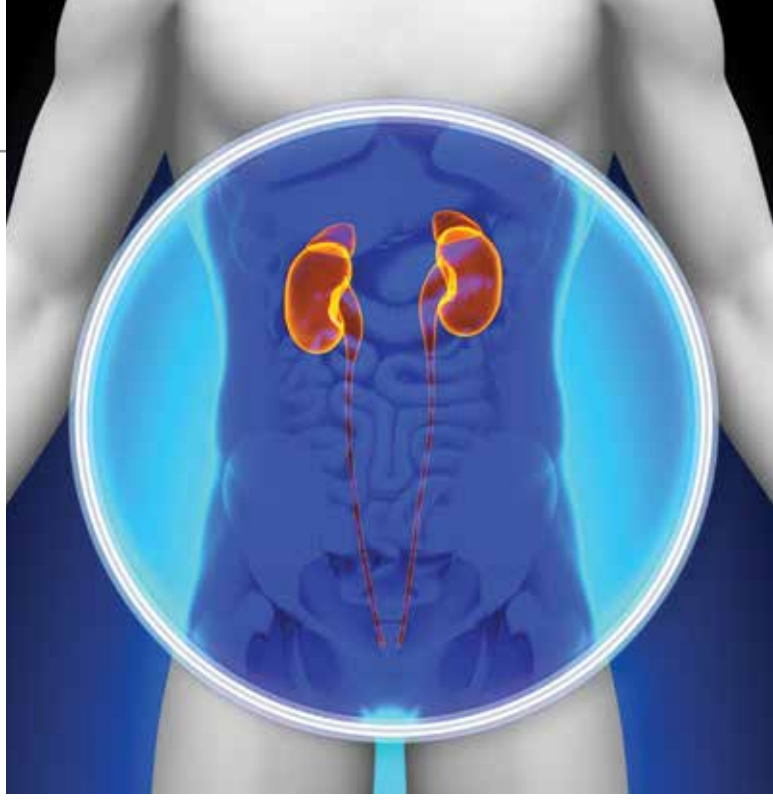
CLINICAL INVESTIGATIONS FROM THE RACP

Investigating patients with impaired renal function



CHII YEAT YEAP MB BS
RANDALL FAULL MB BS, FRACP, FRCP, PhD

Impairment of renal function is associated with high rates of adverse outcomes. The optimal approach to investigation depends on whether the impairment is acute, chronic or acute on chronic. Diagnostic evaluation is further guided by whether the kidney injury is due to prerenal, intrinsic renal or postrenal causes.

KEY POINTS

- The use of age-specific cut-off points of estimated glomerular filtration rate in the diagnosis of renal disease is not currently recommended.
- All patients with acute kidney injury or increases of more than 1.5 times baseline serum creatinine levels should receive appropriate medical attention and treatment.
- Rapid progression of renal impairment or the presence of active urine sediments should prompt urgent referral of the patient to a nephrologist or renal unit.
- Urinalysis and urine microscopy is an essential component in any work-up of a patient with kidney impairment.
- A thorough history and examination supported by additional blood tests are likely to identify the underlying aetiology.

Kidney disease is an important public health problem, contributing to about 15% of all hospitalisations and almost 10% of all deaths in Australia.[1,2] Increasing evidence suggests that any deterioration in kidney function, either acute or chronic, manifested by changes in urine output and blood chemistry, portend serious clinical consequences.[3-5] This article highlights the importance of recognition and appropriate management of kidney damage.

Is abnormal creatinine indicative of renal dysfunction?

Measurement of serum creatinine concentration is the most commonly used clinical laboratory test of kidney function. Estimated glomerular filtration rate (eGFR) can be calculated from plasma creatinine concentration using the Chronic Kidney

MedicineToday 2015; 16(12): 24-28

Dr Yeap is a Nephrology Trainee at Royal Adelaide Hospital, Adelaide. Professor Faull is a Senior Nephrologist at Royal Adelaide Hospital, Adelaide; and Director of Medical Program and Deputy Dean, Faculty of Health Sciences, University of Adelaide, Adelaide, SA.

