Clinical assessment of renal disease

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Abstract

Kidney disease presents in a number of different ways and to a variety of practitioners. The presentation can be non-specific, and a high index of suspicion is required to allow early detection and intervention. A systematic clinical assessment is vital to facilitate the timely referral and appropriate management of renal disease. The history and examination should be tailored to the type of presentation, and is dictated by the degree of chronicity of the disease process. In all cases, the urine dipstick is a crucial part of the clinical examination. This article presents an overview of the approach to evaluation and diagnosis in patients with kidney disease. It is intended to be read in conjunction with the other articles in these chapters.

Keywords Acute kidney injury; chronic kidney disease; MRCP; urinalysis

Key points

- Urine dipstick is a key component of the clinical assessment of any patient with renal disease
- The presence of dipstick haematoproteinuria in the context of rapidly deteriorating renal function should prompt urgent referral to a nephrologist
- Proteinuria can be quantified using a spot urine sample and measuring protein:creatinine ratio, avoiding the inconvenience of a 24-hour urine collection
- Diabetes and hypertension are the most common causes of chronic kidney disease in the UK, and a clinical assessment must involve ascertaining the presence, duration, and control of these risk factors
- Imaging the kidneys and bladder using ultrasound scanning provides valuable information about kidney sizes, any structural abnormalities, and any post-renal cause of renal impairment

Introduction

Symptoms of kidney disease are often non-specific, and people with chronic kidney disease (CKD) can be entirely asymptomatic until the late stages of disease. Reduced appetite, nausea, fatigue, itch or fluid overload can indicate advanced CKD and should prompt appropriate investigation. Patients can present at earlier disease stages with hypertension, haematuria, oedema or symptoms of a multisystem disorder.

Kidney disease can also be detected during assessment or screening of patients with a systemic disease that can involve the kidneys, such as diabetes mellitus or systematic lupus erythematosus (SLE). Asymptomatic patients can come to the attention of a clinician after the discovery of abnormalities in routine blood or urine tests, or on imaging of the renal tract. In this chapter, we outline a practical approach to the assessment and diagnosis of kidney disease in both acute and chronic settings.

History

A detailed history is crucial to identify the aetiology of kidney disease, and to determine the chronicity of the process. The focus of the history depends on the initial mode of presentation but should always be targeted at forming a differential diagnosis, which will inform initial investigations and management.

It is useful to consider the three main clinical presentations: acute kidney injury (AKI), subacute or intrinsic renal disease, and CKD. For convenience, these three scenarios will be discussed separately, but it must be borne in mind that certain intrinsic renal diseases can present as AKI, and the presence of underlying CKD increases the risk of developing AKI, so in practice all aspects of the history are relevant to all cases.

Acute kidney injury

AKI is identified by a rise in serum creatinine concentration or oliguria. The history here is directed at identifying recent precipitating factors, which can be categorized as pre-renal, renal or post-renal. ***Renal*** causes of AKI are be discussed in the section on intrinsic renal disease below.

Pre-renal insults include sepsis, hypovolaemia, low cardiac output or a combination of these, leading to (relative) hypotension and subsequent renal hypoperfusion. A history of preceding infection, cardiac failure or diarrhoea and vomiting should be sought.

The drug history may reveal medications such as angiotensin-converting enzyme inhibitors and non-steroidal anti-inflammatory drugs (NSAIDs), which impair the ability of the kidneys to autoregulate and maintain glomerular filtration rate (GFR). Diuretic use prevents the kidneys from concentrating urine appropriately, thereby exacerbating hypovolaemia. It is important to recognize that, in patients with a history of undertreated hypertension, renal hypoperfusion can occur in the face of normotension.

Aminoglycosides are direct tubular toxins and can cause or worsen AKI. Acute interstitial nephritis can be caused by penicillins or proton pump inhibitors; this has become a growing

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problem with the latter in recent years as they have been prescribed with increasing frequency. Over-the-counter medications are often not recognized by patients as being relevant to their drug history, so specific questions should be asked about purchased NSAIDs and herbal remedies.

