Preventing acute kidney injury: identifying risk and reducing injury

There is currently no specific pharmacological therapy for acute kidney injury. This article describes how to identify patients at risk of acute kidney injury and what measures can be implemented to reduce the risk.

It has been recognized that even small increases in serum creatinine level are associated with worse short- and long-term patient outcomes (Mehta and Chertow, 2003; Lassnigg et al, 2004). It is hoped that the adoption of a universal definition for acute kidney injury, based in part on these relatively small rises in serum creatinine level, will help raise the awareness and recognition of acute kidney injury (Kidney Disease: Improving Global Outcomes, 2011). The importance of this was highlighted in the National Confidential Enquiry into Patient Outcomes and Death (2009) *Adding Insult to Injury* acute kidney injury study, which reported that only 50% of patients who died with a diagnosis of acute renal failure received good care. There were a number of other deficiencies identified, which included a failure to recognize patients at risk of developing acute kidney injury.

In 2009–10 the cost associated with patients developing acute kidney injury in England was estimated to be between £434 million and £620 million, with patients who developed acute kidney injury staying in hospital for an average of 4.7 days longer than patients who did not develop acute kidney injury (NHS Kidney Care, 2011). There is now improved understanding of the long-term consequences of patients developing acute kidney injury, and that the severity of acute kidney injury predicts progression to chronic kidney disease (Chawla et al, 2011). This article will focus on the general principles of prevention of acute kidney injury and will not describe the aetiology or general management of acute kidney injury which has been reviewed (Hussein et al, 2009).

Definitions and epidemiology

Acute kidney injury has replaced the term acute renal failure to better represent the different degrees of kidney injury that occur before kidney function fails and renal replacement therapy is required. Later this year the international guideline group Kidney Disease: Improving Global Outcomes will publish its proposed acute kidney injury definition (Kidney Disease: Improving Global Outcomes, 2011) which harmonises the Acute Dialysis Quality Initiative RIFLE definition (Bellomo et al, 2004) and the Acute Kidney Injury Network definition (Mehta et al, 2007). It is hoped that the adoption of this new universal definition will establish a new paradigm for acute kidney injury, promoting the earlier detection of the disease and its underlying cause. This in turn will allow earlier treatment and reduced kidney injury.

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Definition of acute kidney injury

Acute kidney injury is defined based on one of the following criteria:

- Serum creatinine increase ≥26 μmol/litre within 48 hours or
- Serum creatinine increase 1.5-fold from a reference value which is known, or presumed to have occurred, within 1 week or
- Urine output <0.5 ml/kg/hr for >6 consecutive hours.

The reference serum creatinine level should be the lowest creatinine value which has been recorded within the last 3 months.

It is recognized that the accuracy of urine output measurements outside of the intensive care unit may be less reliable, and most acute kidney injury studies have used serum creatinine criteria. Clinical judgement is necessary in patient assessment, and it is important to realise that patients may develop oliguric as well as non-oliguric acute kidney injury.

If a patient is diagnosed with acute kidney injury it is essential to identify the underlying cause, traditionally considered as pre-renal, renal or post-renal. These causes often co-exist, with 75% of all cases of acute kidney injury being secondary to a combination of pre-renal failure (hypoperfusion) and intrinsic acute tubular injury (hypoperfusion, sepsis and nephrotoxins) (Hou et al, 1983).

In patients defined as having acute kidney injury the severity can be determined using the criteria (serum creatinine or urine output) that correlates to the highest stage (*Table 1*).

Epidemiology

The true epidemiology of acute kidney injury is unclear as a result of the many different definitions that have been used. Based on old definitions it is often quoted that 5% of hospitalized patients have acute kidney injury (Hou et al, 1983). However, the application of more recently proposed definitions (RIFLE) has indicated that the incidence of acute kidney injury in hospitalized patients may be as high as 18% (Uchino et al, 2006).

Prevention of acute kidney injury

The prevention of acute kidney injury is of paramount importance and should include preventing the initial insult in patients at risk, as well as preventing progression once acute kidney injury has developed. It should be considered in primary as well as secondary care. Identification of patients at risk of acute kidney injury in the community would enable appropriate preventative strategies to be used promptly if they were to develop an acute illness or require admission to secondary care for major surgery for example.

In an ever-ageing population patients may be at particular risk as a result of decreased renal reserve and polypharmacy (Wynne and Blagburn, 2010). Many patients are on antihypertensive agents, including angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers and diuretics. A significant proportion of patients will routinely be prescribed non-steroidal anti-inflammatory drugs. Such patients should be advised to contact their GP if they become acutely ill, e.g. vomiting and diarrhoea. There should also be a low threshold for withholding antihypertensive medication if patients become hypotensive, and checking their kidney function. Such patients should be empowered with an understanding of their risk factors for developing acute kidney injury if they were hospitalized.

