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 may 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 timely referral and appropriate management of renal disease. The history and examination should be tailored to the type of presentation, and will be 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 the patient 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; intrinsic renal disease; post-renal; pre-renal; urinalysis

Introduction
Patients with kidney disease may present with hypertension, with impaired kidney function, with symptoms and signs of proteinuria or haematuria, or with features of a systemic disease that is known to involve the kidneys. Asymptomatic patients may also 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 the acute and chronic settings.

History
A detailed history is crucial in order to identify the aetiology of kidney disease, as well as to determine the chronicity of the process. The focus of the history will depend on the initial mode of presentation but should always be targeted at forming a differential diagnosis, which in turn will inform initial investigations and management. It is useful to consider the three main clinical presentations that are encountered: acute kidney injury (AKI), sub-acute or intrinsic renal disease, and chronic kidney disease (CKD). For convenience we will discuss the history in these three scenarios 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 or oliguria. History in this context is directed at identifying recent precipitating factors, which may be categorized as pre-renal, renal or post-renal. The renal causes of AKI will be discussed in the intrinsic renal disease section 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 will prevent 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 exacerbate AKI, and penicillins can cause an acute interstitial nephritis (AIN). Proton pump inhibitors can also cause AIN, which has become a growing problem in recent years during which 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 with the use of iodinated contrast, should also be directly sought. Instrumentation of the aorta for procedures such as percutaneous coronary intervention (PCI) can lead to the shedding of cholesterol emboli into the renal vasculature, causing AKI, which is often irreversible; by comparison, there is a good chance of recovery of function following contrast-induced nephropathy (CIN).

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 all cause kidney disease and therefore risk factors for acquisition of blood-borne viruses should be elicited. A history of bone pain may be due to undiagnosed myeloma. This disease can lead to AKI via a number of mechanisms, including cast nephropathy and hypercalcaemia.

Post-renal – absolute anuria is suggestive of obstruction and a history of preceding prostatic symptoms in men (hesitancy, poor stream, nocturia) is important in this situation. 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
Even in rapidly progressive glomerulonephritides, symptoms can be mild and non-specific. Fatigue, weight loss, nausea and reduced appetite are all relevant, and the time of onset of these symptoms may give some idea about the duration of the disease. Patients should be asked specifically about sinus problems, epistaxis, haemoptysis, rashes, and joint pains that may be associated with systemic vasculitides. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, anti-GBM disease (Goodpasture’s syndrome), lupus nephritis (class IV)
Anti-GBM disease affects the kidneys and lower respiratory tract. Epistaxis or haemoptysis secondary to pulmonary haemorrhage is seen in ANCA-associated vasculitis, which may be manifest as one of several conditions. Upper and lower respiratory tract involvement is reversible damage. The history is key in identifying these conditions. Anti-GBM disease affects the kidneys and lower respiratory tract only (Goodpasture’s syndrome). Lupus nephritis occurs in up to 50% of patients with systemic lupus erythematosus (SLE) and the crescentic form of immunoglobulin A nephropathy can all cause an acute necrotizing glomerulonephritis, which 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 may be manifest as one of several conditions. Upper and lower respiratory tract involvement is reversible damage. The history is key in identifying these conditions.

Acute kidney injury

In the context of AKI, adequate assessment of the circulation is key, in order to identify whether or not there has been a significant pre-renal insult. Volume status should be examined by assessing the jugular venous pressure (JVP), systemic blood pressure (including postural blood pressure) and peripheral circulation. Skin turgor and mucous membrane appearance are notoriously unreliable, especially in the older patient. Blood pressure should be considered in the context of the patient’s usual blood pressure, if known, and the JVP should always be interpreted with caution in patients with a history of lung disease, who may 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 will indicate 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 may be due to hypovolaemia (in which case the JVP will be low, and there will be no pulmonary oedema), or to impaired cardiac function (in which the JVP may be elevated, the apex beat may be displaced, and there may 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 may be secondary to an 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 the cutaneous manifestation 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, or ‘trash feet’, suggests that the same process may be occurring in the kidneys.