SERIES EDITOR: Christopher S. Pokorny, MB BS, FRACP, FRCP, FACG, is Conjoint Associate Professor of Medicine at the University of New South Wales, and Visiting Gastroenterologist, Sydney and Liverpool Hospitals, Sydney, NSW.

Disease Epidemiology Collaboration (CKD-EPI) formula and is usually reported automatically with the results of serum creatinine in individuals aged 18 years or older. However, creatinine measurement concentration is actually a poor reflection of true glomerular filtration rate (GFR) in many patients, because changes in serum creatinine concentration do not precisely correlate with changes in GFR.

The concentration of serum creatinine is influenced by several factors, as detailed below.

TABLE 1. STAGING OF ACUTE KIDNEY INJURY[19]

Stage	Serum creatinine (SCr)	Urine output
1	Increase in SCr ≥26.5 µmoL/L OR Increase in SCr to ≥150% to 200% of baseline	<0.5 mL/kg/hour for >6 hours
2	Increase in SCr to >200% to 300% of baseline	<0.5 mL/kg/hour for >12 hours
3	Increase in SCr to >300% of baseline OR Increase in SCr to ≥350 µmol/L OR Initiation of renal replacement therapy	<0.3 mL/kg/hour for >24 hours OR Anuria for >12 hours

Abbreviation: eGFR = estimated glomerular filtration rate.

- In the setting of kidney disease, creatinine is cleared from the body by the kidney through both glomerular filtration and tubular secretion.
- Certain drugs (e.g. trimethoprim, cimetidine) compete with tubular secretion of creatinine and may increase serum creatinine concentration in the absence of any change in GFR.
- The sex and muscle mass of the patient influence the serum creatinine concentration and can mask changes in GFR. This occurs because muscle is the primary source of creatine, which is converted to creatinine in the liver. Female sex and severe muscle wasting will reduce the production of creatine and limit the increase in serum creatinine levels that would normally accompany a decrease in GFR.

Recognising age-related GFR decline and kidney disease

GFR progressively decreases at an average rate of 8 mL/min/1.73 m^2 per decade after the age of 30 years.[6] Studies suggest that more than one-third of people over the age of 65 years in Australia have an eGFR below 60 mL/min/1.73 m^2.[7-8] This could be due to the effects of hypertension, atherosclerosis or other comorbidities such as cardiovascular disease.[9-11]

Recent evidence suggests that even very elderly patients (those over the age of 80 years) with modest reductions in eGFR (45 to 59 mL/min/1.73 m^2) have a higher prevalence of complications relating to chronic kidney disease (CKD) than those with an eGFR of 60 mL/min/1.73 m^2 or above.[12] Furthermore, in patients whose eGFR decreases below 60 mL/min/1.73 m^2, there is an appreciable increasing incidence of cardiovascular events and mortality.[13,14] As a result, age-specific cut-off points in eGFR for the diagnosis of renal impairment are not currently recommended.[15]

Differentiating acute from chronic kidney disease

It is often difficul
renal disease from those with chronic renal failure, especially when patients do not have complete records of their medical history. It is important to compare the patient's current serum creatinine level with previous levels to determine the duration and acuity of the disease. A high serum creatinine level in a patient with a previously normal documented level suggests an acute process, whereas a rise over weeks to months represents a subacute or chronic process. Caution should be employed and the patient should be assumed to have acute kidney injury (AKI) until proven otherwise.

Routine biochemical measurements, including calcium, phosphate and haemoglobin levels, are not helpful in differentiating acute and chronic renal failure, as patients with either condition can present with hypocalcaemia, hyperphosphataemia or anaemia.[16] Studies have shown that a parathyroid hormone (PTH) measurement with a cut-off set at 18 pmol/L is able to discriminate patients with chronic renal failure with high sensitivity (88%) and specificity (89%),[17] but this is not routine clinical practice.

Renal ultrasound has been proposed as a way to distinguish between AKI and CKD. Loss of renal cortex is considered a feature of CKD, and is often sought as a specific diagnostic sign of CKD. Small kidneys, measuring less than 90 mm in bipolar diameter, usually indicate a chronic disease process;[18] however, false-negative results may be seen in patients with diabetes, myeloma, amyloidosis or tumour infiltration.

