Prevention of acute kidney injury

Acute kidney injury is common and carries a high mortality. Many drugs have been evaluated for their role in preventing acute kidney injury, of which some are of no benefit and others may be harmful. This review discusses current interventions to prevent acute kidney injury and reviews the evidence base for each.

Acute kidney injury describes a spectrum of syndromes characterized by an abrupt and sustained decrease in glomerular filtration rate. Acute kidney injury accounts for 1% of admissions to hospital and complicates more than 7% of inpatient episodes, mostly in patients with pre-existing chronic kidney disease and in older people (Hilton, 2006). In hospital acute kidney injury is most often multifactorial, predominantly resulting from many insults such as sepsis, hypotension and use of nephrotoxic drugs. Despite many advances in medical technology, the mortality and morbidity of acute kidney injury remain high and have not improved significantly during the past two decades.

Acute kidney injury can be defined as an abrupt (within 48 hours) reduction in kidney function manifest as either an absolute increase in serum creatinine or as a percentage increase in serum creatinine or as a reduction in urine output. A staging system for acute kidney injury has been proposed (*Table 1*) (Mehta et al, 2007), which defines the degree of kidney dysfunction at diagnosis and helps track the clinical course.

Acute kidney injury is a powerful predictor of important clinical outcomes such as hospital mortality, need for renal replacement therapy, and prolonged hospital stay in critically ill patients (Barrantes et al, 2008). Even milder forms of acute kidney injury, not just dialysis-dependent acute renal failure, are associated with excess mortality (Ali et al, 2007), so it is important to prevent or hasten the recovery of all stages of acute kidney injury.

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Preventative strategies

A key prerequisite in the prevention of acute kidney injury is to identify at-risk individuals, which includes elderly people, patients with diabetes, hypertension or vascular disease, and patients with pre-existing renal impairment. Specifically the therapeutic goals are to preserve kidney function, to prevent life-threatening complications of acute kidney injury (such as hyperkalaemia, pulmonary oedema and metabolic acidosis) and to prevent the need for long-term dialysis. These goals should be achieved with minimal adverse effects.

In this review, preventative strategies have been divided into non-pharmacological and pharmacological measures.

Non-pharmacological measures

Avoiding dehydration and hypovolaemia

Intravascular volume depletion is an important risk factor for the development of acute kidney injury and in certain settings, such as traumatic rhabdomyolysis, early and aggressive fluid resuscitation is crucial (Sever et al, 2006). Volume expansion and correction of dehydration has a well-established role in preventing contrast-induced acute kidney injury, although there are limited data on the most appropriate choice of intravenous fluid. Isotonic crystalloid (saline or bicarbonate) is probably more effective than half-normal saline but there is no clear evidence with respect to the optimal rate and duration of therapy (McCullough, 2008). Despite several studies the ideal resuscitation fluid for critically ill patients with acute kidney injury has not yet been identified (Ragaller et al, 2001). Adequate intravascular volume expansion to maintain adequate kidney perfusion is the primary goal, but note that overzealous fluid administration can lead to pulmonary oedema, especially in patients with oliguria or anuria.

Table 1. Classification and staging scheme for acute kidney injury

Acute kidney injury stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine ≥26.4 μmol/litre (0.3 mg/dl) or increase to ≥150–200% (1.5–2-fold) from baseline	<0.5 ml/kg/hour for >6 hours
2	Increase in serum creatinine to >200–300% (>2–3-fold) from baseline	<0.5 ml/kg/hour for >12 hours
3	Increase in serum creatinine to >300% (>3-fold) from baseline (or serum creatinine ≥ 354 μmol/litre (≥4.0 mg/dl) with an acute increase of at least 44 μmol/litre (0.5 mg/dl))	<0.3 ml/kg/hour for >24 hours or anuria for >12 hours

Adapted from Mehta et al (2007)