Extensive bruising or a tense and tender muscle compartment may be found in rhabdomyolysis. The presence of compartment syndrome should prompt urgent referral to an orthopaedic surgeon.

Chronic kidney disease

Diabetes mellitus and hypertension are the most common causes of CKD in the UK. However, because these conditions are common, they may co-exist with other causes of CKD. 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, in particular 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 (ADPKD), one should ask about the progression of disease in their relatives, and any family history of sudden death or intracerebral bleed. In patients with a family history of renal disease who do not know the diagnosis, the pattern of inheritance may be informative (e.g. X-linked inheritance of 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 GFR has fallen below 15 ml/minute (stage 5).

Examination

A detailed history will have provided clues as to the underlying cause of renal disease, and a thorough examination will allow the clinician to prioritize the investigations and management appropriately.
surgeon, as relief of the pressure may be necessary to save a compromised limb.

A palpably enlarged bladder is suggested 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 haematuria is the hallmark of glomerular nephritis; in the presence of a rising serum creatinine, a rapidly progressive glomerular nephritis should be suspected and urgent referral to a nephrologist is indicated. ANCA-associated vasculitis and anti-GBM disease can both 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 as to the cause of intrinsic renal disease. The hands may reveal changes of systemic sclerosis (nail-fold infarcts, thickened shiny skin), or long-standing arthritis that may have been treated with regular NSAIDs or other nephrotoxic medications. Rashes may be seen in SLE, HSP or 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 a 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 due to chronic infection. Needle track marks and abscesses around injection sites may be seen in these patients. Patients with nephrotic syndrome will, by definition, have oedema. This can be periorbital, occurring characteristically in the mornings, and postural (pitting oedema of the legs), worsening through the day. Pleural effusions and ascites may also be present.

**Chronic kidney disease**

Ophthalmoscopy provides extremely useful information in cases of chronic kidney disease. 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 increases the likelihood that they have diabetic nephropathy. Similarly, silver wiring, AV nipping and retinal haemorrhages in a patient with hypertension are indicative of suboptimal control, which increases the likelihood of associated renovascular disease. Polycystic kidneys may be easily palpable, and there may be associated hepatomegaly due to liver cysts. Patients with Alport’s disease.

**Urinalysis**

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:

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

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

**Specific gravity**

Specific gravity (SG) is a ratio of the density of a substance to the density of a reference substance, usually water for liquids; it is a measure of the concentration of a solution. Urine specific gravity is directly proportional to urine osmolality and typically ranges between 1.002 and 1.035. The SG of the glomerular filtrate (in Bowman’s space) ranges from 1.007 to 1.010. An SG lower than 1.007 indicates a dilute urine in a state of hydration, whereas an SG over 1.010 indicates relative dehydration. If the urine SG is not more than 1.022 after a 12-hour period without food or water, a deficit in renal-concentrating ability is present. If kidney function is normal, such a deficit may indicate nephrogenic diabetes insipidus. In the context of end-stage kidney disease and acute tubular necrosis, urine SG tends to reflect that of the glomerular filtrate (1.007–1.010). An SG greater than 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 the plasma acid—base status, urine pH can range from as low as 4.5 to as high as 8.0. In isolation, the urine pH is rarely helpful. However, if the urine is strongly alkaline, UTI with a urease-producing organism should be suspected. Urease catalyses the conversion of urea to ammonia. Measuring the urinary pH may be of assistance in the diagnosis of renal tubular acidosis and the evaluation of nephrolithiasis. It may also be useful as a therapeutic target; precipitation of proteinaceous casts (e.g. in myeloma or rhabdomyolysis) is favoured in an acidic urine, and alkalinization of the urine (maintaining pH >6.5) by the oral or intravenous administration of alkali (typically sodium bicarbonate) can help to 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 per ml). A negative result does not
rule out a UTI. The reagent is highly sensitive to air exposure, which may 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 due to UTI. False-positive results may be caused by contamination with vaginal discharge. Elevated urine glucose or oxalic acid concentrations may reduce sensitivity, and this may also be seen in patients taking tetracycline or cefalexin.

