Acute-on-chronic kidney disease:

Prevention, diagnosis, management and referral in primary care

Acute kidney injury that occurs in a community setting accounts for 1% of all hospital admissions. Most of these patients have pre-existing chronic kidney disease (CKD), managed in primary care. Early identification of patients at increased risk of acute kidney injury can prevent deterioration in renal function. General Practitioners need to be aware of the possibility of acute kidney injury, recognise the causative factors, request and interpret initial investigations and determine the urgency of referral for hospital assessment.

Chronic kidney disease is the major risk factor for acute kidney injury

Acute kidney injury is a medical emergency characterised by a rapid (hours to days) fall in glomerular filtration rate. Most people who experience acute kidney injury have some degree of pre-existing chronic kidney disease (CKD).[1] In a study of over 1700 patients with acute kidney injury requiring dialysis, 74% had an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 in the months prior to admission.[1]Rapidly declining renal function is therefore highly likely to be due to an acute deterioration of CKD, termed acute-on-chronic kidney disease. Acute kidney injury accounts for approximately 1% of all hospital admissions.[2] When severe enough to require dialysis, the associated in-hospital mortality rate can exceed 30%.[1] Prompt diagnosis is important, as in most cases the cause is reversible and early treatment may prevent permanent renal damage.

Who is at risk of developing acute kidney injury?

The prevalence of CKD and acute kidney injury increases with age. Between one-quarter and one-third of all adults aged over 64 years have CKD.[3] The incidence of severe acute kidney injury is more than fifty times higher in people aged over 80 years than in people aged under 50 years.[4]

Diabetes mellitus, hypertension, obesity and proteinuria are independent risk factors for acute kidney injury.[1,5] People with co-existing diabetes mellitus and CKD are at even greater risk of developing acute kidney injury.[1] Older people, who have poor mobility and reduced access to fluids when unwell, have an increased risk of pre-renal injury. When this is combined with polypharmacy, including nephrotoxic medicines, the likelihood of an acute-on-chronic decline in renal function is increased.

Acute kidney injury is now the preferred term

Acute kidney injury is the new consensus term that replaces the term acute renal failure. This term was adopted because the condition is understood to be a continuum of injury, rather than a discrete episode of organ failure defined by arbitrary values. It is also being increasingly recognised that even small impairments to renal function, changes too small to be recognised as organ failure, have a significant effect on patient morbidity and mortality.[6]

What are the causes of acute kidney injury?

Most cases of acute-on-chronic kidney injury occur in the presence of an infection or other concurrent illness. Patients with intrinsic renal disease or low grade chronic obstruction may be largely asymptomatic.

The causes of acute kidney injury can be divided into three categories:

1. Pre-renal causes
2. Intrinsic renal causes
3. Post-renal causes

Pre-renal injury

A reduction in blood flow to the kidney is the most common cause of acute kidney injury.[2] The resulting renal injury is due to the inability to maintain renal blood flow via auto-regulation, and is not due to direct damage to the nephron itself. The defining feature of acute pre-renal injury is that if normal blood flow can be re-established, renal function will often rapidly recover. However, a sustained reduction in renal perfusion increases the risk of intrinsic renal injury (acute tubular necrosis), which may result in irreversible damage to the kidney.

The main causes of pre-renal injury are:[2]

- Hypovolaemia, e.g. as a result of diarrhoea, vomiting, diuretics, osmotic diuresis from poorly controlled diabetes, haemorrhage and traumatic or septic shock
- Decreased effective blood volume, e.g. heart failure or cirrhosis
- Vasoregulation, e.g. medicines such as non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), or hypercalcaemia

Intrinsic renal injury

Intrinsic renal injury is characterised by direct damage to the nephrons. It is often complex and may be secondary to another illness.[2] The most common cause of intrinsic injury is acute tubular necrosis as a result of pre-renal injury or direct toxicity (hypotension, hypovolaemia, haemolysis, rhabdomyolysis or nephrotoxic medicines, e.g. NSAIDs, lithium or aminoglycosides).[2, 6] The combination of pre-renal injury and acute tubular necrosis accounts for approximately 90% of cases of acute kidney injury.