Maintaining renal perfusion pressure

Renal blood flow and glomerular filtration rate remain roughly constant across a wide range of mean arterial pressures as a result of autoregulatory changes in pre- and post-glomerular arteriolar resistance. Renal autoregulation mainly depends on a combination of pre-glomerular arteriolar vasodilatation, mediated by prostaglandins and nitric oxide, and post-glomerular arteriolar vasoconstriction, mediated by angiotensin II. Drugs that interfere with these mediators, namely non-steroidal anti-inflammatory agents or cyclo-oxygenase-2 inhibitors, and angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, may provoke pre-renal acute kidney injury in particular clinical settings (Abuelo, 2007). Those at risk include patients with atherosclerotic cardiovascular disease, patients with pre-existing chronic kidney disease, and patients with renal hypoperfusion (*Table 2*).

Low perfusion states and other risk factors for kidney ischaemia should be identified and dealt with promptly. Where possible, blood pressure at the lower end of the normal range should be increased by correction of hypovolaemia and by dose reduction or cessation of antihypertensive medication, or other drugs that may lower blood pressure such as opiate analgesia. The patient should be evaluated for occult infection and any such infection should be treated. In the critically ill patient, vasopressors may be required to improve perfusion pressure, but only after adequate volume repletion is achieved.

Table 2. Major causes of kidney hypoperfusion

Hypovolaemia	Severe bleeding	
	Volume depletion, for example vomiting, diarrhoea or burns	
Hypotension	Cardiogenic shock	
	Distributive shock, for example sepsis or anaphylaxis	
Reduced renal blood flow	Drugs	Non-steroidal anti-inflammatory drugs
		Selective cyclo-oxygenase 2 inhibitors
		Angiotensin-converting enzyme inhibitors
		Angiotensin II receptor antagonists
	Abdominal aortic aneurysm	
	Renal artery stenosis or occlusion	
	Hepatorenal syndrome	
Oedematous states	Cardiac failure	
	Hepatic cirrhosis	
	Nephrotic syndrome	

Minimizing nephrotoxin exposure

Administration of nephrotoxic drugs has been implicated as a causative factor in up to 25% of all cases of severe acute kidney injury in critically ill patients (Pannu and Nadim, 2008). While it is unrealistic to advocate avoidance of all potentially nephrotoxic medication, even in high-risk patients, there are some important strategies that can be adopted to reduce the nephrotoxic potential of some of the more commonly used agents.

Aminoglycosides

Aminoglycoside treatment is relatively commonly associated with nephrotoxicity, occurring in 10–20% of cases. Aminoglycosides are non-protein-bound, and are primarily cleared by glomerular filtration then transported into proximal tubular cells where they accumulate and induce cell death. Risk factors for nephrotoxicity include high peak serum levels, cumulative dose, and duration and frequency of administration. Proximal tubular cell uptake of aminoglycosides is saturable; therefore single large doses permit more of the drug to be excreted without undergoing tubular resorption, so reducing cell injury. Numerous meta-analyses have shown similar clinical efficacy with once-daily aminoglycoside dosing, although none has shown a significant reduction in nephrotoxicity (Pannu and Nadim, 2008). However, given the additional convenience and reduced cost, once-daily dosing should now be the preferred mode of administration, with careful monitoring of trough levels to guide dose adjustment.

Amphotericin B

Amphotericin B has for decades been the antifungal drug of choice for critically ill patients because of its low cost and broad spectrum of activity. However, it is highly nephrotoxic with renal dysfunction reported in up to 80% of patients, the risk relating to cumulative dose (Costa and Nucci, 2001). Over the last few years, randomized trials have shown that lipid-based formulations of amphotericin B are significantly less nephrotoxic. Unfortunately, these agents are considerably more costly, which restricts their use to patients with the highest risk of renal impairment. Recent introduction of additional alternative antifungal agents such as itraconazole, voriconazole and caspofungin has largely supplanted the use of conventional amphotericin B in these high-risk patients.