**Ketones**

Ketone bodies are metabolites of fatty acids, produced once the body has exhausted glycogen reserves and has started to breakdown fat stores. Ketonuria is therefore mainly associated with insufficient insulin availability in type I 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) may suggest diabetes but the positive and negative predictive values of its detection are poor. Glucosuria may also suggest proximal tubular dysfunction (e.g. Fanciuni’s syndrome) or treatment with SGLT2 inhibitors (the 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 of ≥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, if blood is present in at least two out of three dipstick tests, it is not necessary to confirm the result by microscopy. Transient causes, such as UTI, menstrual contamination and vigorous exercise, should be excluded before referral for further investigation.

Individuals aged under 40 years with isolated non-visible haematuria (i.e. without albuminuria) and without impaired kidney function and hypertension, or those aged 40 or more in whom urological causes have been excluded, do not need any further investigation or specialist follow-up. These individuals do have an increased lifetime risk of end-stage kidney disease (ESKD) but the absolute increase in risk remains small. They should remain under primary care follow-up. Table 1 shows a list of causes of haematuria.

### Causes of haematuria

<table>
<thead>
<tr>
<th>Urological causes</th>
<th>Nephrological causes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td></td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>Immunoglobulin A nephropathy (1/100,000 lifetime risk 1/1400)</td>
</tr>
<tr>
<td>Cancer (prostate, bladder, ureter, kidney)</td>
<td>Thin basement membrane disease</td>
</tr>
<tr>
<td>Stones</td>
<td></td>
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<tr>
<td>Infection — cystitis/pyelonephritis/prostatitis/urethritis/schistosomiasis</td>
<td></td>
</tr>
<tr>
<td><strong>Less common</strong></td>
<td></td>
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<tr>
<td>Radiation cystitis</td>
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<tr>
<td>Urethral strictures</td>
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<tr>
<td>Tuberculosis</td>
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<tr>
<td>Medullary sponge kidney (1/5000 population)</td>
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<tr>
<td>Chemical cystitis (e.g. cyclophosphamide or ketamine)</td>
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<tr>
<td><strong>Rare</strong></td>
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<tr>
<td>Arteriovenous malformation</td>
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<tr>
<td>Renal artery thrombosis</td>
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<tr>
<td>Papillary necrosis</td>
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<tr>
<td>Loin pain-haematuria syndrome</td>
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</tbody>
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**Table 1**

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of causes of haematuria. Rhabdomyolysis will give rise to 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 of less than 20 kDa pass easily across the glomerular basement membrane. 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 may occur in up to 7% of healthy subjects. The large number of causes (Table 2) may be categorized as:

- functional
- tubular
- overflow
- glomerular.

More than 90% of cases of persistent proteinuria may 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. due to exercise, fever, high-output heart failure or pregnancy) delivers increased amounts of protein, exceeding the reabsorptive capacity of the proximal tubule. Typically, protein losses are <1 g/day and cease when renal blood flow normalizes.

**Tubular proteinuria** results from tubulo-interstitial disorders that impair the reabsorption of protein by the proximal tubule, leading to excessive urinary protein loss mostly in the form of smaller, low-molecular-weight proteins, such as retinol-binding protein, α2-microglobulin and β2-microglobulin, rather than albumin. However it is unusual for these to exceed 2 g/day. Other defects in tubular function are frequently in evidence (e.g. bicarbonate wasting, glucosuria, aminoaciduria, phosphaturia).

**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. Thus, urine produced during waking hours contains more protein than that produced during the night. The prognosis is excellent and no specific intervention is required.

