Acute Kidney Injury

Thomas Oates MRCP PhD
NIHR Clinical Lecturer, UCL Centre for Nephrology
&
Shabbir Moochhala MRCP PhD
Consultant Nephrologist, UCL Centre for Nephrology

UCL Centre for Nephrology
UCL Medical School
Rowland Hill Street
London NW3 2PF

Introduction

Acute kidney injury (AKI) is defined as any rapid loss of kidney function. It is characterised by the retention of nitrogenous (urea and creatinine) and non-nitrogenous waste products, and disordered regulation of fluid, electrolytes and acid-base balance. The term AKI covers a spectrum from minor changes in urine output and blood results to kidney failure requiring renal replacement therapy. Evidence suggests that even relatively small changes in kidney function may be associated with poor patient outcomes,[1] thus AKI has replaced the older and narrower concept of “acute renal failure” in clinical practice.

Updated definitions and diagnostic criteria for AKI achieved widespread usage concurrently with an increased focus on AKI by healthcare institutions. In 2009 NCEPOD published “Acute Kidney Injury: Adding Insult to Injury”.[2] This report recognised that AKI is a common problem often caused by systemic deficiencies in care and giving rise to significant healthcare costs. Following the publication of the NCEPOD report, the National Institute of Health and Care Excellence (NICE) developed a guideline (CG169) for the prevention, detection and management of AKI which was first published in August 2013.[3] More recently, a UK-wide programme supported both by the NHS and independent funding bodies, “Think Kidneys”, has sought to raise awareness of kidney health with separate strands focusing on both AKI and Chronic Kidney Disease (CKD).

AKI is a syndrome with numerous causes that may complicate many co-existent illnesses. Syndrome focused management may help improve delivery of care for people with multimorbidity and shift focus away from guidance focused on single diseases towards improved generalist care.[4]

Approximately 15-20% of patients admitted to hospital may have AKI[5] and community acquired AKI may both affect younger patients and be more severe.[6] As a result, AKI may have the potential to act as a barometer of safety in patient care delivered across the interfaces between primary and secondary care.

Recognising Risk and Making The Diagnosis

AKI frequently complicates acute illnesses such as sepsis and conditions that result in hypovolaemia. The co-existence of common medical problems with acute illness may increase the risk of patients acquiring AKI (Box 1). Patients presenting with acute illness and any of the risk factors listed in Box 1 should be assessed for AKI. In secondary care, this assessment is by measurement of serum creatinine and comparison to baseline. However, in primary care, the requirement for blood tests will be dictated by clinical circumstances. For example, where there is evidence of sepsis, urgent transfer to an emergency department is the priority. Alternatively, measurement of serum creatinine may not be required for patients with an apparent self-limiting acute illness. Between these two extremes, priority of serum creatinine testing should be given to those patients with the co-existing illnesses seen in Box 1.

The current diagnostic criteria for AKI are shown in Box 2. As can be seen, diagnosis of AKI is based on an increase in a patient's serum creatinine and/or fall in urine output. These diagnostic criteria do not include estimated glomerular filtration rate (eGFR), which is calculated from one of various available formulae that all utilise serum creatinine measurements. This is notably different from the current approach to the diagnosis and staging of CKD in the UK, which is based on eGFR values.[7] Equations used to calculate eGFR were originally derived from patients with CKD without acute illnesses and therefore do not take into account the rapid changes in serum creatinine seen in patients with AKI.

The diagnosis and severity staging of AKI (See Table 1) requires comparison with a baseline serum creatinine reading. There is no standard definition of baseline creatinine, but for each patient this is regarded as the stable creatinine value before they had AKI. Calculated values of baseline creatinine are of little use in the diagnosis of AKI.[8] As a result, it is crucial for clinicians to seek out and use true baseline creatinine measurements. Sometimes this requires going back through notes or electronic records to establish the last lowest and stable value. Where previous measurements of creatinine are not

available, admission serum creatinine should be used as a baseline in patients admitted to hospital.

In 2014 NHS England issued a patient safety alert recommending standardisation of the early identification of AKI using a national algorithm based on the staging system in Table 1. The alert also promoted the development and adoption of electronic alerts for AKI in both primary and secondary care. Whilst the use of these systems is of significant potential use, the gold standard for diagnosis of AKI remains "clinician review of current and previous blood results – taking clinical context into account – and comparing against AKI diagnostic and staging criteria".[9] Maximizing utility of these electronic alerts in primary care whilst minimizing potential burden remains on area of active research but "Think Kidneys" have produced guidance for recommended response times to AKI alerts.[9]

Finding the Cause

Where possible the cause of AKI should be promptly determined. It is estimated that approximately 70% of cases of AKI involve sepsis and hypotension[10] and therefore many causes of AKI can be elucidated on standard clinical assessment. Medicines are also common causes of AKI, and detection or suspicion of AKI should prompt a full review of all prescribed, over the counter, herbal or complimentary medicines, and 'recreational' substances for each patient. Up to 10% of AKI may be due to obstruction.[11] Therefore, symptoms of lower urinary tract obstruction or renal colic should be asked about specifically to guide further investigation.