Medicine-induced interstitial nephritis is the other main form of intrinsic renal disease. There is a high mortality rate associated with intrinsic renal injury, but this is heavily influenced by patient co-morbidity.

Acute glomerulonephritis, particularly as a result of small vessel vasculitis, is an uncommon but important cause of acute kidney injury. Early diagnosis and appropriate treatment prevents end-stage chronic kidney disease.

Post-renal injury

Post-renal injury is caused by a blockage to the flow of urine, resulting in a back pressure to the kidney, causing damage to nephrons. This is obstructive nephropathy and is a relatively uncommon cause of acute kidney injury (5%).[2] Timely diagnosis and treatment can lead to a complete recovery. The most frequent causes of obstructive nephropathy include:[2]

- Urinary tract stones
- Prostatic hypertrophy
- An intra-abdominal process encasing the ureters, e.g. retroperitoneal fibrosis or prostatic and other pelvic malignancy

The site, degree and speed of onset of the obstruction determine the clinical symptoms and signs.

Preventing acute kidney injury

The first focus of primary care is to prevent acute-on-chronic kidney disease from occurring. Patients with CKD, presenting with an acute illness, should have an early assessment of renal function. Blood pressure and volume maintenance, combined with avoidance of nephrotoxic medicines and healthy lifestyle choices, are the recommended strategies for reducing the risk of acute kidney injury in people with CKD.[7] Patients who have had a previous acute decline in renal function should be flagged and identified as being at risk of future kidney injury.

Kidney health checks should be performed regularly

Patients with CKD or risk factors for CKD should have their renal function assessed as indicated by CKD guidelines.

See: "Making a difference in chronic kidney disease", BPJ 22 (Jul, 2009).

Patients with CKD have altered auto-regulation of glomerular blood flow. As a result their creatinine and GFR varies according to their blood pressure. This results in the serum creatinine fluctuating in the absence of clear precipitants. Creatinine often varies by 10–20% in this setting and a repeat creatinine test to exclude further progression is required.

Some medicines should be used with caution

Medicines are reported to contribute to acute kidney injury in approximately 20% of cases.[7] In particular, the triple combination of NSAIDs, ACE inhibitors (or ARBs) and diuretics can cause acute renal injury by interfering with homeostatic mechanisms.[8] This occurs when blood flow to the kidney is compromised, as prostaglandin-mediated afferent arteriolar vasodilation is blocked by NSAIDs, and blood flow from the kidney cannot be reduced, as efferent arteriolar vasoconstriction is prevented by either ACE inhibitors or ARBs. The combined effect is a decline in the glomerular filtration rate which is exacerbated in people who are also taking diuretics.[8] People taking this combination of medicines, particularly those with established CKD and an acute concurrent illness, require regular monitoring of serum creatinine and potassium.

Many other medicines can cause intrinsic acute renal injury, including; furosemide, proton pump inhibitors, beta-lactam antibiotics, aminoglycosides, cyclosporin, sulphonamides, colchicine, phenytoin, lithium and paracetamol (high dose or chronic use).[6,9] Patients who are unwell or develop allergic-type symptoms (allergic nephritis) after starting a new medicine may need their renal function checked.

Acute kidney injury is often associated with acute illness

In primary care, acute-on-chronic kidney disease is often caused by hypovolaemia due to an episode of concurrent illness, e.g. upper or lower respiratory tract infection, urinary tract infection, sepsis or gastrointestinal illness. Maintenance of fluid and electrolyte balance when people are unwell is an important preventative strategy. It may be appropriate for people with CKD and an acute illness to discontinue, or reduce, the dose of potentially nephrotoxic medicines. They should also be advised to avoid taking nephrotoxic medicines, including over-the-counter medicines, e.g. NSAIDs.