A history of recent intervention, or imaging using iodinated contrast, should be directly sought. Instrumentation of the aorta for procedures such as percutaneous coronary intervention can cause cholesterol emboli to shower into the renal vessels causing an AKI which is frequently irreversible. By comparison, there is a good chance of recovery of function after contrast-induced nephropathy.

A history of crush injury or prolonged immobility, for example after a drug overdose, raises the possibility of rhabdomyolysis. HIV, hepatitis B and hepatitis C can cause kidney disease, so risk factors for the acquisition of blood-borne viruses should be elicited. A history of bone pain can result from undiagnosed myeloma; this disease can cause AKI via a number of mechanisms, including cast nephropathy and hypercalcaemia.

Post-renal causes in men include obstruction, suggested by absolute anuria and a history of preceding prostatic symptoms (hesitancy, poor stream, nocturia). A history of gynaecological malignancy, radiotherapy or recent pelvic surgery in women raises the possibility of bilateral ureteric obstruction. In anuric patients, imaging of the renal tract should be a priority.

Subacute or intrinsic renal disease

Symptoms can be mild and non-specific even in rapidly progressive glomerulonephritides. Relevant symptoms include fatigue, weight loss, nausea and reduced appetite, and their time of onset can give some idea about the duration of the disease. Patients should be asked specifically about sinus problems, epistaxis, haemoptysis, rashes and joint pains, which can be associated with systemic vasculitides.

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-glomerular basement membrane (GBM) disease (Goodpasture's syndrome), lupus nephritis (class III/IV) and the crescentic form of immunoglobulin A (IgA) nephropathy can cause acute necrotizing glomerulonephritis; this leads to a rapid deterioration in renal function and requires urgent nephrological assessment and treatment to prevent irreversible damage. The history is key in identifying these conditions. Upper and lower respiratory tract involvement is seen in ANCA-associated vasculitis, which can manifest as epistaxis or haemoptysis secondary to pulmonary haemorrhage. Anti-GBM disease affects the kidneys and lower respiratory tract only. Lupus nephritis occurs in 50–60% of patients with SLE and can be its presenting feature[1] however, in many cases other systemic manifestations such as arthralgia, rash, hair loss, mouth ulcers, previous miscarriages or venous thromboses predate overt nephritis.

Fevers and night sweats can occur in vasculitis but also raise the possibility of an infectious aetiology such as tuberculosis or bacterial endocarditis. A history of sore throat or skin infection 2–3 weeks before the development of renal impairment suggests post-streptococcal glomerulonephritis, whereas visible haematuria associated with IgA nephropathy classically occurs within a few days of an upper respiratory tract infection (synpharyngetic). A purpuric rash on the extensor surfaces of the legs and buttocks, along with arthralgia, abdominal pain and dipstick haematoproteinuria, is highly suggestive of Henoch–Schönlein purpura.

Oedema may be the only presenting feature of nephrotic syndrome, although some patients notice that their urine has become 'frothy' because of heavy proteinuria. Venous thromboembolism is occasionally the presenting feature of this syndrome, so it should be considered in patients presenting with unexplained pulmonary embolism or deep vein thrombosis.

Chronic kidney disease

Diabetes mellitus and hypertension are the most common causes of CKD in the UK. However, because these conditions are common, they can coexist with other causes. It is essential to ascertain the underlying burden of disease, which is a function of the duration and adequacy of control of these conditions. Both hypertension and diabetes can be present for many years before diagnosis, and it is crucial to ask about complications of disease in other organs (e.g. diabetic retinopathy, including the need for laser therapy, symptoms of peripheral or autonomic neuropathy, vascular disease) in order to assess the likelihood of associated nephropathy. Whatever the primary cause of renal disease, optimal control of blood glucose and blood pressure is a key factor in reducing the rate of progression.

A history of vascular disease, particularly peripheral vascular disease, raises the possibility of associated renovascular disease. Frequent childhood urinary tract infection (UTI) or prolonged nocturnal enuresis suggests reflux nephropathy.