### Causes of proteinuria

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular</td>
<td>Primary glomerular disorders (e.g. membranous nephropathy, minimal change disease, focal segmental glomerulosclerosis)</td>
</tr>
<tr>
<td></td>
<td>Secondary glomerular disorders (e.g. diabetic nephropathy, pre-eclampsia, post-infectious glomerulonephritis, lupus nephritis, amyloidosis)</td>
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<tr>
<td>Tubular</td>
<td>Fancon's syndrome</td>
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<tr>
<td></td>
<td>Acute tubular necrosis</td>
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<tr>
<td>Overflow</td>
<td>Monoclonal gammapathy</td>
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<tr>
<td></td>
<td>Multiple myeloma</td>
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<tr>
<td></td>
<td>Rhabdomyolysis</td>
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<td></td>
<td>Polymyositis</td>
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<tr>
<td>Functional</td>
<td>Fever</td>
</tr>
<tr>
<td></td>
<td>Intense exercise</td>
</tr>
<tr>
<td>Unknown</td>
<td>Orthostatic</td>
</tr>
</tbody>
</table>

**Table 2**

**Quantification of proteinuria**

Once detected on dipstick testing, it is essential to quantify the amount of urinary protein excretion. Normal urine protein excretion is less than 150 mg/day of which approximately 20% is low-molecular-weight proteins (such as immunoglobulin or β2-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, largely due to improper timing and missed samples, resulting in over- and under-collection. Thus, when performing a 24-hour collection, we recommend that simultaneous measurement of urine creatinine excretion be undertaken.

In general, an adequate collection will contain 15–20 mg of creatinine per kg of body weight, and in men 20–25 mg/kg. Alternatively, the expected weight (g) of excreted creatinine can be estimated (in men) using the formula:

\[
\text{Excreted creatinine (g)} = \frac{140 – \text{age}}{2} \times \text{weight in kg} / 5000
\]

The result is multiplied by 0.85 in women.

**Albumin and creatinine ratios**

Because of the inherent inaccuracies and inconvenience of performing timed collections, the spot albumin:creatinine ratio (ACR or PCR) has become common 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 equivalent to 1 g/day. Dividing the ACR by 8.84 converts the units (from μg/mg or mg/g to mg/mmol).

**Classification of proteinuria**

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

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KDIGO guidelines for albuminuria

\(< 30 \text{ mg/g} = < 3.0 \text{ mg/mmol} = \text{ normal to mildly increased} = A1\)

\(30–300 \text{ mg/g} (3.0–30 \text{ mg/mmol}) = \text{ moderately increased} = A2\)

\(> 300 \text{ mg/g} (> 30 \text{ mg/mmol}) = \text{ severely increased (overt albuminuria)} = A3\)

Albuminuria has been shown to be an independent risk factor for progressive kidney disease and risk of ESKD.²

Selective and non-selective proteinuria

Proteinuria in the context of minimal change disease (MCD) is largely restricted to albumin (selective) in contrast to focal segmental glomerulosclerosis (FSGS) and membranous nephropathy (unselective).

Nephrotic syndrome

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

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

Some authorities would include:
- hypercholesterolaemia
- lipiduria.

Nephrotic range proteinuria

The term nephrotic range proteinuria, describes heavy proteinuria (within the nephrotic range >3.5 g/day) but without the other features of the nephrotic syndrome (e.g. oedema and low serum albumin). The commonest 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