Recognition of risk factors

There are a number of different general risk factors to consider (*Table 2*) when trying to identify patients who need increased attention to detail with respect to preventing acute kidney injury. In many patients there will be more than one risk factor to acknowledge.

Age

Age >75 years has been proposed as a risk factor for acute kidney injury in terms of the associated reduction in kidney function that occurs with advanced years. There also needs to be increased recognition that the kidney function, as determined by the estimated glomerular filtration rate, will have less overall reserve at times of acute illness or during major surgery.

Chronic kidney disease

Patients with chronic kidney disease stage 3 (estimated glomerular filtration rate <60 ml/min/1.73m^2) are considered to be at an increased risk of acute kidney injury. This is the result of potential further decreased functional reserve at times of acute illness or during major surgery.

Table 1. Kidney Disease: Improving Global Outcomes staging system for acute kidney injury

Stage	Serum creatinine criteria	Urine output criteria
1	↑ creatinine ≥26 μmol/litre or ↑ creatinine ≥1.5–1.9-fold from baseline	<0.5 ml/kg/hr for >6 consecutive hours
2	↑ creatinine ≥2–2.9-fold from baseline	<0.5 ml/kg/hr for >12 hours
3	↑ creatinine ≥3-fold from baseline or ↑ creatinine of ≥354 μmol/litre or renal replacement therapy irrespective of stage	<0.3 ml/kg/hr for >24 hours or anuria for 12 hours

From Kidney Disease: Improving Global Outcomes (2011)

Liver disease

Patients with liver disease, particularly those with obstructive jaundice, are at risk of acute kidney injury. Patients with liver cirrhosis will have a reduced intravascular volume as a result of third space fluid loss and ascites, which can compromise perfusion of the kidneys.

Diabetes mellitus

Patients with diabetes mellitus may have underlying diabetic nephropathy and therefore an increased risk of acute kidney injury. Good control of blood glucose is recommended but with careful attention to avoiding hypoglycaemia.

Cardiac failure

More patients survive with significant degrees of cardiac failure as a result of the use of angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers. At times of acute illness or major surgery these patients are at risk of developing decompensated heart failure or the cardiorenal syndrome relating to poor perfusion of the kidneys (Butler et al, 2004).

Table 2. Risk factors for acute kidney injury

Age >75 years
Chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m^2)
Liver disease
Diabetes mellitus
Cardiac failure
Atherosclerotic peripheral vascular disease
Nephrotoxins
Hypotension (compared to baseline blood pressure)
Sepsis
Hypovolaemia

Atherosclerotic peripheral vascular disease
Patients with atherosclerotic peripheral vascular disease will have a degree of vascular dysfunction which may manifest in decreased kidney perfusion and a higher risk of underlying renal artery stenosis.

Nephrotoxins
Patients should routinely have a full medication review, including over-the-counter medications. There are a number of drugs that should be considered as potentially nephrotoxic (*Table 3*). Some medications, that are not strictly nephrotoxic, can place patients at increased risk of acute kidney injury if they become hypotensive, such as antihypertensive medication including diuretics. There is currently no robust evidence for routinely stopping pre-operative angiotensin-converting enzyme inhibitor and angiotensin-receptor blockers. Medication charts should be reviewed regularly following admission with adjustments made dependent upon the patient's clinical status.

Hypotension
It is important to identify a patient's baseline blood pressure and determine whether there has been a significant reduction in comparison, as this will compromise renal perfusion. The underlying cause of hypotension should be identified and corrected promptly. This may be secondary to causes such as hypovolaemia, sepsis or primary cardiac pathology (arrhythmias, myocardial infarction). Vasopressor support may be necessary to maintain haemodynamic status.

Sepsis
Patients who develop sepsis are at increased risk of acute kidney injury as a result of hypotension and compromised kidney blood flow. Early recognition and treatment of sepsis is essential to prevent acute kidney injury in patients at risk. Implementation of goal-directed therapy results in a more rapid reversal of shock and a decrease in the incidence of acute kidney injury (Lin et al, 2006).

Hypovolaemia
All acutely ill patients, or those undergoing major surgery, should have a careful evaluation of their volume status to determine a fluid management plan with defined end points and plans for further review.

