considered, but investigation inconclusive, a pragmatic trial of antegrade stent insertion should be undertaken. Improvement of renal function confirms obstruction. Retrograde urethrocystography is performed in women to detect lower urinary tract abnormalities, such as fistulas or urethral diver- ticula. Sequential films taken during micturition may detect active reflux. In men, urethrocystography can be complicated by trauma Table 21.4.6 Comparison of standard methods for radiological imaging of the kidney Imaging method Advantages Disadvantages General Imaging General Imaging Ultrasonography Noninvasive Safe Versatile Cost (cheap) First-line imaging for excluding obstruction Can be used to guide intervention Operator/machine dependent Dependent on patient having suitable body habitus Intravenous urography (IVU) Cost (cheap) Good for definition of upper tract anatomy Contrast exposure Good images not obtainable with eGFR <20 ml/min Multislice three- dimensional CT Widely available High resolution, allowing best anatomical definition Radiation dose CT KUB (kidneys, ureter, and bladder) No contrast exposure First-line imaging for urinary stones Can detect nonrenal pathology Limited study Not good at detecting small blood clots CT urography First-line imaging for upper tract Contrast exposure Good images not obtainable with eGFR <15 ml/min Limited for imaging of bladder pathology CT angiography First-line imaging of renal arteries Contrast exposure MRI without contrast Noninvasive Avoidance of radiation dose allows repeated studies Good anatomical definition Can visualize the whole of the urinary tract Good for staging of renal carcinoma Good for assessment of complex renal cysts Patient needs to be able to hold their breath Cost (expensive) Not possible in all patients, e.g. prevented by cardiac pacemaker, cochlear implant, intracranial clips MRI with contrast (gadolinium)— urography and angiography Used to confirm normal vascular anatomy, e.g. in assessment of potential kidney donors Careful consideration if eGFR <30 ml/min (nephrogenic systemic fibrosis) Tends to overestimate the significance of stenoses Likely to miss small accessory renal arteries Renal angiography The gold standard investigation for renal artery stenosis and brisk renal bleeding Can be therapeutic as well as diagnostic, e.g. stent/angioplasty, embolization by coiling/gel foam Invasive Contrast exposure Requires considerable technical expertise Risk of plaque rupture, vessel dissection, haemorrhage Contrast nephrotoxicity with iodinated-based contrast agents is increased when eGFR <60 ml/min per 1.73 m2.

section 21 Disorders of the kidney and urinary tract 4796 and infection to the lower urinary tract, hence suprapubic bladder puncture is recommended. Retrograde studies may be helpful in imaging ileal or colonic loop bladders to exclude outflow and ureteric inflow stenoses.
Renal ultrasonography The normal kidney and chronic kidney disease The normal adult kidney is between 10 and 12 cm long, with a thin, bright capsule surrounded by highly reflective perinephric fat. The healthy cortex returns mid-level grey echoes, the pyramids are darker, and the renal sinus, containing fat and the major vascular pedicle, is bright with high reflectivity. Colour (flow) Doppler ultra- sonography can be used to visualize the flow of urine from the native ureters into the bladder. In most causes of chronic kidney disease, the kidneys become smaller, with reduced cortical thickness and increased cortical re- flectivity when qualitatively compared with the liver. Diastolic blood flow is reduced on the Doppler scan in chronic kidney dis- ease, but can also be reduced in acute kidney injury due to increased intrarenal interstitial pressure, but this is nonspecific and can also be found in cases of pyelonephritis and obstruction. The renal ultra- sound appearances are characteristic in some conditions, including focal segmental glomerular sclerosis secondary to HIV infection, in which the kidney is reported to be large and the cortex uniformly of a

high reflectivity, greater than that of the renal sinus. Scars, either vascular or infective, may often be too small to be detected by ultra- sound examination, especially in the neonate. Renal masses Ultrasonography is useful in the assessment of renal masses. Benign cysts have a smooth outline with well-demarcated borders and an echo-free centre, whereas renal tumours are usually irregular with (b) (a) Fig. 21.4.4 Antegrade puncture of the collecting system of the left kidney: (a) the nephrostomy needle (arrowed) has punctured an upper pole calyx, confirmed by injection of contrast medium that can be seen outlining the dilated pelvicalyceal collecting system, with some flow into the upper ureter; and (b) the nephrostomy needle has been replaced by an antegrade nephrostomy tube (arrowed), with injection of contrast medium demonstrating a block to flow (due to retroperitoneal fibrosis in this case) in the mid ureter. Fig. 21.4.5 Abdominal radiograph showing a double JJ stent placed in the left ureter. This was placed antegradely (from the kidney); some contrast medium from the preceding antegrade ureteropyelogram remains in the renal pelvis.