**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)
Ur:Cr ratio is typically 1:20, disproportionately elevated Ur:Cr suggests renal hypoperfusion due to hypovolaemia or heart failure
Full blood count (FBC) | Anaemia — advanced CKD, auto-immune disease, microangiopathic haemolytic anaemia (MAHA)
Leucocytosis — sepsis, lymphoma
Eosinophilia — drug-induced tubulo-interstitial nephritis, cholesterol emboli syndrome
Thrombocytopenia — MAHA (a feature of HUS and malignant hypertension
Thrombocytosis — inflammation, esp. polyangitis with granulomatosis
Bone profile | Hypoalbuminaemia — nephrotic syndrome, malnutrition, inflammation, liver failure
Hypocalcaemia — advanced CKD, rhabdomyolysis, pancreatitis
Hypocalcaemia — bony metastases, esp. myeloma, sarcoid
Serum C-reactive protein (CRP) | Elevated in inflammatory states such as sepsis and vasculitis. Exception is SLE, which classically does not increase CRP; an elevated CRP in the setting of known lupus suggests an alternative aetiology (e.g. sepsis)
Bicarbonate | Reduced in RTA and advanced CKD (stage 4 and 5)
Cholesterol | Atherosclerotic risk factor
HbA1c | Poor glycaemic control increases likelihood of microvascular complications of DM including nephropathy
Immunoglobulins, serum protein electrophoresis, | Serum IgA may be elevated in some patients with IgA nephropathy
If blood 1+ or proteinuria 1+ present on dipstick | Screen for multiple myeloma in all patients over 40
Viral serology | Hep BsAg, Hep C IgG, HIV — may be pathogenic, inducing secondary GN. Also important in patients likely to require haemodialysis with respect to infection control
ANA, dsDNA, ENA | To be requested if lupus or connective tissue disease suspected
C3/C4 | Consumed in number of immune complex mediated GN (e.g. lupus, MCGN). May also be reduced in endocarditis
RhF | Antibody directed against the Fc portion of IgG. Frequently positive in the presence of cryoglobulins
Cryoglobulins | Prone to false negative results and need to be taken under specific conditions into warmed tubes and kept warm in transit to the laboratory
ANCA | cANCA — granulomatosis with polyangitis (Wegner’s granulomatosis)
pANCA — microscopic polyangitis
In patients with oligo-anuric AKI | Anti-GBM antibodies — Associated with Goodpasture’s syndrome

*Table 3*
kidney function, so it is important to contact the GP and other hospitals the patient might have visited previously. See Table 3 for suggested blood tests; other specialist tests may 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:

- Exclusion of urinary obstruction
- Normal anatomy (i.e. two equally sized kidneys)
  - Asymmetry in kidney size may indicate renal artery stenosis, especially in the context of other atherosclerotic risk factors, or renal dysplasia; more than 1.5 cm difference may be pathological
  - Bipolar length — normal adult kidneys are 11 ± 1 cm in length; bipolar length correlates with indices of body size, so one may allow for some reduction in a small adult
- Cortical thickness — loss of cortical thickness implies chronic kidney disease, frequently ischaemic in aetiology, but may be seen in a chronically obstructed kidney
- Cortico-medullary differentiation — loss of cortico-medullary differentiation and increased echogenicity of the kidneys are non-specific signs of kidney disease, usually implying chronicity (Box 1)
- Cortical scars following pyelonephritis may be seen
- Cysts — simple or complex/septated cysts (possibly malignant)
- Stones — in general poorly seen on USS, better evaluated with low-intensity CT scanning.

**Differential diagnosis**

Nephrologists will arrive at a differential diagnosis by considering the:

- Age of the patient
- Speed of onset/chronicity
- Presence of impaired excretory function, 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 performed primarily 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 tubulointerstitial disease
- AKI without explanation or which fails to resolve, and occasionally for prognostic purposes

**REFERENCES**

The management of acute kidney injury

Carolyn E Amery
Annette Davies
Lui G Forni

Abstract
Acute kidney injury affects up to 15% of inpatients in the acute hospital setting. Although accurate history-taking, careful physical examination and meticulous monitoring of volume balance are essential, there is, to-date, little evidence supporting any intervention that may reverse this process. Acute kidney injury presents a unique set of metabolic derangements that, if untreated, will result in death. We outline the initial management of acute kidney injury as well as specific treatments that may be required. Some consideration is also given to the use of renal replacement therapies.

Keywords Acute kidney injury; glomerular filtration rate; haemofiltration; hyperkalaemia; metabolic acidosis; uraemic encephalopathy; uraemic pericarditis

Introduction
In 2004, the Acute Dialysis Quality Initiative group (ADQI) proposed the RIFLE classification of acute kidney injury (AKI) encompassing two separate criteria, the calculated glomerular filtration rate (GFR) and urine output. The previously adopted acronym RIFLE provides diagnostic definitions for the three grades of increasing severity of AKI and the two outcome variables of loss (L) and end-stage renal disease (E). The grades of severity of injury include the stage at which injury can be prevented (risk, R), when the kidney has already been damaged (injury, I) and when renal failure has occurred (failure, F). In 2007, the Acute Kidney Injury Network (AKIN) modified the RIFLE criteria. The AKIN criteria refer to the same stages (risk, injury and failure) but the time frame for diagnosis of AKI is reduced to 48 hours, and a lower threshold for the rise of serum creatinine from baseline to peak value is used. Both sets of criteria have been validated for in-hospital mortality in numerous settings. Although accurate history-taking, careful physical examination including assessment of the venous pressure, capillary refill time, pulse and postural blood pressure changes are elementary tools for assessing volume status. Hourly urine-output and accurate fluid-input charts need to include all fluid replacement therapies.