Table 3. Nephrotoxic medications predisposing to acute kidney injury in at-risk patients

Non-steroidal anti-inflammatory drugs
Gentamicin
Iodinated contrast media
Angiotensin-converting enzyme inhibitors
Angiotensin-receptor blockers

Optimization of volume status and intravenous fluid therapy

It is recommended that patients identified with risk factors for acute kidney injury who are acutely ill or who are undergoing major surgery have careful monitoring of their volume status (*Table 4*) and kidney function. Intravenous fluid therapy may be required dependent upon the patient's clinical status and volume assessment. A detailed description of invasive monitoring techniques used intraoperatively or on intensive care units is beyond the scope of this article.

Intravenous fluid therapy
Intravenous fluid therapy may be necessary to optimize the volume status of patients at risk of acute kidney injury. The nature of the fluid requirements must be assessed, and can be broadly considered as resuscitation or maintenance fluids (Powell-Tuck et al, 2009).

Resuscitations fluids
If the patient is deemed to be clinically hypovolaemic the choice of fluid replacement should be guided by the nature of the fluid loss. Patients developing hypovolaemia secondary to haemorrhage will require packed red blood cell transfusion if available. If packed red blood cells are not available, or in other cases of hypovolaemia, fluid replacement can be achieved through rapid infusion of crystalloid or colloid solutions. There are some provisos to these recommendations particularly relevant to patients who develop progressive acute kidney injury, and may be at risk of developing hyperkalaemia. Potassium-containing solutions (Hartmann's and Ringer's lactate) should be avoided in these circumstances because of the risk of worsening hyperkalaemia. A crystalloid solution without potassium (e.g. 0.9% sodium chloride) or a colloid should be used instead.

Fluid bonuses of 250 ml crystalloid or colloid solution can be given with close attention to the clinical response (*Table 4*). A central venous pressure line and urinary catheter can be considered to aid volume status assessment in the acutely ill patient, but is not mandatory and could introduce infection. If large volumes of colloid are administered it is important to also administer an equal volume of crystalloid solution to provide sufficient water for urine production and avoid a hyperoncontic state.

Patients who have a provisional diagnosis of pre-renal acute kidney injury should be considered as having either volume responsive or unresponsive acute kidney injury. It should be recognized that despite adequate volume replacement, in some cases the patient will remain oliguric and unresponsive to fluid. In this scenario it is prudent to temporise further administration of intravenous fluid to avoid precipitating pulmonary oedema. In patients who are fluid responsive, further fluid replacement can be prescribed as hourly fluid input equal to the previous hour's output plus 30 ml, but this will need regular review.

Maintenance fluids

Maintenance fluids will be necessary in patients deemed to be euvolaemic who are unable to take fluids orally, because of their acute illness or as a result of the surgical process. It is important to review the need for intravenous fluids on a regular basis and aim to resume oral intake as soon as possible. If maintenance fluids are necessary it is preferable to prescribe a combination of crystalloid solutions that provide the patient's daily electrolyte and fluid requirements, e.g. 0.45% sodium chloride/dextrose (Na+ 75 mmol/litre, Cl- 75 mmol/litre) or 0.18% sodium chloride/dextrose (Na+ 30 mmol/litre, Cl- 30 mmol/litre). Inappropriate prescription of 0.9% sodium chloride (Na+ 154 mmol/litre, Cl- 154 mmol/litre) can potentially lead to a metabolic hyperchloraemic acidosis and significant fluid overload which contributes to postoperative morbidity and mortality.

Pharmacological therapy

There is currently no evidence to support the use of a specific pharmacological therapy in the prevention of acute kidney injury. A meta-analysis of nine randomized controlled trials concluded that furosemide is not associated with any significant clinical benefits in the prevention and treatment of acute kidney injury in adults (Ho and Sheridan, 2006). Dopamine has been proposed to prevent acute kidney injury by improving renal blood flow. However, a multitude of studies, reviewed in a meta-analysis, have concluded that there is no good evidence to support any important clinical benefits to patients with or at risk of acute kidney injury (Friedrich et al, 2005). Dopamine is associated with side effects which include cardiac arrhythmias, and myocardial and intestinal ischaemia.

Contrast-induced acute kidney injury

Contrast-induced acute kidney injury is rare in patients with normal kidney function. However, the risk of contrast-induced acute kidney injury increases in those with recognized risk factors (*Table 2*) and can occur up to 72 hours following the procedure. The risk is further amplified in patients who receive more than 100 ml of contrast or multiple contrast studies within 48–72 hours (Lewington and Kanagasundaram, 2011). There is no clear benefit in using iso-osmolar contrast media in preference to low-osmolar contrast media in patients at risk of contrast-induced acute kidney injury (Heinrich et al, 2009). Patients who require a radiological study using iodinated contrast should be discussed with radiology, with suitable consideration as to whether an alternative study would be appropriate.