The presence of a systemic disease such as SLE, myeloma, sarcoidosis or scleroderma in a patient with CKD naturally raises the possibility of secondary renal involvement. However, it is also important to consider whether any medications used to treat the systemic disease could be nephrotoxic.

A family history of hypertension, diabetes or inherited primary renal diseases must be elicited. In patients with a family history of autosomal dominant polycystic kidney disease, ask about the progression of disease in their relatives, and any family history of sudden death or an intracerebral bleed. In patients with a family history of renal disease who do not know the diagnosis, the pattern of inheritance can be informative (e.g. X-linked inheritance in Alport's disease).

Symptoms attributable to CKD itself – 'uraemic symptoms', such as fatigue, nausea, vomiting, itching, weight loss, hiccups and altered taste – occur late and do not tend to manifest until the GFR has fallen to <15 ml/minute (stage 5).

Examination

A detailed history will have provided clues to the underlying cause of the renal disease, and a thorough examination then allows the clinician to prioritize the investigations and management appropriately.

Acute kidney injury

In the context of AKI, adequate assessment of the circulation is key, to identify whether or not there has been a significant prerenal insult. Volume status should be examined by assessing the jugular venous pressure (JVP), systemic blood pressure

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(including postural blood pressure) and peripheral circulation. Skin turgor and appearance of the mucous membranes are notoriously unreliable, especially in older individuals.

Blood pressure should be considered in the context of the patient's usual blood pressure, if known, and the JVP should be interpreted with caution in patients with a history of lung disease, who can have impaired right ventricular function. If the patient has postural hypotension or is in frank circulatory shock, assessment of the peripheral circulation, including pulse volume, temperature of the peripheries and capillary refill indicates the underlying pathology. Warm, dilated peripheries with a high-volume pulse and tachycardia suggest the high cardiac output state of sepsis. Cold, shut-down peripheries with a low-volume pulse indicate reduced cardiac output. This can be the result of hypovolaemia (in which case the JVP is low, and there is no pulmonary oedema), or impaired cardiac function (in which the JVP can be elevated, the apex beat can be displaced, and there can be a third heart sound, peripheral oedema and basal crackles on auscultation of the lungs).

In the absence of any signs of pre-renal injury, other findings that could indicate the cause of AKI must be sought. Hypertension along with salt and water overload can be secondary to acute nephritis. Accelerated-phase hypertension can itself be a cause of AKI, and ophthalmoscopy may reveal hypertensive retinopathy with flame haemorrhages (grade 3) or even papilloedema (grade 4).

The skin should be carefully examined for maculopapular erythematous rashes associated with drug reactions, or cutaneous manifestations of a systemic vasculitis. Patients should be examined for systemic signs of bacterial endocarditis such as splinter haemorrhages, Roth spots and a new or evolving heart murmur. Evidence of cholesterol embolization in the feet ('trash feet'), suggests that the same process is occurring in the kidneys.

Extensive bruising or a tense and tender muscle compartment can be found in rhabdomyolysis. The presence of compartment syndrome should prompt urgent referral to an orthopaedic surgeon, as relief of the pressure may be necessary to save a compromised limb.

A palpably enlarged bladder is suggestive of outflow tract obstruction (post-renal AKI).

Subacute or intrinsic renal disease

The most important part of the physical examination in cases of intrinsic renal disease is the urine dipstick. Dipstick haematoproteinuria is the hallmark of glomerular nephritis. In the presence of rising serum creatinine concentration, a rapidly progressive glomerular nephritis should be suspected; urgent referral to a nephrologist is indicated. ANCA-associated vasculitis and anti-GBM disease can be associated with life-threatening pulmonary haemorrhage. The presence of haemoptysis, crackles in the lungs, and blood and protein on the urine dipstick necessitates urgent investigation of this severe disease manifestation.

Examination of the skin and joints can provide additional clues to the cause of intrinsic renal disease. The hands can reveal changes of systemic sclerosis (nail fold infarcts, thickened shiny skin), or long-standing arthritis that might have been treated with regular NSAIDs or other nephrotoxic medications. Rashes may be seen in SLE, Henoch–Schönlein purpura and ANCA-associated vasculitis (AAV). A saddle-shaped nose can be a manifestation of upper respiratory tract involvement in AAV, and examination of the peripheral nervous system may reveal mononeuritis multiplex.