21.4 Clinical investigation of renal disease 4797 heterogeneous echo reflectivity. Typical standard, real-time, two- dimensional B mode ultrasonography may be able to detect renal masses and/or cysts as small as 2 to 3 mm in size, depending on the experience of the operator and the specification of the scanner, but this ability is reduced by several patient factors including high-density fat and muscle, and position, particularly when the kidneys are covered by the ribcage. Most tumours are vascular, with high flow during both systole and diastole on colour Doppler scanning, and adenocarcinomas in particular may be seen to extend into the renal vein. Renal transitional cell carcinomas are not readily detected unless large because ultrasonography does not visualize individual calyces well. Angiolipomas may have a characteristic appearance due to their fat content which has high reflectivity, but confirmatory CT scanning is required. In adult polycystic kidney disease, the kidneys are typically en- larged with multiple bilateral cysts. Middle-aged women (particu- larly but not exclusively) may also have hepatic cysts. It is important to remember that, if patients are scanned in their teenage years or before, then cysts may not have developed to a size detectable by ultrasonography. Haemorrhage, infection, or malignant change all result in complex echoes within cysts, which cannot be differenti- ated by ultrasound scanning. Autosomal recessive polycystic kidney disease can be detected in utero with antenatal scanning. There is an increased incidence of cystic change in the kidneys of patients with endstage renal failure, and occasionally these cysts may become malignant. It has been suggested that dialysis patients should be screened by ultrasonography every 3 years, and then an- nually if cystic changes develop. Urinary obstruction In most centres, ultrasonography of the urinary tract is the first in- vestigation performed when urinary obstruction is suspected. When urinary obstruction has been present for some time, the high reflect- ivity of the central renal sinus becomes replaced by echo-free urine, with distension of the calyces (Fig. 21.4.6). However, it is important to recognize that in acute obstruction, and in cases where the kidney and ureter are encased (usually the result of tumour), the standard ultrasound examination may appear normal. In these circumstances, a colour Doppler scan may show reduced diastolic blood flow due to increased intrarenal pressure, and a difference in resistivity index (RI)—which equals (peak systolic velocity − end diastolic velocity)/ peak systolic velocity)—of more than 0.1 between the two kidneys is thought to be a reliable parameter for diagnosing acute unilateral ureteric obstruction. Similarly, absence of the normal pulsatile jets of urine from the ureter into the bladder may be demonstrated on the side with acute obstruction. Urethral valves and vesicoureteric reflux may be detected on ante- natal ultrasonography, with hydronephrosis. Ultrasonography is not usually diagnostic of the cause of obstruc- tion, but it may detect para-aortic nodes, a bladder mass, prostatic en- largement, or a ureterocoele. Further investigation with transvaginal, transrectal, or transurethral ultrasonography may confirm the cause of obstruction, with transrectal ultrasonography being particularly useful in the detection of local invasion from prostatic carcinoma. Urinary tract stones Renal stones appear on ultrasonography as a bright echogenic focus with a distal acoustic shadow. Ultrasonography can be used to follow up patients with renal calculus disease by assessing the number and size of stones. Nephrocalcinosis may result in an increase in medul- lary echoreflectivity due to calcium deposition, which usually affects the whole medulla, whereas calcification from papillary necrosis has an appearance more like that of a renal stone. Renovascular disease Colour Doppler can be used to investigate renal arterial and venous disease. Thrombosis of major vessels produces absent flow or changes to the intrarenal blood flow pattern. More recently, colour Doppler scanning has been used as a screening test for renovascular disease, as the higher the stenotic gradient in the renal artery, the slower and smoother the systolic upstream with identical diastolic velocity. This so-called parvus–tardus flow results in a decrease in RI, which can be compared with the contralateral kidney, and an RI difference of more than 0.05 (based on three to six measurements) between the kidneys has been reported to be a reliable parameter to detect significant uni- lateral renal artery stenosis. Furthermore, one study suggested that assessment of the RI in patients with atherosclerotic renovascular disease had prognostic value: those patients with an RI above 0.8 did not improve following renal artery angioplasty. Atherosclerotic renal artery stenosis occurs bilaterally in 20 to 30% of cases, and often affects the ostium, hence blood flow velocity at the ostium and along the renal artery should both be assessed. Thresholds ranging from 1.8 to 2.0 m/s (flow rate is accelerated in a narrowed stenotic artery) have been reported to have sensitivity and specificity of 70 to 90%, respectively, for renal artery stenosis, but the procedure is difficult and time-consuming, and even with an experi- enced operator it will be impossible to visualize the renal arteries ad- equately in some 20% of patients. Colour Doppler ultrasonography is thus not a routine technique for screening for or investigating cases of renal artery stenosis, except in centres that have particular interest and expertise in the technique. Renal transplantation Ultrasound examination is an important investigation in the man- agement of renal transplant recipients. Compared with the native kidney, the calyces and ureter are frequently visible in otherwise normal allografts, so experience is required in the interpretation of mild or even moderate calyceal dilatation. Early graft dysfunction mandates investigation to exclude a technical problem with either the renal artery or vein, or a urinary leak. Fig. 21.4.6 Ultrasound scan of an obstructed kidney showing a massively dilated pelvicalyceal system.