Where no clear acute illness is present but AKI is diagnosed, it is important to consider less common causes such as myeloma or systemic vasculitis. The "3Hs and 3Rs" (haemoptysis, haemolysis, hypercalcaemia, rash, recent vascular intervention, raised creatine kinase)[12] are a useful screening tool for uncommon causes of AKI and the presence of any of these with a raised creatinine should prompt referral to secondary care (see Table 2).

Dipstick urinalysis for blood, protein, leucocytes, nitrites and glucose is a mandatory investigation in AKI. The presence of dipstick abnormalities is often sensitive but not necessarily specific, and AKI often occurs with a normal dipstick analysis. Patients with urinary catheters or a urological history (e.g. ureteric stents or chronic cystitis) may have chronically abnormal dipstick results. On the other hand, patients with volume depletion alone will often have a normal dipstick. Large amounts of blood and protein (2+ or greater) on dipstick without another obvious cause for AKI should raise the possibility of a diagnosis of glomerulonephritis, and necessitate urgent referral to nephrology services.

Additional diagnostic testing may include urinary tract ultrasonography. It may not be necessary to obtain an ultrasound if the cause of AKI is obvious i.e. profound volume depletion. However, if symptoms and assessment suggest an obstructed and infected kidney in the presence of AKI (e.g. known stone disease, fevers, loin pain, solitary kidney) then ultrasound scanning should be performed within 6 hours.[3] Where no obvious cause is found for AKI then ultrasound scanning should be performed within 24 hours. Ultrasonography is particularly important in patients who do not present with an acute illness or AKI risk factors (Box 1), as these patients may have urological obstruction. Asking about new or worsening urological symptoms may suggest this as a cause for AKI.

<u>Management of acute kidney injury</u>

Many different causes of AKI exist, so management will vary from patient to patient. For example, where urinary retention is present, or ultrasound scanning reveals upper urinary tract obstruction (i.e. hydronephrosis), the focus of management will be urological relief of obstruction.

Some patients will develop stage 3 AKI (see Table 1) and require renal replacement therapy (RRT). Indications for RRT include hyperkalaemia, metabolic acidosis, fluid overload, pulmonary oedema, and symptoms of uraemia (e.g. encephalopathy). Patients with these complications of AKI, regardless of the cause, should be immediately discussed with nephrology or

critical care[3] to ensure rapid transfer of care to the correct specialists during their emergency hospital admission (see Table 2).

The Importance of Medicines Optimisation

In all cases of AKI, knowing what to do with medications is a key part of initial patient management. If a patient with AKI is taking medication that may impair kidney function then these medicines should be withheld. The key medicines to consider withholding are:

- ACE inhibitors
- Angiotensin Receptor Blockers (ARBs)
- Diuretics
- NSAIDs

In addition, some medicines e.g. metformin, sulfonylureas, antibiotics and opiates, may accumulate in AKI and lead to harmful side effects. In the majority of cases of stage 2 or 3 AKI all of these medicines should be suspended.

The “Think Kidneys” programme has recently published guidance on “sick day rules” for patients at risk of AKI. The anti-hypertensives and oral hypoglycaemic medicines listed above are commonly prescribed to patients with diabetes, CKD, and heart failure, which all increase the risk of AKI (see Box 1). Furthermore, patients with CKD and diabetes may be treated to a more aggressive blood pressure target of <130/80mmHg[7] thus increasing the risk of hypoperfusion of the kidneys and subsequent AKI. “Sick day rules” suggest that patients should temporarily discontinue drugs such as NSAIDs, ACE inhibitors, ARBs, diuretics, metformin, sulfonylureas and trimethoprim during periods of acute illness such as vomiting, diarrhoea, fevers or sweats.

The appropriateness of using “sick day rules” in all patients on relevant medicines remains a topic of debate and the “Think Kidneys” programme have acknowledged that the evidence for reduction of harm in association

with this initiative is “very weak”.[13] As a result, where patients are deemed to be at high risk for AKI, the key may be to focus counselling both on cessation when unwell but also restarting medicines when well in order to avoid suboptimal treatment of medical conditions after an acute illness.

One final consideration for optimisation of medicines is that the antibiotic trimethoprim and the H_2 blockers ranitidine and cimetidine, reduce creatinine secretion into the tubules of the kidney and may increase the serum creatinine without truly reducing kidney function. This may confuse interpretation of serum creatinine measurements and lead to false positive diagnoses of AKI. A clue is often that the plasma urea concentration is relatively unchanged, compared to the creatinine.