Contrast media

Contrast-induced acute kidney injury is an important complication in the use of iodinated contrast media, and is the third commonest cause of hospital-acquired acute kidney injury (Nash et al, 2002). Patients at particular risk include those with pre-existing renal impairment, diabetes mellitus, volume depletion, haemodynamic instability or those receiving other nephrotoxic medications. These risk factors have an additive effect. The type and volume of contrast also influences the risk of contrast nephropathy. Numerous studies have shown that iso-osmolar contrast media are less nephrotoxic than low-osmolar contrast media, particularly in high-risk patients (McCullough, 2008). In high-risk patients alter-

native imaging should be considered where possible, but otherwise the lowest volume necessary of non-ionic iso-osmolar contrast medium should be used.

Pharmacological measures

Acute kidney injury is frequently multifactorial. In critically ill patients the commonest cause is sepsis, often accompanied by multi-organ failure. Primary mechanisms of sepsis-induced acute kidney injury include inflammation, oxidative stress and epithelial dysfunction rather than more traditional concepts of ischaemia (Schrier and Wang, 2004). It is not therefore surprising that drug strategies aimed at increasing kidney blood flow or decreasing oxygen consumption have generally been unsuccessful in preventing of acute kidney injury. Although many agents can be shown to improve kidney blood flow, glomerular filtration rate or urine output, clinical benefit has not yet consistently been demonstrated using any agent.

Loop diuretics

Loop diuretics act at the medullary thick ascending loop of Henle to inhibit the Na+/K+/Cl- pump on the luminal cell surface and so, theoretically, may reduce tubular oxygen demand (Bagshaw et al, 2008). Furthermore, the oliguria that accompanies acute kidney injury is, in part, the result of tubular obstruction caused by debris, potentially allowing back leak of glomerular filtrate into the interstitium so perpetuating renal injury. Hence, promoting a higher urine flow to 'flush out' the tubules with loop diuretics might in theory accelerate recovery in oliguric acute kidney injury (Venkataraman, 2008).

However, numerous meta-analyses and observational studies have shown no benefit from loop diuretics in terms of hospital mortality, need for renal replacement therapy, or number of dialysis sessions needed. Indeed, the use of high doses of furosemide is associated with an increased risk of ototoxicity and in one study with a significantly increased risk of death or non-recovery of renal function (Mehta et al, 2002). Thus, although useful and even necessary in the management of volume overload, loop diuretics have no role in the prevention of acute kidney injury and may be harmful.

Dopamine agonists

Dopamine is a catecholamine with dose-dependent effects on the systemic and renal vasculature. Low-dose dopamine increases renal blood flow and promotes natriuresis through stimulation of renal D1, D2, and D4 receptors. Dopamine has thus been evaluated extensively in the prevention and treatment of acute kidney injury. A large meta-analysis of 61 trials including more than 3000 patients showed no effect of low-dose dopamine on mortality, need for renal replacement therapy or adverse events (Friedrich et al, 2005). Low-dose dopamine increased urine output, but improvements in serum creatinine and creatinine clearance were clinically insignificant. Thus, low-dose dopamine offers transient improvements in kidney physiology, but no important clinical benefits to patients with or at risk for acute kidney injury. This may be because of the divergent effects of specific dopamine receptors in the kidney.

Fenoldopam is a selective dopamine receptor-1 agonist originally developed as an antihypertensive agent but which also has renal vasodilatory and natriuretic properties. The only large randomized controlled trial evaluating the role of fenoldopam in the prevention of contrast nephropathy showed no benefit (Stone et al, 2003). However, two recent meta-analyses, each including over 1000 patients, showed that fenoldopam is associated with a significantly lower incidence of acute kidney injury and overall mortality in critically ill patients (Landoni et al, 2007) and in patients undergoing cardiovascular surgery (Landoni et al, 2008). Further studies are warranted.