Intravenous drug users are at risk of kidney disease from acquired blood-borne viruses, bacterial endocarditis (classically right-sided in these cases) and AA amyloid caused by chronic infection. Needle track marks and abscesses around injection sites may be seen in these individuals.

Patients with nephrotic syndrome, by definition, have oedema. This can be peri-orbital, occurring characteristically in the mornings, and postural (pitting oedema of the legs), worsening through the day. Pleural effusions and ascites can also be present.

Chronic kidney disease

Ophthalmoscopy provides extremely useful information in CKD. The retinal changes of hypertension and diabetes are representative of systemic microvascular disease. The presence of cotton wool spots, dot-blot haemorrhages or scars from retinal laser therapy in a patient with diabetes mellitus increases the likelihood that they have diabetic nephropathy. Similarly, silver wiring, arteriovenous nipping and retinal haemorrhages in a patient with hypertension are indicative of suboptimal control, at least historically.

Renal bruits may be heard in patients with renovascular disease. The presence of femoral bruits and weak or absent peripheral pulses indicates significant peripheral vascular disease, which increases the likelihood of associated renovascular disease.

Polycystic kidneys can be easily palpable, and there can be associated hepatomegaly caused by liver cysts. Patients with Alport's syndrome may require hearing aids for hearing loss caused by abnormal collagen IV in the basement membrane of the inner ear.

In advanced renal disease, there can be signs of overt uraemia such as a pericardial rub, uraemic fetor, nodular prurigo (a nodular rash caused by persistent itch) or, rarely, uraemic frost.

Urinalysis

The humble urine dipstick is a powerful tool in the diagnosis of kidney disease. Dipstick urinalysis is essential in the evaluation of all patients with known or suspected kidney disease and can be used to test the urine for:

- specific gravity (SG)
- pH
- nitrites
- leucocytes
- ketones
- glucose
- blood (haematuria)
- protein.

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Urobilinogen, bilirubin and β-human chorionic gonadotropin are also commonly tested for using a urine dipstick. However, these have limited bearing on the assessment of kidney disease and are therefore not discussed here.

Specific gravity

SG is a ratio of the density of a substance to the density of a reference substance, usually water when liquids are being considered; it is a measure of the concentration of a solution. Urine SG is directly proportional to urine osmolality and is typically 1.002−1.035.

The SG of the glomerular filtrate (in the Bowman's space) ranges from 1.007 to 1.010. SG <1.007 indicates a dilute urine in a state of hydration, whereas SG >1.010 indicates relative dehydration. If urine SG is not >1.022 after a 12-hour period without food or water, a deficit in the kidney's concentrating ability is present. If kidney function is normal, such a deficit can indicate nephrogenic diabetes insipidus. In the context of end-stage kidney disease and acute tubular necrosis, the SG of the urine tends to reflect that of the glomerular filtrate (1.007 −1.010). SG >1.035 suggests contamination of the urine or a very high concentration of an osmotically active substance, such as glucose or iodinated contrast.

pH

Depending on plasma acid−base status, urine pH can range from as low as 4.5 to as high as 8.0. In isolation, urine pH is rarely helpful. However, if the urine is strongly alkaline, a UTI with a urease-producing organism should be suspected: urease catalyses the conversion of urea to ammonia. Measuring urinary pH can help in the diagnosis of renal tubular acidosis and the evaluation of nephrolithiasis. It can also be useful as a therapeutic target: precipitation of proteinaceous casts (e.g. in myeloma or rhabdomyolysis) is favoured in an acidic urine, and alkalization of the urine (maintaining pH >6.5) by the oral or intravenous administration of alkali (typically sodium bicarbonate) can help prevent this. Loop diuretics have the opposite effect and should in general be avoided.