Colour Doppler scanning provides valuable information about the vascular supply of the graft (Fig. 21.4.7), and as with renovascular disease can be used to assess iliac artery and anastomotic stenoses. Estimation of the RI has been advocated to monitor early graft func- tion, but acute tubular necrosis, acute rejection, acute renal vein thrombosis, graft pyelonephritis and acute calcineurin toxicity all cause increased intrarenal pressure with reduced diastolic flow and increased RI. Similarly, by affecting the end-diastolic velocity, the RI can be reduced by tachycardia, and increased by bradycardia, com- pression of the transplant with the transducer, or Valsalva’s man- oeuvre through breath-holding. In addition, the RI is affected by vascular compliance, and older transplant recipients with stiffness of the prerenal vessels (aorta and iliac) will have an increased RI in- dependently of graft function. Thus, the RI cannot be used solely to monitor graft function, but serial measurements can guide the timing of graft biopsy. Fluid collections (commonly lymphoceles) appear as echo-free or echo-poor areas, and such perinephric collections can be drained under ultrasound guidance for diagnostic purposes or to relieve ob- struction. As with the native kidney, percutaneous nephrostomy is the emergency treatment of choice for obstruction of a renal transplant. Colour Doppler scanning can detect the presence of arteriovenous fistulas, which are not uncommon following transplant biopsy. Contrast agents for ultrasonography Colour Doppler ultrasonography can detect bubbles present in injected contrast medium. Application of this technique can change the use of ultrasonography from simple anatomical visualization of the kidneys to dynamic testing by assessment of the perfusion quotient. However, this remains an experimental investigation and not in routine clinical use, although it potentially has the capacity of allowing ultrasonography to determine relative renal function, and improve investigation for obstruction, renovascular disease, and vascular rejection in renal transplants. CT scanning Ultrafast multislice CT scanning, with workstation reconstruction down to a resolution of 2 to 3 mm or less, has become the mainstay of renal imaging (Fig. 21.4.8). CT urography can be performed with a combination of unenhanced, nephrogenic-phase and excretory- phase imaging. The unenhanced images are ideal for detecting urinary calculi. Renal masses can be detected and characterized with the combination of unenhanced, nephrogenic- and excretory-phase imaging. The excretory phase provides imaging of the urothelium. As with the standard IVU, iodine-based contrast media may cause renal impairment, but only a single dose is required and contrast exposure is usually much less than that required for coronary angiography. Unenhanced CT scanning For patients with suspected renal colic due to stones, low-dose, unenhanced helical CT has become the gold standard investiga- tion, particularly for patients with ureteric obstruction and kidney failure. CT allows both the cause and the level of the obstruction to be determined. Practically all stones (apart from indinavir) can be detected, hydronephrosis with perinephric stranding can usu- ally be readily identified, and there may be hydroureter down to the level of the obstruction. In cases where a stone has passed, oe- dema may be noted at the vesicoureteric junction, with residual stranding around the ureter. Other pathology may be identified in patients presenting with loin pain, such as renal enlarge- ment with perinephric fat stranding, or oedema in cases of acute pyelonephritis, renal vein thrombosis, or acute arterial occlusion. Fig. 21.4.7 Doppler ultrasound scan of a renal transplant showing normal systolic and diastolic waveform (resistivity index <0.65). (a) (b) Fig. 21.4.8 CT imaging: (a) showing dilatation of both renal pelvices (arrowed) in a case of urinary obstruction; and (b) after relief of obstruction by placement of double JJ stents in both ureters (arrowed).

21.4 Clinical investigation of renal disease 4799 Small blood clots can be difficult to identify. Other nonrenal path- ology may be identified, including leaking abdominal aorta, diver- ticular disease, or appendicitis. CT angiography Contrast administration allows a CT angiogram phase to be ac- quired (Fig. 21.4.9). Compared with magnetic resonance angiog- raphy (MRA), CT angiography is more sensitive in detecting small accessory renal arteries and it does not overestimate the length and severity of stenoses, which appear greater during MRA due to the combination of slower speed of data acquisition and blood flow. The main indications for CT angiography include the evaluation of acute renal trauma, tumour blood supply in cases of nephron- sparing surgery, the diagnosis of renal artery stenosis and/or aneur- ysms, defining the arterial supply in potential living renal donors, and prior to pyeloplasty for ureteropelvic junction obstruction, as endoluminal pyelomyotomy is not as successful as laparoscopic or open pyelomyotomy if there are posterior and/or anterior vessels. Three-dimensional reconstruction can help detect aberrant vessels, and partial obstruction to flow as found in the nutcracker syndrome. Some centres have used CO_2 as a contrast agent to reduce the risk of contrast nephropathy and volume loading, but the images are not as good as with conventional CT angiography and tend to overestimate strictures. CT imaging of the renal parenchyma Due to the speed of data acquisition, there is a cortical phase fol- lowed by an excretory phase, which allows imaging of both the cortex and then the medulla. Thus CT scanning is useful in the in- vestigation of congenital and anatomical abnormalities of the renal tract (such as renal agenesis), nephrocalcinosis (before calcification can be detected on plain films), and papillary sloughing. Apart from the investigation of cystic renal disease, CT scanning is used to investigate renal masses. Renal cell carcinomas vary in appearance: some show calcification both within and surrounding the tumour on nonenhanced scans, some are solid, and others are cystic or have necrotic centres. Most tumours are vascular and readily enhance with contrast, but those with heavy calcifica- tion may not. CT scanning is important in tumour staging and in determining the extent of perirenal spread, renal vein involvement, and enlargement of local lymph nodes. Occasionally, secondary deposits due to metastatic spread and secondary involvement in lymphomas and leukaemia can be found on contrast-enhanced renal scans. These are usually small, multiple intrarenal masses, often bilateral, typically homogeneous, and solid in lymphomas. Although ultrasonography is used to screen and assess Wilms’ tumours in children, CT scanning is important in excluding pul- monary metastases. Angiolipomas can be recognized with ultrasonography but should be confirmed on CT scanning as some renal cell carcinomas may contain small amounts of fat. In tuberous sclerosis, angiolipomas may be associated with renal cysts. Although angiolipomas are benign mesenchymal tumours, they can rarely rupture, especially those with intrarenal haematomas and aneurysms. Early detection by CT scanning allows prophylactic embolization of these vascular lesions. Renal oncocytomas, another benign renal tumour, may have a central lucent area due to fibrosis on CT scanning. However, a pro- portion of oncocytomas may become malignant, hence any small renal lesion which is not a simple cyst or angiolipoma must be re- garded as potentially malignant and surveillance with repeat CT scanning (or ultrasonography) should be recommended. Renal tract imaging in patients with acute pyelonephritis is usu- ally requested to exclude the presence of obstruction, or when there has been an inadequate response to treatment. CT scanning defines the extent of disease better than ultrasonography, detects abscesses, and can also exclude obstruction. Whereas focal acute bacterial pyelonephritis should respond to antibiotics, renal abscesses may require drainage. CT scanning may also detect gas bubbles within the renal parenchyma or perirenal space, which is characteristic of the emphysematous pyelonephritis that is typically found in people with diabetes Similarly, CT scanning may establish a diagnosis of xanthogranulomatous pyelonephritis, with an enlarged kidney con- taining areas of scarring, focal loss of renal parenchyma, and mul- tiple low-density masses, often following recurrent infections in patients with staghorn calculi. CT urography Scanning during the excretory phase provides a CT urogram of high definition, which may detect filling defects within the collecting system, such as transitional cell carcinoma, blood clot, or stone, and also external compression due to vasculature. Review of three- dimensional formatted images allows surgical planning. The use of CT urography is currently limited to assessing local extravesicle extension or metastatic disease in the staging of bladder tumours. With further developments in computer software, it will be possible to perform virtual cystoscopy to detect intravesicle lesions of at least 5 mm or in size after distending the bladder with CO2 or saline. Functional CT An estimate of GFR can be made using nonionic contrast media, which may be helpful when deciding on nephron-sparing surgery for renal tumours, and assessing patients with renovascular disease before and after interventional stenting. MRI CT scanning and ultrasonography are good reliable techniques for detecting and evaluating renal masses. MRI is an alternative in Fig. 21.4.9 Contrast-enhanced CT scan showing thrombosed aorta and renal arteries.