Volume resuscitation
In hypovolaemia, volume expansion is recommended. However, uncontrolled volume substitution may result in clinical deterioration with an increased risk of morbidity and mortality in patients with AKI and should be avoided. Isotonic crystalloids remain the mainstay of volume replacement therapy. Crystalloids expand plasma volume by about 25% of the infused volume, correcting sodium depletion as well as restoring solute and water diuresis. However, large-volume infusion of sodium chloride can lead to so-called ‘hyperchloraemic acidosis’, which may be associated with renal vasoconstriction and gut hyperperfusion. Colloids, such as albumin, gelatins and hydroxyethyl starch, result in volume expansion approximate to the infused volume but, if administered in isolation in AKI, can lead to osmotic nephrosis (osmotic tubular damage). Hydroxyethyl starches are highly polymerized sugars characterized by their molecular weight, grade of substitution and concentration. They are degraded through hydrolytic cleavage, the remnants of which are excreted by the kidney, and should be avoided in AKI particularly when this has resulted from sepsis.

Volume overload
The volume status of a patient with AKI should be assessed carefully. Although somewhat unfashionable, careful bedside examination including assessment of the venous pressure, capillary refill time, pulse and postural blood pressure changes are elementary tools for assessing volume status. Hourly urine-output and accurate fluid-input charts need to include all fluid replacement therapies.

General management of AKI
Early recognition and treatment of AKI saves nephrons and prevents further decline in GFR. It is important to remember that measured serum creatinine may not rise appreciably until GFR has fallen significantly. This is of particular relevance in individuals of small build, vegetarians and the undernourished, such as patients with hepatic failure, in whom a serum creatinine in the normal range can be misleading. Tubular secretion of creatinine is increased as GFR falls, and this may also lead to an overestimation of renal function in AKI. Treatment in AKI is aimed at minimizing further damage to the kidney while providing support until there are signs of functional recovery. This includes restoration of the circulating volume, relief of outflow obstruction if present, removal of tubular toxins and specific treatment of glomerular disease. Early restoration of renal perfusion in precipitant AKI due to presumed acute tubular necrosis is essential. Recovery of GFR depends on the number of remaining functional nephrons that will increase their filtration to maintain GFR. However, continued hyperfiltration may result in progressive glomerular sclerosis and nephron death, leading to end-stage renal failure. (See Assessment and initial management of acute kidney injury on pp 440–445 of this issue.)

Specific problems

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losses, including estimated insensible losses, drain/stoma output and nasogastric losses where appropriate. If possible, patients should be weighed daily. A central venous catheter and an arterial cannula can be helpful where multi-organ failure (MOF) is imminent. In established MOF, absolute measurement of central venous pressure can be misleading, especially in the ventilated patient in whom high intrathoracic pressures may be present, and further invasive monitoring may be required.

Where volume overload is encountered in the setting of AKI, symptoms can be alleviated by high-flow oxygen. Where pulmonary oedema is refractory to pharmacological management while preparing the patient for urgent RRT, continuous positive airway pressure ventilation (CPAP) should be considered. Trials using diuretics, such as furosemide and mannitol, and ‘low-dose’ dopamine have yielded inconsistent results in AKI.6,9 Although loop diuretics may promote diuresis in oliguric renal failure, there is little evidence that they influence outcome,10 and the large doses of furosemide often required for diuresis in AKI can result in ototoxicity. Similarly, the use of dopamine does not reduce mortality or accelerate the recovery of renal function and, in the critically ill, dopamine use can lead to peripheral vasoconstriction, causing gut ischaemia, tissue necrosis and digital gangrene.