The “Think Kidneys” programme has produced a document advising on the use of numerous common medicines in patients with AKI.[14]

Referral and Follow Up

Many patients with AKI may be appropriate for referral to hospital acute services such as ED or acute medicine for assessment and management of coexistent and causative acute illnesses such as sepsis.

NICE guideline CG169 contains recommendations for when a specific referral to nephrology is appropriate in AKI. Clearly where indications for RRT are met, this requires immediate referral to nephrology or critical care services. CG169 suggests referral to or discussion with a nephrologist within 24 hours in a number of situations and these are summarised in Table 2. Local arrangements to meet this 24-hour recommendation will vary by region and may include telephone and email advice, dedicated ”hot” clinics or pre-specified arrangements that use general acute medicine services.

When AKI has resolved it is important to ensure appropriate follow-up and patient education. Some responsibilities, such as discussion of the risk of recurrent AKI, and the potential causative role of dehydrating illnesses and

nephrotoxic drugs such as NSAIDs, will be shared by primary and secondary care.

Medicines that may have been discontinued during AKI may need to be restarted when stability of renal function is attained. If stability is attained during hospital admission this can be addressed in secondary care, otherwise secondary care physicians will need to provide discharge advice to facilitate restarting medicines in primary care. If ACE inhibitors and ARBs are restarted in the community, monitoring of renal function 2 weeks after restarting is mandatory. Kidney function may stabilise at a higher creatinine than previously, thus requiring re-assessment of baseline creatinine and eGFR. This may be particularly relevant to the use of metformin.[15]

Monitoring of kidney function after an episode of AKI will depend on the underlying cause. In the absence of a specialist diagnosis such as glomerulonephritis, monitoring should be carried out as per NICE guidance on CKD.[7] Briefly, patients with an eGFR >45ml/min/1.73m^2 can be reviewed at least annually, apart from where they have significant proteinuria. Patients with an eGFR of between 30 and 44ml/min/1.73m^2 should be reviewed twice yearly or more and patients with an eGFR of beneath 30ml/min/1.73m^2 considered for outpatient referral to a nephrologist.

More generally, data indicates that following an episode of AKI, patients may be at increased risk of mortality, development or progression of CKD and readmission to hospital,[6] suggesting that an episode of AKI may imply vulnerability and patient care may need to be individualized to address this.

Conclusion

AKI is common in both the community and in hospital, and is associated with high morbidity, mortality, and healthcare costs. Early recognition and potential prevention of AKI may be associated with improved patient outcomes. Patients who are at high risk of AKI should be educated about action they can take themselves to detect and reduce the severity of future AKI episodes. Whilst the spectrum of disease described by the term AKI is broad, increased

understanding of its association with acute illness, and the patient benefits associated with optimisation of relevant medicines, has the potential to transform management of this condition and remove the “insult from the injury”.

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Box 1. Conditions that may increase the risk of AKI in the presence of acute illness. Adapted from recommendation 1.1.1 of NICE CG169

Pre-existing Chronic Kidney Disease
Heart Failure
Liver Disease
Diabetes
History of AKI
Oliguria
Neurological or cognitive impairment that may limit access to fluids
Hypovolaemia
Use of medicines which impair kidney function
Use on iodinated contrast within the past week
Urological obstruction
Sepsis
Age over 65 years

Box 2. The Definition of Acute Kidney Injury. Adapted from KDIGO Clinical Practice Guideline for Acute Kidney Injury, 2012

AKI is defined as any of the following:

- Increase in serum creatinine by ≥26.5μmol/l within 48 hours; or
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume <0.5ml/kg/h for 6 hours

Table 1. Staging of AKI

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline OR ≥26.5 μmol/l increase	<0.5ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	<0.5ml/kg/h for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥353.6μmol/l OR Initiation of renal replacement therapy	<0.3ml/kg/h for ≥24 hours OR Anuria for ≥12 hours

Table 2. Referring to Nephrology when AKI is present. Adapted from section 1.5 NICE CG169

Immediate referral
• If meet criteria for renal replacement therapy
Referral within 24 hours
• A possible diagnosis that may need specialist treatment (e.g. myeloma, vasculitis) • AKI of unclear cause • Inadequate response to treatment • Complications associated with AKI • Stage 3 AKI • A kidney transplant • Pre-existing stage 4 or 5 CKD
Consider referral
• Where patients have severe illness that might benefit from treatment, but there is uncertainty as to whether they are nearing the end of their life
Do not refer
• Patients who have a clear cause for acute kidney injury and are demonstrating a rapid response to medical management, **unless** they have a kidney transplant.