It is important that patients who would benefit clinically from an iodinated contrast study are not excluded purely based on the perceived risk of contrast-induced acute kidney injury. If there is any doubt such patients should be discussed with the renal team. Standard measures to reduce the risk of contrast-induced acute kidney injury include optimization of the volume status following clinical assessment. Patients deemed to be at high risk of contrast-induced acute kidney injury, i.e. chronic kidney disease (estimated glomerular filtration rate <60 ml/min/1.73m^2) or acutely ill patients with the presence of acute kidney injury risk factors (*Table 2*), should receive intravenous volume expansion. It is currently recommended that either intravenous 0.9% sodium chloride or isotonic sodium bicarbonate should be used for volume expansion in patients at risk of contrast-induced acute kidney injury (Hoste et al, 2010). Currently there is no compelling evidence for the use of N-acetylcysteine, which can distract from the importance of optimizing volume status appropriately (Nallamothu et al, 2004). Nephrotoxic medications must be avoided and patients must have a daily clinical volume status assessment and urea and electrolytes check.

Table 4. Clinical assessment of volume status

Assessment of volume status	Considerations
Temperature	Increased insensible loss if febrile
Capillary refill	Decreased if poorly perfused
Skin turgor	Poor indicator of volume status
Mucous membranes	May be dry if mouth breathing
Axillary perspiration	Absence of perspiration indicates hypovolaemia
Pulse rate	Beta blockers or diltiazem prevent tachycardic response to hypovolaemia
Jugular venous pressure	Sensitive indicator of intravascular volume status
Blood pressure	Postural drop >20/10 mmHg (systolic/diastolic) indicates significant hypovolaemia (exclude autonomic neuropathy)
Heart sounds	Presence of a third heart sound is an early indicator of hypervolaemia
Examination of lungs	Pulmonary oedema
Peripheral oedema	May indicate hypervolaemia but consider other causes, e.g. hypoalbuminaemia secondary to sepsis. Do not assess in isolation
Urine output monitoring	Sensitive indicator, but not always accurately recorded
Daily weights	Reliable indicator of volume status trend during admission

Rhabdomyolysis

Rhabdomyolysis results from skeletal muscle injury and cell lysis, with the release of myoglobin and other muscle breakdown products. There are a number of causes including trauma, burns, compartment syndrome and drugs (ecstasy and statins). Myoglobin is freely filtered by the kidneys and is directly toxic to the tubular epithelial cells (Blanco and Echeverria, 2002), particularly in the setting of hypovolaemia and acidosis. If the urine is acidic myoglobin is more likely to crystallize in the renal tubules, contributing to the development of acute kidney injury (Block and Manning, 2001).

Prevention of rhabdomyolysis causing acute kidney injury requires aggressive fluid resuscitation and alkalization of the urine. Fluid resuscitation with intravenous 0.9% sodium chloride solution is preferred at a rate of 10–15 ml/kg/hour to establish a urine output >100 ml/hr. During treatment it is important that patients receive careful assessment of their volume status to avoid pulmonary oedema, particularly in the setting of oliguria. Sodium bicarbonate and mannitol therapy can be considered but there is no evidence that either are superior to aggressive fluid resuscitation with 0.9% sodium chloride in preventing acute kidney injury in the setting of rhabdomyolysis.

Conclusions

Acute kidney injury has both a significant clinical and economic impact in the UK. The mortality associated with acute kidney injury has remained the same for several decades. The mainstay of treatment for acute kidney injury is supportive, with no specific pharmacological therapy available. Acute kidney injury is an antecedent to chronic kidney disease, with its severity predicting future disease progression. Prevention of acute kidney injury is therefore essential and is dependent upon identifying patients at risk of developing the disease. This assessment should occur in both primary and secondary care. Patients with risk factors for acute kidney injury are particularly vulnerable at times of acute illness or following major surgery. Increased clinical vigilance is required in these patients with close attention to the optimization of volume status, treatment of sepsis and avoidance of nephrotoxins. **BJHM**

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KEY POINTS

- Relatively small rises in serum creatinine level are associated with worse patient outcomes.
- The new definitions of acute kidney injury are based on small rises in serum creatinine or reductions in urine output.
- In 2009–10 acute kidney injury cost the NHS £434–630 million.
- It has been proposed that up to 30% of cases of acute kidney injury could be prevented.
- Acute kidney injury is an antecedent for chronic kidney disease, with its severity predicting progression of disease.
- The prevention of acute kidney injury requires careful evaluation of acute kidney injury risk factors, avoidance of nephrotoxins and optimization of volume status.
- Local guidelines must be established to prevent patients developing acute kidney injury.