Nitrites

Microbial nitrates are produced by many Gram-negative bacteria, including *Escherichia coli*, and are excreted as urinary nitrites. A positive test for nitrites suggests the presence of significant numbers of bacteria (>10,000/ml). A negative result does not, however, rule out a UTI. The reagent is highly sensitive to air exposure, which can cause a false-positive response.

Leucocytes

The reagent strip relies on the detection of leucocyte esterase produced by neutrophils. A positive result suggests pyuria, which is most often the result of a UTI. False-positive results can be caused by contamination with vaginal discharge. Elevated urine glucose or oxalic acid concentrations can reduce sensitivity, as can tetracycline or cefalexin use.

Ketones

Ketone bodies are metabolites of fatty acids produced once the body has exhausted its glycogen reserves and started to break down fat stores. Ketonuria is therefore mainly associated with insufficient insulin availability in type 1 diabetes mellitus, potentially indicating diabetic ketoacidosis or some form of carbohydrate deprivation (anorexia, prolonged vomiting, diarrhoea, fever, starvation, Atkins diet).

Glucose

Dipstick reagent strips frequently test for reducing sugar or glucose but this is of little practical value. Glycosuria (the presence of reducing sugar) can suggest diabetes but the positive and negative predictive values of its detection are poor. It can also suggest proximal tubular dysfunction (e.g. Fanconi's syndrome) or treatment with sodium glucose co-transporter 2 (SGLT-2) inhibitors (gliflozins).

Blood

The term 'visible haematuria' should be used in preference to macroscopic or gross haematuria, and 'non-visible haematuria' (both symptomatic and asymptomatic) should replace microscopic haematuria or dipstick-positive haematuria.

A urine dipstick test for blood is generally sufficient. It is sensitive when performed on fresh voided urine when no preservatives (i.e. boric or tartaric acid) are present. A score ≥1+ is positive; a trace amount is considered negative. The presence of haemolysed red blood cells should be treated in the same way as non-haemolysed red cells. Further assessment is warranted in patients with urinary tract symptoms and non-visible haematuria, apparent as ≥1+ blood on a single dipstick test.

In patients with asymptomatic non-visible haematuria, it is not necessary to confirm the result by microscopy if blood is present in at least two out of three dipstick tests. Transient causes, such as UTI, menstrual contamination and vigorous exercise, should be excluded before referral for further investigation.

Individuals aged <40 years with isolated non-visible haematuria (i.e. without albuminuria) and without impaired kidney function and hypertension, or those aged ≥40 years in whom urological causes have been excluded, do not need any further investigation or specialist follow-up. These individuals have an increased lifetime risk of end-stage kidney disease but the absolute increase in risk remains small.[2] They should remain under primary care follow-up.

Table 1 shows a list of causes of haematuria. Rhabdomyolysis produces a false-positive result.

Protein

Proteins pass into glomerular filtrate in an inverse proportion to their size and negative charge. Proteins with a molecular weight <20 kDa pass easily across the GBM.[3] By contrast, albumin, with a molecular weight of 66.5 kDa and a negative charge, is prevented from crossing under normal conditions. The smaller proteins are predominantly reabsorbed in the proximal tubule, with only small amounts excreted in the urine. Transient proteinuria occurs in up to 7% of healthy subjects. The large number of causes (Table 2) can be categorized as:

- functional
- tubular
- overflow
- glomerular.

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Causes of haematuria

	Urological causes	Nephrological causes
Common	Benign prostatic hyperplasia Cancer (prostate, bladder, ureter, kidney) Stones Infection — cystitis, pyelonephritis, prostatitis, urethritis, schistosomiasis	
Less common	Radiation cystitis Urethral strictures Tuberculosis Medullary sponge kidney Chemical cystitis (e.g. cyclophosphamide, ketamine)	IgA nephropathy Thin basement membrane disease