Diagnostic procedures may increase the risk of acute kidney injury

People with CKD, particularly in combination with diabetes, are at increased risk of developing acute kidney injury when undergoing procedures requiring radiocontrast media.[6] If contrast-enhanced imaging is required, then consider discontinuing diuretics or any nephrotoxic medicines according to local radiology protocols. Metformin is contraindicated in procedures involving iodine-containing contrast media.[10] Colonoscopy requires bowel preparation which can increase the risk of diarrhoea and volume depletion. When referring people with CKD for colonoscopy, a history of kidney disease should be noted on the referral form and the risk of adverse events discussed with the patient.

Managing acute kidney injury

Acute kidney injury should be considered a medical emergency. If there is a clearly identifiable cause then this should be managed. If the cause of deterioration is not clear, consider discussion with or referral to nephrology services.

Preventative strategies reduce the risk of acute-on-chronic kidney disease and slow the progression of underlying CKD. However, they cannot remove the risk completely or reverse renal damage caused by CKD. Despite sound management, a patient may be found to have an elevated serum creatinine level when assessed as part of routine monitoring, or following investigation of a concurrent illness. If this occurs, the first step is to determine whether the decline in renal function is due to CKD or acute kidney injury – as the management of the two conditions varies.[2]

Distinguishing acute kidney injury from CKD

Previous creatinine measurements are the most useful tool for confirming and assessing the severity of acute kidney injury. The length of time between creatinine measurements will vary from patient to patient and clinical judgement is required to interpret the significance of current levels. The *bestpractice* Decision Support "Chronic Care Module" provides a method to recognise significant rates of change and acute decline in renal function. See Page 5 for further information.

Where there is uncertainty surrounding an assessment of renal function, consultation with a nephrologist is recommended.

Patients who have a single raised serum creatinine and no baseline serum creatinine measurements should be assumed to have acute kidney injury. In the absence of another creatinine result every effort should be made to find a past result. Creatinine levels should be retested to determine the rate of continuing decline. The timeframe for repeat testing depends on the clinical scenario, but should be no longer than 14 days.[9] Where acute decline is suspected and the clinical picture indicates concurrent illness the creatinine should be repeated within 24 hours.

A clinical history may suggest an obvious cause

The findings of the clinical history and physical examination will largely determine whether the patient can be managed in primary care, or if hospital referral is required.

Key points within the history include:

- Any recent acute illness
- Symptoms suggestive of outflow obstruction such as prostate symptoms or abdominal pain in acute obstruction
- A history of abdominal or pelvic malignancy causing obstruction or myeloma causing intrinsic injury from heavy proteinuria
- Systemic symptoms, such as a rash, joint or muscle pain suggesting an underlying systemic disease or vasculitis
- Current prescribed and over-the-counter medicine use or recent contrast radiology
- Pre-existing conditions or a family history of renal disease

Physical examination

Assess whether the patient is dehydrated (e.g. thirst, dry mucous membranes, reduced urinary output, tachycardia) or fluid overloaded (e.g. raised jugular venous pressure, features of pulmonary and peripheral oedema). Look for features of systemic disease, such as fever, skin rashes, joint swelling, iritis or vascular disease, e.g. absent peripheral pulses and cool peripheries. The abdomen should be examined for masses, organomegally, abdominal aortic aneurysm and the bladder palpated and percussed for possible outflow obstruction.[11]

Urinalysis

Where a clinical history and physical examination suggest acute renal injury a urine dipstick test should be performed in order not to miss a renal inflammatory process.[11] Urinalysis that is negative for blood and protein suggests reduced renal blood flow or urinary tract obstruction. However, the later can be complicated by co-existing urinary infection as suggested by the presence of white blood cells or nitrites.[11] Glomerular disease is likely to cause a strongly positive urinalysis for blood and protein (an active urinary sediment).[11] The presence of protein but little or no blood is suggestive of tubular damage or interstitial disease.[11] Macroscopic haematuria may suggest the presence of urinary tract stones or malignancy.