**Hyperkalaemia**

This life-threatening complication arises through cellular shifts of potassium or release from lysed cells, together with decreased renal excretion of potassium, and requires immediate treatment. Acidosis, hyponatraemia and hypocalcaemia all potentiate the harmful effects of hyperkalaemia on cardiac function and must also be corrected. Muscle weakness may be present and, if severe, can lead to flaccid paralysis, although symptoms are rarely apparent until the serum potassium exceeds 7.0 mmol/litre. The most serious effect is on cardiac conduction, which classically presents as a shortened QT interval with a tall peaked T wave on the electrocardiogram (ECG). Without treatment, progressive lengthening of QRS duration and PR interval ultimately lead to a ‘sine wave’ appearance, followed by ventricular standstill or fibrillation. A variety of other conduction disturbances may occur, including bundle-branch block, bifascicular block and advanced atrioventricular block. Asymptomatic patients with serum potassium <6.5 mmol/litre, or whose ECG does not manifest signs of hyperkalaemia, should be treated with a low potassium diet; additional sources of potassium intake should be withheld and any potentiating drugs discontinued. (Specific treatment of hyperkalaemia is set out in the article Assessment and initial management of acute kidney injury (Table 3) on pages 440–445 of this issue.)

**Acidosis**

Metabolic acidosis in AKI results from increased acid production, increased acid retention and decreased renal reabsorption of bicarbonate. Acidosis is exacerbated by sepsis, malnutrition and some drugs, and is very common among critically ill patients and acute admissions. Metabolic acidosis is easily detected by measuring venous serum bicarbonate in the above patient groups when requesting routine blood tests. (Specific treatment of acidosis is set out is set out in the article Assessment and initial management of acute kidney injury (Table 3) on pages 440–445 of this issue.)

**Uraemic pericarditis**

Uraemic pericarditis is observed in 6–10% of patients with advanced renal failure, resulting from inflammation of both the visceral and parietal membranes of the pericardial sac. Pericarditis in AKI presents with fever and pleuritic chest pain, characteristically worse in the recumbent position. A pericardial rub may be heard on auscultation, although the ECG does not show the typical diffuse ST and T wave elevations observed with other causes of acute pericarditis. The development of pericarditis in a patient with AKI is an indication to institute RRT, unless there are signs of cardiac tamponade due to a pericardial effusion. Under such conditions, heparin-free haemodialysis or haemofiltration should be used because of the risk of increased bleeding into the pericardial sac with anticoagulation.

**Uraemic encephalopathy**

Like uraemic pericarditis, uraemic encephalopathy tends to be related to the degree of uraemia. Early clinical features include rambling speech, disorientation, lethargy, irritability, hallucinations and, more rarely, coma. Commonly encountered signs include tremor, myoclonus and asterixis, which tend to occur with deterioration in mental status. Transient focal signs, such as hemiparesis or reflex asymmetry, occur rarely but resolve with treatment, although mental state may not improve for up to 48 hours. If the signs do not resolve, other pathologies should be excluded.