Rare	Arteriovenous malformation
	Renal artery thrombosis
	Papillary necrosis
	Loin pain—haematuria syndrome
		Acute glomerular disease:
		• Post-infectious glomerulonephritis
		• Systemic lupus nephritis
		• Vasculitis
		• Henoch—Schönlein purpura
		• Haemolytic—uraemic syndrome
		• Goodpasture's disease
		• Chronic primary glomerulonephritis
		  • Focal segmental glomerulonephritis
		  • Mesangio-capillary glomerulonephritis
		  • Membranous nephropathy
		Familial causes:
		• Polycystic kidney disease (autosomal dominant or recessive)
		• Hereditary nephritis (Alport's syndrome)
		• Fabry's disease
		• Nail—patella syndrome

Table 1

More than 90% of cases of persistent proteinuria can be attributed to glomerular disease resulting from an increase in glomerular permeability. The presence of blood and protein in the urine is thus the hallmark of glomerular disease.

Functional proteinuria occurs when increased renal blood flow (e.g. caused by exercise, fever, high-output heart failure or pregnancy) delivers increased amounts of protein, exceeding the reabsorptive capacity of the proximal tubule. Protein losses are typically <1 g/day and cease when renal blood flow returns to normal.

Causes of proteinuria

Mechanism	Examples
Functional	Fever Heart failure Intense exercise
Tubular	Fanconi's syndrome Acute tubular necrosis Tubulo-interstitial nephritis
Overflow	Monoclonal gammopathy Multiple myeloma Rhabdomyolysis Polymyositis
Glomerular	Primary glomerular disorders (e.g. membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis) Secondary glomerular disorders (e.g. diabetic nephropathy, pre-eclampsia, post-infectious glomerulonephritis, lupus nephritis, amyloidosis)
Unknown	Orthostatic

Table 2

Tubular proteinuria results from tubulo-interstitial disorders that impair the reabsorption of protein by the proximal tubule. This leads to excessive urinary protein loss, mostly in the form of smaller, low molecular weight proteins, such as retinol-binding protein, α_2-microglobulin and β_2-microglobulin, rather than albumin. However, it is unusual for these to exceed 2 g/day. Other defects in tubular function (e.g. bicarbonate wasting, glucosuria, aminoaciduria, phosphaturia) are frequently evident.

Overflow proteinuria occurs when excessive amounts of small plasma proteins (e.g. immunoglobulin light chains produced in multiple myeloma or rhabdomyolysis) exceed the reabsorptive capacity of the proximal tubules. It is important to remember that urine dipstick tests are usually specific for albumin.

Orthostatic proteinuria is a benign condition, occurring mainly in children and adolescents, in which proteinuria occurs chiefly when the patient is upright. Urine produced during waking hours thus contains more protein than that produced during the night. The prognosis is excellent, and no specific intervention is required.

Quantification of proteinuria

Once urinary protein excretion has been detected on dipstick testing, it is essential to quantify the amount. Normal urine protein excretion is <150 mg/day, of which approximately 20% is low molecular weight proteins (e.g. immunoglobulin, β_2-microglobulin), up to 40% (<30 mg/day) is higher molecular weight protein (predominantly albumin), and 40% is Tamm—Horsfall protein secreted by the distal tubule.

The amount of protein excreted in the urine during a 24-hour period is still considered to be the gold standard. However, 24-hour collections are inconvenient and impractical for patients to perform. They are also prone to significant collection errors,

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Routine blood tests normally indicated in patients with suspected kidney disease