Acute kidney injury – when to refer

Following a diagnosis of acute kidney injury, management should be guided by a discussion with a nephrologist or general medicine physician, especially in the presence of active sediment (positive blood and protein on analysis). An exception to this would be patients with an obvious pre- or post-renal cause of their condition, where the clinician is confident that the patient can be managed in a community setting and treatment will result in a rapid reversal of kidney function, e.g. dehydration following an acute episode of diarrhoea. If there is clinical uncertainty, or an intrinsic renal cause for the condition is suspected, then the patient should be referred to hospital without delay.

Red flags requiring urgent hospital admission include:[7]

- Negligible urine output for 6 hours or < 200 mL over 12 hours
- Serum potassium > 7.0 mmol/L or > 5.5 mmol/L with ECG changes[12]
- Volume overload
- Creatinine concentration > 300 µmol/L or a change of 50% (can be determined using a decision support tool)

Management in the community

Community-based care of patients with acute kidney injury should only be undertaken when the clinician is confident that it can be treated without complications developing, and the patient will be well supported and issues around continuity of care, especially after hours provision, have been addressed. The patient will require daily monitoring of renal function and often assistance from a carer.

The focus of management of acute kidney injury is to:

1. Restore renal blood flow
2. Treat urinary obstructions
3. Review medicine use

Best practice tip: All instances of acute kidney injury should be highlighted in the patient record to prompt future kidney health assessments and prevention of future acute-on-chronic decline. Consider creating a patient alert in the patient management system.

Restoring renal blood flow

Restoration of renal perfusion is the goal in the treatment of pre-renal causes of acute kidney injury. Fluid replacement is the simplest way of achieving this. However, post-renal obstruction first needs to be excluded. Treatment should also target the reason for the volume loss, e.g. diarrhoea or vomiting.

Treating urinary obstructions

Obstruction relief is the goal of treatment in patients with post-renal acute kidney injury. This is necessary to prevent

irreversible kidney damage and for patient comfort.[6] A urethral or suprapubic catheter will relieve obstructions located at the level of the urethra or bladder, respectively.[6] If an obstruction of the upper urinary tract is suspected, then the patient should be referred to an urologist. Once relief of the obstruction has been achieved diuresis may occur, requiring the patient's fluid and electrolyte balance to be monitored.[6]

Medicine review

Patients with acute kidney injury should discontinue non-essential, nephrotoxic medicines, e.g. NSAIDs.[7] Patients with dehydration and pre-renal injury should have their ACE inhibitors, ARBs or diuretics withheld until renal function has recovered. A complete medicine review should also be undertaken either in primary or secondary care as appropriate.

Lifestyle modification to reduce future risk

Following an acute-on-chronic episode all people with CKD should be advised of healthy lifestyle choices that can be made to reduce their risk of a recurrent episode. Salt intake should be limited by using minimal salt when cooking, not adding salt to food and reducing consumption of processed meats and other high-salt food. In the presence of proteinuria, a low protein diet is recommended. Alcohol consumption should be limited Smoking cessation advice in the "ABC" format (ask, brief advice, cessation support) should also be given to all current smokers.

Managing an emergency when hospital admission is delayed

When an acute kidney injury occurs, electrolytes can accumulate and cause life-threatening complications, such as cardiac arrest. Urgent referral to secondary care is recommended for patients with serum potassium > 7.0 mmol/L.[12] An ECG is recommended for patients with serum potassium levels greater than > 5.5 mmol/L with urgent referral if ECG changes are noted (See: "A primary care approach to sodium and potassium imbalance" Best Tests, Sept 2011).[12] If there will be a significant delay in hospital referral, e.g. in an isolated rural setting, then hyperkalaemia should be treated as an emergency.[13] This should be discussed with the on-call renal team at the nearest hospital.

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