Recognising acute kidney injury

Kidney Disease Improving Global Outcomes (KDIGO) defines stage 1 AKI as any of the following (Table 1):[19]

- an increase in serum creatinine level of 26.5 µmol/L or more within 48 hours
- an increase in serum creatinine level to 1.5 times or more above baseline, which is known or presumed to have occurred within the previous seven days
- urine volume less than 0.5 mL/kg/hour for six hours.

Stages 2 and 3 AKI are as defined in Table 1. AKI is a broad

TABLE 2. HISTORY AND EXAMINATION FINDINGS FOR CATEGORISING ACUTE KIDNEY INJURY

History findings	Physical examination findings
Prerenal causes of AKI	
• Volume depletion (e.g. vomiting, diarrhoea, excessive diuretic use, haemorrhage, burns) • Thirst • Reduced fluid intake	• Weight loss • Hypotension • Tachycardia • Postural hypotension
Intrinsic renal causes of AKI	
Acute tubular necrosis • History of use of nephrotoxins (e.g. ACE inhibitor, ARB, NSAIDs) including over-the-counter, illicit and herbal • History of sepsis • Trauma or myalgia suggesting rhabdomyolysis • Recent exposure to radiographic contrast agents	• Muscle tenderness • Assessment of volume status and sepsis
Glomerular • History of recent pharyngitis or cellulitis (postinfectious GN) • Symptoms related to connective tissue disorders (e.g. SLE, systemic sclerosis) • Hepatitis B or C infections • Haemoptysis, dyspnoea or cough (renal pulmonary syndrome)	• Periorbital, sacral and lower extremity oedema from nephrotic syndrome • Rash, uveitis, calcinosis, etc suggestive of underlying connective tissue disorder
Interstitial • Medication use (e.g. antibiotics, proton pump inhibitors) • Rash • Fever	• Fever • Drug-related rash
Vascular • Trauma, flank pain, haematuria • History of atheroembolic disease, vessel catheterisation or vascular surgery	• Livedo reticularis • Abdominal bruits
Postrenal causes of AKI	
• Urinary urgency or hesitancy • Gross haematuria • Polyuria • Stones	• Bladder distension • Pelvic mass • Prostate enlargement

Abbreviations: ACE = angiotensin converting enzyme; AKI = acute kidney injury; ARB = angiotensin receptor blocker; GN = glomerulonephritis; HIV = human immunodifficiency virus; NSAIDs = nonsteroidal anti-inflammatory drugs; SLE = systemic lupus erythematosus.

clinical syndrome encompassing various aetiologies and is intended to highlight the potentially reversible nature of the injury, whereas the term acute renal failure implies renal impairment that is sustained.

The inclusion of a time constraint of 48 hours is based on data that showed worse outcomes associated with small changes in the serum creatinine when the rise in creatinine was observed within 24 to 48 hours.[20] The presence of any stage of AKI should prompt methodical clinical assessment of the patient to ensure that potentially reversible causes are rapidly diagnosed and treated to preserve kidney function. Patients with stage 2 or 3 AKI should be referred urgently to hospital.

Clinical presentation

The clinical presentation of the patient with renal impairment varies with the cause and severity of renal injury and associated diseases. Most patients with mild to moderate kidney injury are asymptomatic and are identified on laboratory testing. Patients with severe impairment, however, may be symptomatic and present with listlessness, confusion, fatigue, anorexia, nausea, vomiting, weight gain or loss, or oedema.[21] Patients can also present with oliguria (urine output less than 400 mL/day), anuria (urine output less than 100 mL/day) or nonoliguric AKI with normal volumes of urine output. Other presentations of AKI may include the development of uraemic pericarditis, rarely uraemic encephalopathy, anaemia or bleeding caused by uraemic platelet dysfunction.

History and clinical findings

A patient history and physical examination, with an emphasis on assessing the patient's volume status, are crucial for determining the cause of kidney injury (Table 2). The history should identify the use of any nephrotoxic medications or systemic illnesses that might cause poor renal perfusion or directly impair renal function. The physical examination should assess intravascular volume status and any skin rashes indicative of systemic illness.