Test	Interpretation
Serum urea, creatinine and electrolytes	• Hyperkalaemia — a potentially life-threatening complication of kidney disease (>6.5 mmol/litre is a medical emergency) • Urea:creatinine ratio is typically 1:20; a disproportionately elevated value suggests renal hypoperfusion caused by hypovolaemia or heart failure
Full blood count	• Anaemia — advanced CKD, autoimmune disease, MAHA • Leucocytosis — sepsis, lymphoma • Eosinophilia — drug-induced tubulointerstitial nephritis, cholesterol emboli syndrome • Thombocytopenia — MAHA (a feature of haemolytic–uraemic syndrome and malignant hypertension) • Thombocytosis — inflammation, especially polyangitis with granulomatosis
Bone profile	• Hypoalbuminaemia — nephrotic syndrome, malnutrition, inflammation, liver failure • Hypocalcaemia — advanced CKD, rhabdomyolysis, pancreatitis • Hypercalcaemia — bony metastases, especially myeloma, sarcoid
Serum CRP	• Elevated in inflammatory states such as sepsis and vasculitis. The exception is SLE, which classically does not show increased CRP; elevated CRP in the setting of known SLE suggests an alternative aetiology (e.g. sepsis)
Bicarbonate	• Reduced in renal tubular acidosis and advanced CKD (stages 4 and 5)
Cholesterol	• Atherosclerotic risk factor
HbA_{1c}	• Poor glycaemic control increases likelihood of microvascular complications of diabetes mellitus, including nephropathy
Immunoglobulins, serum protein electrophoresis	• Serum IgA is elevated in some patients with IgA nephropathy • Screen for multiple myeloma in all patients aged >40 years
If blood 1+ or proteinuria 1+ present on dipstick	
Viral serology	• Hepatitis B surface antigen, hepatitis C IgG, HIV — can be pathogenic, inducing secondary GN. Also important in patients likely to require haemodialysis, in relation to infection control
Antinuclear antibody, double-stranded DNA antibodies, antibodies to extractable nuclear antigens	• To be requested if SLE or connective tissue disease is suspected
Complement C3/C4	• Used up in a number of immune complex-mediated GNs (e.g. SLE, mesangiocapillary glomerulonephritis) • Can also be reduced in endocarditis
Rheumatoid factor	• Antibody directed against the Fc portion of IgG. Frequently positive in the presence of cryoglobulins
Cryoglobulins	• Prone to false-negative results; blood should be taken under specific conditions into warmed tubes and kept warm in transit to the laboratory
ANCA	• Cytoplasmic (cANCA) — granulomatosis with polyangitis • Perinuclear (pANCA) — microscopic polyangitis
In patients with oligo-anuric acute kidney injury	
Anti-GBM antibodies	• Associated with Goodpasture's syndrome

CRP, C-reactive protein; HbA_{1c}, glycated haemoglobin; Ig, immunoglobulin; MAHA, microangiopathic haemolytic anaemia.

Table 3

largely from improper timing and missed samples, resulting in over- and undercollection. Thus, when performing a 24-hour collection, we recommend that simultaneous measurement of urine creatinine excretion be undertaken. In general, an adequate collection contains 15–20 mg of creatinine per kilogram of body weight in women, and in men 20–25 mg/kg. Alternatively, the expected weight (grams) of excreted creatinine can be estimated (in men) using the formula:

$$\text{Excreted creatinine (g)} = (140 - \text{age in years}) \times \text{weight in kg} / 5000$$

For women, the result using this formula is then multiplied by 0.85.

Albumin and creatinine ratios: because of the inherent inaccuracies and inconvenience of performing timed collections, the spot albumin:creatinine ratio (ACR) or total urinary protein:creatinine ratio (PCR) is commonly used in clinical practice. The ACR or PCR in the first morning void correlates most closely with 24-hour excretion. As a rule of thumb, 100 mg/mmol or 1 g/g is considered to be equivalent to 1 g/day. Dividing the ACR by 8.84 converts the units (from micrograms/mg or mg/g to mg/mmol).

Classification of proteinuria

Several terms are used to describe the magnitude of proteinuria: microalbuminuria, overt albuminuria/proteinuria and nephrotic range proteinuria.

The Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for albuminuria[4] classify it as:

- <30 mg/g (<3 mg/mmol) = normal to mildly increased = A1
- 30–300 mg/g (3–30 mg/mmol) = moderately increased = A2

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- >300 mg/g (>30 mg/mmol) = severely increased (overt albuminuria) = A3.

Albuminuria has been shown to be an independent risk factor for progressive kidney disease and risk of end-stage kidney disease.

Selective and non-selective proteinuria: proteinuria in the context of minimal change disease is largely restricted to albumin (selective proteinuria), in contrast to focal segmental glomerulosclerosis and membranous nephropathy (unselective proteinuria).