patients who are allergic to conventional iodine-based radiocontrast media, but the current generation of MRI scanners does not have the resolution of the ultrafast three-dimensional CT scanners. Gadolinium contrast used in MRI is taken up by the proximal tubule in a similar manner to aluminium. The dose of gadolinium-based contrast agent required is much less than those of standard iodinated contrast agents. Their biological half-life is increased in severe renal impairment, and they can result in spurious hypocalcaemia for up to 24 h after administration due to chelation with the commonly used automated assays for measuring serum calcium. Although gadolinium-based contrast agents generally have a good safety profile, there are a few reports of acute kidney injury following their administration, in particular with high doses and intra-arterial administration, and they have also been found to cause nephrogenic systemic fibrosis/nephrogenic sclerosing dermopathy.

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis is caused by exposure of patients with renal impairment to gadolinium-based contrast agents. The first cases were identified in 1997 and the condition first clearly described in 2000. Within weeks, months or (less commonly) years of exposure, patients develop a scleroderma-like disease, usually recognized with the development of areas of thickened and hardened skin that can progress rapidly to produce flexion contractures and joint immobility. The lungs, myocardium, and skeletal muscle can be involved. Gadolinium can be detected in skin biopsy specimens. Mortality is up to 30% in some series. There is no known effective treatment, and dialysis immediately after exposure does not prevent the condition. It is difficult to determine the incidence of nephrogenic systemic fibrosis because mild cases undoubtedly go undetected. Release of free gadolinium ions (Gd^{3+}) appears to be crucial in pathogenesis, hence not all gadolinium-based contrast agents are equally culpable. Those with a cyclical structure are less likely to do so (and are therefore considered safer) than those with a linear nonionic structure, which in turn are better than those with a linear ionic structure. Most cases have been related to gadodiamide, with perhaps 2 to 4% of patients with significant renal impairment who received this agent developing the condition, although much higher rates (up to 25%) have been reported in some series. Recognition of nephrogenic systemic fibrosis has led to the recommendation that cyclical gadolinium-based contrast agents should be cautiously used in patients with an eGFR of less than 30 ml/min (chronic kidney disease stage 4 and stage 5), and in patients with an eGFR of between 30 and 60 ml/min (chronic kidney disease stage 3) the clinician should consider whether the necessary imaging information could better be obtained by another imaging technique. Although some authorities recommend haemodialysis immediately after gadolinium-enhanced MRI scanning, this has not been shown to prevent the development of nephrogenic systemic fibrosis. If MRI is the best imaging technique, then to reduce the risk of nephrogenic systemic fibrosis the cumulative exposure to gadolinium should be considered, a cycle chelate preferred, with use of the minimum dose required. Spurious hypocalcaemia may occur post MRI scanning as free gadolinium may interact with colourimetric methods used to determine serum calcium by modern day automated biochemical analysers.

Plain and conventional gadolinium-enhanced MRI

MRI is expensive, but does have some advantages over conventional CT. Tissues surrounded by fat, such as enlarged lymph nodes, or tumour extension into the renal vein, and angiomyolipomas are better demonstrated on MRI than CT. Thus MRI is useful in staging renal cell carcinoma, and by being able to distinguish blood from tissue can help to differentiate simple cysts complicated by haemorrhage from those that are malignant. The fact that MRI does not expose the patient to radiation also offers an obvious advantage over CT in those requiring repeated imaging. The whole of the urinary tract can be visualized, in a manner similar to an IVU, by using a heavily weighted T2 fast spin-echo sequence. This rapid acquisition and relaxation enhancement scan can be used to as- sess potential live donors for renal transplantation, by demonstrating the renal vasculature, renal anatomy, and urinary drainage with one investigation. The quality of image provided by MRI can be very high (Figs. 21.4.10 and 21.4.11), and in general MRI can distinguish an Fig. 21.4.10 Gadolinium-enhanced MRI showing left-sided pyelonephritic scarring, with a reduction in cortical thickness and scarring. Fig. 21.4.11 Gadolinium-enhanced MRI showing a hydronephrotic left kidney and dilated upper two-thirds of the ureter following gynaecological surgery.