**Renal replacement therapy**

Renal replacement therapy (RRT) does not cure acute kidney injury but it is a safe and efficient way of replacing renal function while the kidneys recover from disease or injury. Historically, single-organ AKI has been treated with either peritoneal or intermittent haemodialysis, which are the mainstay of chronic renal replacement therapy. Hospitals with acute nephrology services will perform haemodialysis in haemodynamically stable patients, although RRT is most commonly performed acutely in a level 2 or 3 facility employing haemodialysis or more commonly continuous therapies such as haemofiltration or haemodiafiltration. However, more recently there has been a trend towards using hybrid therapies such as prolonged intermittent renal replacement therapy (PIRRT). Although superficially similar, the mechanisms by which the composition of the blood is altered differ markedly.11,12 In haemodialysis, blood flows along one side of a semipermeable membrane as a solution of crystalloids (the dialysis fluid) is pumped against the direction of the blood flow along the other side of the membrane. Molecules diffuse across the membrane from higher to lower concentrations driven by the law of mass action. The composition of the dialysis fluid allows as near normalization of the plasma as possible. The dialysis-fluid compartment is under lower pressure, generating a transmembrane pressure gradient enabling the removal of salt and water. Haemofiltration in its simplest form involves the passage of blood under pressure passing down one side of a highly permeable membrane, allowing water and other molecules up to a size of about 20 kDa to pass through the membrane by convection. Thus, filtrate is discarded and replaced by an idealized buffered replacement fluid, the crystalloid components of which are at physiological concentration. Haemodiafiltration as the name implies is a combination of the two therapies.
offering theoretically enhanced clearances of some middle molecules. Indications for renal replacement depend on the clinical and biochemical derangements outlined above and, although these are general indications, use will be guided by the clinical situation. In the intensive care unit, for example, treatment may begin before the absolute indications are reached, as there is uncertainty surrounding the optimal timing of the initiation of renal support. There is some evidence that, in the critically ill intensively managed patient, early treatment may result in improved outcome. However, a randomized controlled trial from India in 2013, using intermittent therapies in a non-ITU population, found that time to recovery of renal function was longer in the group with early initiation of dialysis. A large multicentre randomized controlled trial in critically ill patients is currently recruiting participants.

**Practical aspects of renal replacement therapy**

RRT requires access to the circulation. Various double-lumen vascular catheters are commercially available, allowing blood flow rates up to 200 ml/minute. Adequate venous access is critical in preventing technical difficulties with blood flow from the patient and potential problems with clotting, leading to a loss of the extracorporeal circuit. In most cases anticoagulation is required, with unfractionated heparin being commonly used to prime the circuits, and a continuous infusion is maintained through the inflow side of the circuit. If the patient is thrombocytopenic, alternative anticoagulants can be used, including sodium chloride, citrate or protacyclin, but care must be taken with the latter given its vasodilator effects. More recently, regional anticoagulation with citrate has increased in popularity with citrate acting as both an anticoagulant and a buffer. Citrate is administered as sodium citrate before the filter and chelates calcium ions. The associated regional hypocalcemia in the filter inhibits the generation of thrombin and thereby the clotting process. Citrate is partially removed by filtration or dialysis and the remainder is rapidly metabolized in the citric acid (Krebs) cycle — especially in the liver, muscle and renal cortex. The chelated calcium is released and the lost calcium replaced after the filter. Systemic anticoagulation is therefore unaffected. For adequate anticoagulation, the citrate dose is adjusted to blood flow to attain an ionized calcium concentration <0.4 mmol/litre in the filter; it follows that the lower the calcium concentration, the higher the degree of anticoagulation, with various protocols being employed.

In haemofiltration the flow rate, which reflects the rate of ultrafiltrate produced and solute clearance, is taken as a surrogate for the dose. In 2000 Ronco et al. demonstrated survival rates to be significantly lower in patients treated with ultrafiltration rates of 20 mL/kg/h compared to 35 mL/kg/h. However more recently the Randomised Evaluation of Normal versus Augmented Level of renal replacement therapy in ICU (RENAI) studied a dose of 35 mL/kg/h compared to 20 mL/kg/h and found there to be no difference in mortality between the two groups at 90 days. The Acute Renal Failure Trial Network (ATN) demonstrated similar findings when comparing the two doses and, interestingly, recorded more hypotensive episodes in those receiving the higher dose. High-volume haemofiltration (HVHF) defined as a treatment dose of greater then 50 mL/kg/h has been cited as a potential method of reducing cytokine levels and thereby reducing mortality in patients with both AKI complicated by sepsis. However, the IVOIRE (Impact of High-volume Venovenous Continuous Haemofiltration in the Early Management of Septic Shock Patients with Acute Renal Failure) study, which compared patients treated with 70 ml/kg/h or 35 ml/kg/h, found no evidence that HVHF leads to a reduction in mortality at 28 days or contributes to early improvements in organ function.

**REFERENCES**


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