Nephrotic syndrome: this is seen only with glomerular disease. The cardinal features are:

- proteinuria >3–3.5 g/day (PCR >300 mg/mmol)
- hypoalbuminaemia <30 g/litre
- oedema.

Some authorities also include:

- hypercholesterolaemia
- lipiduria.

Nephrotic range proteinuria: this term describes heavy proteinuria (within the nephrotic range, >3.5 g/day) but without the other features of nephrotic syndrome (e.g. oedema, low serum albumin). The most common cause is advanced diabetic nephropathy.

Blood tests

Blood tests provide the most convenient means of evaluating kidney function. Important information can be garnered in order to refine the differential diagnosis. Crucially, review of historic blood results can define the speed of deterioration in kidney function, so it is important to contact the GP and other hospitals the patient has previously visited.

Table 3 outlines suggested blood tests, but other specialist tests can be indicated.

Imaging

Ultrasound scanning is the principal imaging modality used to evaluate kidney disease. It is relatively cheap and readily available, and has the further advantage of avoiding exposure to ionizing radiation.

Key findings include the following:

- Urinary obstruction can be excluded.
- Normal anatomy (i.e. two equally sized kidneys) can be confirmed or deviation from this identified.
  - Asymmetry in kidney size can indicate renal artery stenosis, especially in the context of other atherosclerotic risk factors, or renal dysplasia; >1.5 cm difference in size can be pathological.
  - The bipolar length of normal adult kidneys is 11 ± 1 cm; some reduction can, however, be allowed in a small adult as bipolar length correlates with indices of body size.[5]
- Loss of cortical thickness implies CKD, frequently ischaemic in aetiology, and can also be seen with a chronically obstructed kidney.
- Loss of corticomedullary differentiation – loss of corticomedullary differentiation and increased echogenicity of the kidneys are non-specific signs of kidney disease, usually implying chronicity (Table 4).
- There may be cortical scars from pyelonephritis.
- Cysts can be simple or complex/septated (possibly malignant).
- Stones are in general poorly seen on ultrasonography, and better evaluated with low-dose computed tomography (CT) scanning.

CKD with preserved or increased bipolar length

- Amyloid
- Diabetic nephropathy
- HIV-associated nephropathy (HIVAN)
- Polycystic kidney disease
- Obstructive uropathy

Table 4

Differential diagnosis

Nephrologists arrive at a differential diagnosis by considering the:

- age of the patient
- speed of onset/chronicity
- presence of impaired excretory function, and reduced GFR
- presence or absence of hypertension
- magnitude of proteinuria
- presence of hypoalbuminaemia
- presence or absence of haematuria
- associated/systemic features
- examination findings.

Kidney biopsy

A kidney biopsy is primarily performed to identify treatable causes of kidney disease. Therapy most often takes the form of immunosuppression. Typical indications include:

- heavy proteinuria
- overt nephrotic syndrome
- CKD without explanation where there are grounds to suspect tubulo-interstitial disease
- AKI without explanation or which fails to resolve, and occasionally for prognostic purposes. ◆

KEY REFERENCES

1 de Zubiria Salgado A, Herrera-Diaz C. Lupus nephritis: an overview of recent findings. *Autoimmune Dis* 2012; **2012:** 849684.

2 Vivante A, Afek A, Frenkel-Nir Y, et al. Persistent asymptomatic isolated microscopic hematuria in Israeli adolescents and young adults and risk for end-stage renal disease. *J Am Med Assoc* 2012; **306:** 729–36.

3 Haraldsson B, Nyström J, Deen WM. Properties of the glomerular barrier and mechanisms of proteinuria. *Physiol Rev* 2008; **88:** 451–87.

4 Kidney Disease: Improving Global Outcomes. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. http://www.kdigo.org/clinical_practice_guidelines/pdf/CKD/KDIGO_2012_CKD_GL.pdf.

5 Kang K-Y, Lee YJ, Park SC, et al. A comparative study of methods of estimating kidney length in kidney transplantation donors. *Nephrol Dial Transplant* 2007; **22:** 2322–7.

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