21.4 Clinical investigation of renal disease 4801 acute process, such as pyelonephritis, from scarring from previous in- fections, but current MRI resolution is not as good as the new gener- ation of ultrafast three-dimensional CT scanners. In some cases, abnormal signal intensity on MRI is sufficiently characteristic to allow a specific radiological diagnosis. For ex- ample, low-signal magnetic resonance images are seen in three main categories: haemolysis (e.g. paroxysmal nocturnal haemoglobin- uria, cortical haemosiderin deposition from mechanical haemolysis, sickle cell disease, haemorrhagic fever with renal syndrome), vas- cular disease (renal arterial infarction, acute renal vein thrombosis, renal cortical necrosis, acute renal transplant rejection), and acute nonmyoglobinuric renal failure. MRI has become the standard in- vestigation for prostate cancer and targeting suspicious areas for bi- opsy, termed fusion-guided prostate biopsies. As with the developments in CT, three-dimensional MRI scanners coupled with greater data acquisition are being developed to increase image resolution. New contrast agents such as gadolinium DTPA (see ‘Dynamic imaging—radiolabelled DTPA and MAG3’) are being trialled with some success in a technique known as dynamic con- trast magnetic resonance renography (MRR), which has the potential to provide complete anatomical and physiological kidney-specific evaluation. Similarly, functional MRI techniques, including perfu- sion, diffusion-weighted imaging, and blood oxygen level-dependent (BOLD) MRI, have been developed to investigate renal blood flow and oxygen uptake in the kidney in disease states and in response to drugs. However, these currently remain research investigations re- quiring further technical and clinical validation, and demonstration of cost-effectiveness before they enter routine clinical practice. Magnetic resonance angiography This technique (Fig. 21.4.12) overemphasizes any stenotic area or other vascular abnormality and may miss minor accessory renal arteries. MRA is useful in confirming normality, and is commonly used in the preoperative assessment of living related kidney donors. A normal study of the renal arteries excludes renal artery stenosis and significant intrarenal vascular disease. MRA has become the screening technique of choice for excluding renal transplant artery stenosis in renal transplant patients with otherwise unexplained raised serum creatinine or difficult-to-control hypertension. Newer techniques are being developed to improve image acqui- sition and reduce respiratory artefacts to improve image resolution, including high-resolution three-dimensional unenhanced ECG-gated respiratory-navigated MRA of the renal arteries, and balanced steady- state free precession, which do not require gadolinium contrast. Magnetic resonance venography As with MRA, magnetic resonance venography using gadolinium contrast can be used to assess renal venous patency. Patients with nephrotic syndrome and those with renal adenocarcinoma may de- velop renal venous thrombosis, which can be difficult to positively diagnose with other imaging techniques. Angiography and digital subtraction angiography Although formal renal angiography remains the gold standard tech- nique for assessing renovascular disease (Fig. 21.4.13), it has largely been replaced by ultrafast CT angiography and MRA in clinical practice. However, given that (as stated previously) current MRA techniques overestimate stenosis, angiography is then often used to confirm the severity of a stenosis, allowing both the anatomy and direct pressure measurements to be assessed before proceeding to angioplasty/stenting. Renal angiography is not without hazard: it involves an arterial punc- ture and the use of potentially nephrotoxic contrast agents, and carries the risk of dislodging aortic and renal artery plaques, which can result in intrarenal, intra-abdominal, and peripheral cholesterol embolization. Aside from the investigation of suspected chronic renovascular disease, renal and coeliac arteriography can establish a diagnosis of classical macroscopic polyarteritis nodosa. Occasionally, renal angiography is helpful in assessing renal tumour vascularity, and in determining whether partial nephrectomy can be performed. In some cases of persistent nonglomerular haematuria, formal renal angiography reveals a vascular abnormality as the underlying cause. Digital subtraction angiography (DSA) uses a venous injection of contrast and computer-derived images to view the major renal ar- teries and intrarenal vessels. High doses of contrast media may be Fig. 21.4.12 Magnetic resonance angiogram showing a tight proximal stenosis in the single left renal artery (arrow) with post-stenotic dilatation. There is a single right renal artery, without significant stenosis. Fig. 21.4.13 Renal arteriogram showing fibromuscular hyperplasia of the renal artery.