Urinalysis

Urinalysis is a key component of any work-up in a patient with kidney impairment especially in the acute setting. Table 3 outlines various urine test results found in some of the different causes of AKI.

Blood tests

Which laboratory tests to order is directed by the differential diagnosis postulated after a complete history has been taken and physical examination performed, coupled with urinalysis results. Basic tests include full blood count and measurement of electrolytes to assess for complications associated with renal impairment.

TABLE 3. URINALYSIS AND MICROSCOPIC EXAMINATION OF THE URINE SEDIMENT IN ACUTE KIDNEY INJURY

Test	Causes of acute kidney injury				
	Prerenal	**Vascular**	**Acute tubular necrosis**	**Interstitial**	**Postrenal**
Specific gravity	High	Normal/high	Isosmotic to plasma	Isosmotic	Isosmotic
Blood (dip)	Negative	Positive	+/-	+/-	+/-
Protein (dip)	Negative	Positive	Negative	+/-	Negative
Sediment examination	Negative, hyaline casts	RBC casts, dysmorphic RBCs	Granular casts	WBC casts, eosinophils	Negative, sometimes WBCs/RBCs

Abbreviations: RBC = red blood cell; WBC = white blood cell.

Evidence of systemic disease with active urine sediments should prompt directed testing looking for specific autoimmune disease (i.e. antineutrophil cytoplasmic antibody [ANCA] for vasculitis, antinuclear antibody [ANA] and double-stranded DNA for systemic lupus erythematosus, complement level, etc). Useful diagnostic tests for patients with AKI are summarised in Table 4.

Imaging

Diagnostic imaging plays an important role in the evaluation of patients with suspected AKI. The modality most often employed is ultrasound of the kidneys, ureters and bladder. This test provides information about kidney size (large or small) and parenchyma (echogenicity), status of the pelvis and urinary

TABLE 4. DIAGNOSTIC TESTS AND CORRESPONDING DISEASES IN PATIENTS WITH ACUTE KIDNEY INJURY

Investigations	When to order	Associated diseases/conditions
Antineutrophil cytoplasmic antibody (ANCA), antiglomerular basement membrane antibody (anti-GBM Ab)	Suspected acute glomerulonephritis with active urine sediments; pulmonary renal syndrome	ANCA vasculitis; Goodpasture syndrome
Antistreptolysin O titre	Recent infection (e.g. pharyngitis, cellulitis) with acute nephritic syndrome	Poststreptococcal glomerulonephritis
Creatine kinase and myoglobin levels	Recent trauma; muscle injury; dipstick positive for blood but negative for blood cells	Rhabdomyolysis
Prostate-specific antigen (PSA) level	Older man with urinary obstructive symptoms	Prostate hypertrophy; prostate cancer
Eosinophiluria	Fever; rash following new medications	Interstitial nephritis
Evidence of haemolysis (schistocytes on peripheral blood smear; decreased haptoglobin level; elevated bilirubin level with elevated lactate dehydrogenase level [LDH])	Fever; anaemia; thrombocytopenia; diarrhoeal illness	Haemolytic uraemic syndrome; thrombotic thrombocytopenic purpura; systemic lupus erythematosus; other autoimmune diseases
Monoclonal spike on serum protein electrophoresis; Bence Jones proteinuria	Anaemia; proteinuria; acute kidney injury in elderly patients	Multiple myeloma
Antinuclear antibody level; double-stranded DNA antibody level	Proteinuria; skin rash; arthritis	Systemic lupus erythematosus; other connective tissue disease
Positive hepatitis B or C serology	Intravenous drug users; immigrants; liver disease	Hepatorenal syndrome; membranous or mesangiocapillary glomerulonephritis

collecting system (hydronephrosis), and the presence of structural abnormalities (stones, masses, and enlarged lymph nodes).

In the setting of AKI, the biggest use of renal ultrasound is for rapidly confirming or excluding the presence of hydronephrosis or obstructive uropathy. A CT scan provides information about the aetiology of postrenal AKI when ultrasound is negative or inconclusive, but intravenous contrast should be avoided due to the risk of worsening renal dysfunction.