section 21 Disorders of the kidney and urinary tract 4802 required, but even so insufficient anatomical definition is obtained in between 5 and 20% of cases. Interventional renal arteriography Interventional renal arteriography should only be undertaken by experienced interventional radiologists with the support of vas- cular surgeons because it may be complicated by renal artery dis- section or rupture. Embolization with gel foam or metal coils can be used to selectively control renal haemorrhage, which is par- ticularly useful when this follows renal biopsy, and also in cases of arteriovenous malformation or tumour. Occasionally, a whole kidney is embolized. Some atheromatous renovascular stenotic le- sions can be usefully treated by transluminal angioplasty and/or stenting. Renal venography Selective renal venous catheterization for blood sampling is still useful in patients with severe renovascular disease. The relative renal vein renin concentrations may aid the decision-making process in deciding whether to perform a surgical or medical nephrectomy in a patient with a small, poorly functioning kidney due to severe renal artery stenosis. Renal venography is the gold standard test to diag- nose the rare nutcracker syndrome, a clinically manifest variant of the renal vein entrapment syndrome, or mesoaortic compression of the left renal vein. Nuclear medicine The main uses of renal nuclear medicine scans are given in Box 21.4.1. Static imaging—radiolabelled DMSA Technetium-labelled dimercaptosuccinic acid (DMSA) binds to renal proximal tubular cells, and after an intravenous injection some 70% of the dose is taken up by viable tubules within 3 to 4 h. This can be detected by a gamma camera. DMSA scans provide information about the relative function of each kidney, and show areas of scarring due to renal stone disease, infection, and vascular disease. In children with urinary tract sepsis suspected of having re- flux nephropathy, serial DMSA scans are used to assess progressive cortical scarring. During acute pyelonephritis, the DMSA scan may appear to show scars. These photopenic areas are due to inflamma- tion and increased intrarenal pressure and can return to normal following resolution of infection. DMSA scans are also used to con- firm the congenital absence of a kidney, to detect ectopic kidneys and other congenital malformations such as horseshoe kidney, du- plex systems, and cross/fused ectopia, and to confirm absence of renal function. More recently, the introduction of single-photon emission CT (SPECT) DMSA scans has improved resolution, although this starts to fade at GFRs below 30 ml/min. These scans have shown that renal scars occur more frequently than previously thought, both in pa- tients with acute pyelonephritis and also following lower urinary tract infection in renal transplant recipients (Fig. 21.4.14). Dynamic imaging—radiolabelled DTPA and MAG3 Technetium-labelled DTPA and MAG3 are both filtered by the glomerulus and then rapidly excreted by the kidney. MAG3 is now largely replacing DTPA as it has a better extraction efficiency and therefore offers improved image definition, particularly in patients with chronic kidney disease, with a lower absorbed radiation dose. The renograms produced have three phases: vascular, accumulation within the kidney, and excretion. Renal artery stenosis and acute tubular necrosis can reduce uptake, flattening the second and third phases of the renogram. Similarly, intrinsic renal disease flattens the second phase, and makes interpretation difficult when renal func- tion is impaired. Urinary obstruction Radiolabelled DTPA and MAG3 scans are used to assess urological obstruction (Fig. 21.4.15), and can be useful in the management of patients with urinary calculi in assessing the functional significance of any obstruction, monitoring progress and the timing of intervention, ureterocoele, cases of differential obstruction such as a duplex kidney where obstruction is more likely to affect the upper pole, and possible obstruction following urinary diversion. Occasionally, patients with polycystic kidney disease present with severe pain due to the obstruction of a cyst, and DTPA/MAG3 scanning provides a dynamic test to confirm this. In cases of ob- struction, the scan shows retention of tracer in the pelvicalyceal Box 21.4.1 Main uses of renal nuclear medicine scans • DMSA (dimercaptosuccinic acid):

— Estimation of differential renal function

— Imaging of scarring (reflux) • MAG3 (mercaptoacetyltriglycine):

— Detection of obstruction

— Estimation of differential renal function

— Screening for renal artery stenosis

— Renal transplant monitoring Fig. 21.4.14 A SPECT DMSA scan showing a large wedge-shaped defect within the upper pole of the renal transplant. There is another smaller peripheral defect suggestive of renal scarring.

21.4 Clinical investigation of renal disease 4803 system, and the first change noted in the curve is a flattening of the third phase. When obstruction is established, the second phase is prolonged and the third phase continues to rise, and at worst all three phases are affected due to ensuing poor renal function. In cases of vesicoureteric reflux, MAG3 renograms with late films, de- layed until the child voids, can be used as an indirect micturating cystogram. In patients with dilated collecting systems, it is important to dif- ferentiate congenital megaureter from obstruction. Excretion may be slow due to pooling in a dilated system, but obstruction is un- likely if there is a brisk washout following the administration of intravenous furosemide, although patients with impaired renal function may have a reduced response to furosemide, making inter- pretation of the renogram less reliable. Thus, in cases with impaired renal function, direct pressure measurement within the renal pelvis following percutaneous puncture may be required to exclude partial obstruction (Stamey test). DTPA/MAG3 scans are also used to detect and monitor reflux in children, as reflux may be demonstrated during the ‘emptying’ phase of the renogram. If not, then an indirect micturating cystogram can be performed using the radioactivity which has passed into the child’s bladder. Hypertension The main role of nuclear medicine in hypertension is the screening and diagnosis of renal artery stenosis (Fig. 21.4.16). Patients with renal artery stenosis may have a delay in uptake time (the time taken from injection to peak activity) and an increased intensity and dur- ation of MAG3 accumulation (due to increased tubular salt and water reabsorption, not seen in the case depicted in Fig. 21.4.16). If there is significant stenosis of a major branch artery, perfusion to one pole may be delayed. Two scans are performed to improve the sensitivity and specifi- city of the MAG3 renogram in the detection of renal artery sten- osis, one with and one without prior administration of captopril. The captopril–MAG3 renogram can also be used as a screening test to determine whether the use of angiotensin converting enzyme in- hibitors or angiotensin II receptor blockers might be detrimental to renal function in patients with an increased risk of atheromatous renovascular disease, including those with severe cardiac failure or diabetes and elderly hypertensive patients, but it is rarely used for this purpose—the usual practice is to measure the serum creatinine before and 1 to 2 weeks after starting these drugs, and then stopping them (and considering imaging of the renal arteries) if this has risen by more than 20 to 30%. As MAG3 can provide an assessment of divided renal function (although not as accurately as DMSA, particularly in infants), serial scanning may be helpful in monitoring patients over time to de- termine whether intervention with angioplasty or stenting is war- ranted, and similarly postintervention. Bilateral disease is more difficult to diagnose, but usually one kidney is more affected than the other. Following kidney transplantation, serial MAG3 isotope scans can be used to monitor graft function. In cases of major arterial or venous thrombosis, and hyperacute rejection, the graft appears to have no perfusion. Acute tubular necrosis, rejection, and calcineurin toxicity may all have similar appearances. MAG3 scans may also re- veal perirenal haematoma, lymphocele, and urinary leaks before they are clinically manifest. Later isotope scans may detect obstruc- tion due to ureteric stenosis. MAG3 can be used in anuric patients with acute renal failure to show vascular supply, such as those developing acute kidney injury after aortic surgery. Other isotopes Methyldiphosphonate (MDP) is filtered by the glomerulus, pro- viding an immediate dynamic renogram. It is later taken up by inflamed muscles (found in patients with myositis and rhabdo- myolysis) and the skeleton (detecting single or multiple bone me- tastases, and also metabolic bone disease in patients with endstage renal failure). Right Left 1750 1500 1250 1000 750 500 250 00 4 8 12 16 20 Counts per minute Minutes Fig. 21.4.15 DTPA renogram showing increasing uptake by the right kidney in a case of right-sided ureteric obstruction. Right Left 150 125 100 75 50 25 0 0 4 8 12 16 20 Counts per minute 153 Minutes Fig. 21.4.16 MAG3 renogram demonstrating reduced uptake by the left kidney in a case of left-sided renal artery stenosis.

section 21 Disorders of the kidney and urinary tract 4804 Combination techniques PET scanning, using fluoride-labelled deoxyglucose (FDG), in combination with CT scanning was introduced to improve ana- tomical localization of tumours. Combining PET with standard CT improves lesion localization and characterization, and tumour staging (Fig. 21.4.17). The role of PET/CT in primary staging of renal and prostate cancer has yet to be established, but it does have a role in detecting testicular tumours and in managing patients with advanced/metastatic renal and bladder cancer. However, PET/CT scanning also localizes areas of infection and inflam- mation and hence can be used to image and monitor response to treatment in a variety of circumstances, for example, infected cysts in patients with adult polycystic kidney disease, large-vessel vasculitis in cases of Takayasu’s arteritis (Fig. 21.4.18), and retro- peritoneal fibrosis. Renal biopsy Indications A renal biopsy should be considered in any patient with disease af- fecting the kidney when the clinical information and other labora- tory investigations have failed to establish a definitive diagnosis or prognosis, or when there is doubt as to the optimal therapy. However, renal biopsy has the potential to cause morbidity and (on rare occasions) mortality, hence its risk must be outweighed

by the potential advantages of the result to the individual patient. Biopsies which would be ‘of interest’ but ‘not in the patient’s interest’ should not be performed. Indications for renal biopsy must be considered on an individual basis, with the clinical presentations that warrant native renal biopsy given in Box 21.4.2. Diabetic patients with proteinuria would not normally be bi- opsied unless they had other conditions, such as haematuria or sudden-onset nephrotic-range proteinuria, suggesting there might be an alternative or additional diagnosis to diabetic nephropathy.
Fig. 21.4.17 FDG-PET scan highlighting a renal cell cancer (arrow) that developed in a patient with adult polycystic kidney disease. Fig. 21.4.18 FDG-PET scan from a patient with aortitis showing increased uptake in the aortic arch (arrows point to the ascending and descending aorta). Box 21.4.2 Possible indications for native kidney biopsy • Asymptomatic proteinuria less than or equal to 1.5 g/day:

— With controlled hypertension

— With dysmorphic haematuria

— With reduced GFR

— With any combination of the above • Asymptomatic proteinuria greater than 1.5 g/day • Nephrotic syndrome • Nonvisible or dysmorphic haematuria:

— Hereditary condition

— Insurance company requirement

— Patient request

— With proteinuria

— With hypertension

— With reduced GFR • Acute kidney injury—exclude ischaemic ATN:

— With abnormal urinary sediment

— With proteinuria

— Positive ANCA/ANA/anti-GBM

— Severe hypertension

— No obvious cause

— Prolonged history • Acute kidney injury—presumed ischaemic ATN:

— Delayed recovery • Chronic kidney disease (reasonable, equal-sized kidneys):

— With proteinuria

— With dysmorphic haematuria • Known renal diagnosis (reasonable equal-sized kidneys):

— Sudden unexplained reduction in GFR

— Unexplained increase in proteinuria Indications may be clear-cut (e.g. acute kidney injury of unknown cause with abnormal urinary sediment; adult with nephrotic syndrome) but they are not always so, and not all nephrologists would recommend biopsy in all of the circumstances listed (e.g. many would elect not to biopsy, but to arrange continued monitoring, for patients with asymptomatic proteinuria and stable renal function). ANA, antinuclear factor; ANCA, antineutrophil cytoplasmic antibody; ATN, acute tubular necrosis; GBM, glomerular basement membrane.