Nephrologist referral and multidisciplinary care

Urgent referral of the patient to a specialist renal service may be considered when the renal impairment is rapidly progressive or the cause is not clear. The presence of protein, red blood cells or red blood cell casts in the urine warrants further investigation to determine the intrinsic renal cause. A renal biopsy is important when clinical assessment and laboratory investigations suggest a diagnosis that requires confirmation before specific therapy (e.g. immunosuppressive medications) is instituted.

Conclusion

There are many differential diagnoses of kidney injury and therefore different investigations are required depending on the clinical suspicion. The urgency of diagnostic process depends on both the severity of renal impairment and whether it is stable or declining. Also, the consequences of kidney injury need to be identified and rapidly managed to avoid serious adverse events. MT

References

1. Australian Institute of Health and Welfare. An overview of chronic kidney disease in Australia, 2009. Canberra: AIHW; 2009.
2. Australian Institute of Health and Welfare. Chronic kidney disease hospitalization in Australia 2000-01 to 2007-08. Canberra: AIHW; 2010.
3. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (2 Suppl 1): S1-266.
4. Levey AS, Eckardt KU, Tsukamoto Y, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005; 67: 2089-2100.
5. Levey AS, de Jong PE, Coresh J, et al. The definition, classification and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int 2011; 80: 17-28.
6. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalance of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003; 41: 1-12.
7. Chadban SJ, Briganti EM, Kerr PG, et al. Prevalence of chronic kidney disease in Australia adults: the AusDiab kidney study. J Am Soc Nephrol 2003; 14 (7 Suppl 2): S131-138.
8. White SL, Polkinghorne KR, Atkins RC, Chadban SJ. Comparison of the prevalence and mortality risk of CKD in Australia using the CKD Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD study GFR estimating equation: the AusDiab (Australia Diabetes, Obesity and Lifestyle) study. Am J Kidney Dis 2010; 55: 660-670.
9. Baggio B, Budakovic A, Perissinotto E, et al. Atherosclerotic risk factors and renal function in the elderly: the role of hyperfibrinogenaemia and smoking. Results from the Italian Longitudinal Study on Ageing (ILSA). Nephrol Dial Transplant 2005; 20: 114-123.
10. Fliser D, Franek E, Joest M, Block S, Mutschler E, Ritz E. Renal function in the elderly: impact of hypertension and cardiac function. Kidney Int 1997; 51: 1196-1204.
11. Lindeman RD, Tobin J, Shock NW. Longitudinal studies on the rate of decline in renal function with age. J Am Geriatr Soc 1985; 33: 278-285.
12. Bowling CB, Inker LA, Gutierrez OM, et al. Age specific associations of reduced glomerular filtration rate with concurrent kidney disease complications. Clin J Am Soc Nephrol 2011; 6: 2822-2828.
13. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events and hospitalisation. N Engl J Med 2004; 351: 1296-1305.
14. Keith DS, Nicholas GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organisation. Arch Intern Med 2004; 164: 659-663.
15. Johnson DW, Jones GR, Mathew TH, et al. Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations. Med J Aust 2012; 197: 224-225.
16. Davenport A, Jones SR, Goel S, Astley JP, Hartog M. Differentiation of acute from chronic renal impairment by detection of carbamylated haemoglobin. Lancet 1993; 341: 1614-1617.
17. Ozmen S, Danis R, Akin D, Cil T, Yazanel O. Parathyroid hormone as a marker for the differential diagnosis of acute and chronic renal failure. Renal Failure 2007; 29: 509-512.
18. Ozmen CA, Akin D, Bilek SU, Bayrak AH, Senturk S, Nazaroglu H. Ultrasound as a diagnostic tool to differentiate acute from chronic renal failure. Clin Neph 2010: 74: 46-52.
19. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012; 2: 1-138.
20. Bellomo R, Kellum JA, Ronco C. Acute kidney injury: time for consensus. Intensive Care Med 2001; 27: 1685-1688.
21. Meyer TW, Hostetter TH. Uraemia. N Engl J Med 2007; 357: 1316-1325.

COMPETING INTERESTS: None.