21.4 Clinical investigation of renal disease 4805 Most paediatricians would treat small children presenting with nephrotic syndrome with steroids and only consider renal biopsy if they did not respond to treatment. Some conditions, in particular lupus nephritis and membranous glomerulonephritis, may change histological grading, so requiring repeat biopsy. Renal biopsy is an important investigation in the management of patients with a renal transplant. Postoperative oliguria and/ or deterioration in renal function requires urgent investigation to differentiate acute ischaemic tubular necrosis from calcineurin (ciclosporin or tacrolimus) or other drug toxicity, acute rejection (vascular and/or cellular), urinary obstruction and/or leakage, and even frank infarction. Serial biopsies may be required to monitor the response to antirejection therapy, and at a later stage to examine for recurrence of the original renal disease, or de novo glomerulonephritis in the graft. Contraindications Percutaneous renal biopsy should not be undertaken in patients with polycystic kidney disease. Similarly, patients with renal masses, such as tumours or cysts, should only be biopsied under direct vision, either by real-time ultrasonography or CT scanning, or by formal open surgical biopsy. Patients with a solitary (or solitary functioning) native kidney are normally considered only for open surgical biopsy, although the transjugular approach may be an option. Haemorrhage is more likely to occur in patients with uncontrolled hypertension or hereditary or acquired coagulation disorders, and in those taking anticoagulants or antiplatelet agents, and both anaemia and uraemia impair platelet aggregation. Blood pressure should be controlled and coagulation abnormalities treated before biopsy. Patients with renal amyloid also have an increased risk of haemorrhage, as may those with classic polyarteritis nodosa. Patients with chronic renal failure and bilaterally small kidneys should not undergo biopsy. This would be technically difficult (the kidneys are small and hard) and the biopsy appearances of endstage renal failure are exceedingly unlikely to provide any information that might alter the clinical course or management. Percutaneous renal biopsy should not be performed in patients with untreated acute pyelonephritis due to the risk of developing a perinephric abscess. Technique ‘Blind’ biopsy of the native kidney, meaning biopsy without imaging for localization, should not be performed unless there are truly exceptional circumstances. It is possible to visualize the kidney and biopsy under fluoroscopic control after injection of radiocontrast medium as for an IVU, but the most commonly used method for directing biopsy is ultrasound guidance. This can either be used to record the depth of the lower pole from the skin and mark the surface position vertically above it on inspiration, or to provide real-time guidance. Occasionally, CT guidance is required. Percutaneous renal biopsy should be carried out using sedation and local anaesthesia. Children may require general anaesthesia. For ultrasound-guided biopsy of the native kidney, the patient should be placed prone on top of pillows or folded sheets to compress the upper abdomen and lower ribs and fix (to some degree) the position of the kidneys. Under real-time ultrasonography, the kidneys are visualized, the patient asked to take and hold a deep breath in inspir- ation, and the kidney which is thought to be technically the easiest to biopsy is targeted. To avoid major vessels, the aim should be for the lateral border of the lower pole. Either 14- or 18-gauge Tru-Cut-type needles are commonly used, with most centres now using an auto- mated spring-loaded biopsy gun. Under direct vision, the needle tip is advanced to the renal capsule, and with the kidney fixed in inspir- ation, biopsy is performed. The advent of colour Doppler means that the operator can deliberately avoid the major intrarenal vessels. Transjugular biopsy can be performed in patients who have an increased likelihood of bleeding complications. Technical develop- ments have now allowed biopsy needles to be passed reliably from the renal vein into the renal cortex, such that in the author’s own institution, all such biopsies in the last 8 years have been diagnostic. Occasionally, open surgical biopsy is required, with the biopsy taken under direct vision and local bleeding controlled. Renal transplants, usually placed in one or other iliac fossa, are biopsied in the supine position. Pillows can be placed under the side with the transplant to help move bowel and fat pad away from the transplant. Biopsies are taken from the lateral border of the upper pole, avoiding the major vessels and ureter. The obvious risk of renal biopsy is haemorrhage. All patients should be placed on strict bed rest for at least 6 h after the procedure, and pulse and blood pressure should be checked frequently during this period. Hypotension, tachycardia, abdominal/back pain, and macroscopic haematuria are indications for urgent medical review. Complications Routine imaging after renal biopsy has shown that most patients de- velop a perirenal haematoma (Fig. 21.4.19), which is usually asymp- tomatic. Arteriovenous fistulas may also develop acutely following biopsy, most of which disappear spontaneously with time, with only the occasional one requiring treatment by the interventional radiologist. Macroscopic haematuria occurs in fewer than 10% of patients, and bleeding sufficient to warrant blood transfusion in around 1%. Rarely, severe haemorrhage may necessitate treatment with the insertion of coils or gel foam embolization. Exceptionally, death may occur, usually due to failure to detect haemorrhage and provide appropriate resuscitation. Complication rates are increased in patients with both acute and chronic renal failure. Uraemia prolongs the bleeding time, even when Fig. 21.4.19 CT scan showing haemorrhage (arrow) around the right kidney following a biopsy.

section 21 Disorders of the kidney and urinary tract 4806 the conventional coagulation screening is normal (prothrombin time, activated partial thromboplastin time, and peripheral platelet count). The risk of uraemic haemorrhage can be at least partially reversed prior to biopsy by good dialysis to improve platelet function, correc- tion of the haematocrit and any underlying coagulation defect, and by giving an infusion of deamino-d-arginine vasopressin (DDAVP) immediately prior to the procedure (0.3 µg/kg body weight, over 30 min), but vasopressin may cause cardiac ischaemia and should be avoided in patients with critical coronary or vascular artery disease. FURTHER READING Urine microscopy Birch DF, et al. (1994). A color atlas of urine microscopy. Chapman and Hall, London. Chawla LS, et al. (2008). Urinary sediment cast scoring index for acute kidney injury: a pilot study. Nephron Clin Pract, 110, c145–50. Fogazzi GB, et al. (2015). The urinary sediment. An integrated view, 3rd edition. Masson, Milan. Renal function Alpern RJ, Moe OW, Caplan M (2013). The kidney: physiology and pathology, 5th edition. Academic Press, London. Schrier RW (2017). Renal and electrolyte disorders, 8th edition. Lippincott Williams & Wilkins, Philadelphia. Skorecki K, et al. (2015). Brenner & Rector’s the kidney, 10th edition. Elsevier, Philadelphia. Turner N, et al. (2015). Oxford textbook of clinical nephrology, 4th edi- tion. Oxford University Press, Oxford. White SL, et al. (2009). Diagnostic accuracy of urine dipsticks for de- tection of albuminuria in the general community. Am J Kidney Dis, 58, 19–28. Witte EC, et al. (2011). First morning voids are more reliable than spot urine samples to assess microalbuminuria. J Am Soc Nephrol, 20, 436–43.

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