N-acetylcysteine

N-acetylcysteine is an acetylated derivative of the amino acid cysteine which has both antioxidant and vasodilatory effects. The role of N-acetylcysteine in prevention of contrast nephropathy has been extensively evaluated with conflicting results. As most of the published studies are small, numerous meta-analyses have been undertaken, again with conflicting conclusions, the main problem being the marked clinical heterogeneity between studies which limits the usefulness of meta-analysis (Fishbane, 2008). Since N-acetylcysteine has no significant side effects and is inexpensive, it is not inappropriate to use it in high-risk patients to reduce the risk of contrast nephropathy. A recent randomized controlled trial in patients with pre-existing chronic kidney disease found that extended prophylactic administration of N-acetylcysteine did not prevent acute kidney injury after heart surgery (Adabag et al, 2008). Furthermore, there was no difference in secondary outcomes such as requirement for renal replacement therapy, length of stay or mortality.

Natriuretic peptides

Atrial natriuretic peptide is synthesized by the cardiac atria, and increases glomerular filtration rate by dilating afferent arterioles while constricting efferent arterioles. Atrial natriuretic peptide also blocks tubular reabsorption of sodium and chloride, redistributes renal medullary blood flow, disrupts tubuloglomerular feedback, and reverses endothelin-induced vasoconstriction. While atrial natriuretic peptide improves glomerular filtration, urinary output and kidney histopathology in animal models, in clinical studies infusions of synthetic atrial natriuretic peptide did not reduce the need for dialysis and were associated with decreased survival in non-oliguric patients with acute kidney injury (Vesely, 2006). The therapeutic role of atrial natriuretic peptide is hampered by its short half-life, short duration of action and associ-

ated hypotension, and it is now considered more harmful than helpful in the treatment of acute kidney injury. Interestingly, a study has shown that a continuous infusion of low-dose recombinant human atrial natriuretic peptide decreased the need for dialysis and improved dialysis-free survival in post-cardiac surgery patients (Swärd et al, 2004). The difference in this study was that a very low dose of atrial natriuretic peptide was used for a long period of time and that particular efforts were made to avoid hypotension.

Allopurinol and rasburicase

Allopurinol is a xanthine oxidase inhibitor which has been used for decades to prevent tumour lysis syndrome. Rasburicase, a recombinant intravenous form of urate oxidase, catalyses oxidation of uric acid to the much more water-soluble allantoin, and is more effective than allopurinol for prevention of tumour lysis syndrome, although significantly more expensive (Mayne et al, 2008). In lower risk patients, allopurinol remains the drug of choice as its safety and efficacy is well established. Higher risk patients with a high tumour burden, rapid cell turnover and highly chemo-sensitive tumours may warrant treatment with rasburicase as a result of its superior efficacy, and also because intravenous allopurinol is unlicensed, hard to obtain and less effective.

Adenosine antagonists

Animal studies suggest that the renal haemodynamic response to radiocontrast is biphasic, consisting of initial vasodilatation followed by prolonged vasoconstriction. The vasoconstrictive response is partly mediated by adenosine and can be blunted with theophylline in animal models. A small meta-analysis of randomized controlled trials using theophylline or aminophylline to prevent contrast nephropathy showed a statistically significant reduction in the decline in kidney function after radiocontrast exposure although it is not clear whether this would translate into a clinically meaningful benefit such as reduced need for dialysis or in-hospital mortality (Ix et al, 2004).

Conclusions

Acute kidney injury is a life-threatening illness with high mortality despite advances in supportive care. There is an additional cost in terms of patient morbidity and the high demands acute kidney injury places on health-care resources. The priorities in management of acute kidney injury include early recognition, institution of appropriate preventative measures, optimization of fluid balance, identification and treatment of underlying causes, and timely initiation of renal replacement therapy where appropriate. Many cases can be treated quickly by replacing volume, treating infection, or stopping medications such as non-steroidal anti-inflammatory agents, diuretics, and antihypertensive agents, especially angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers. In spite of much research, to date no pharmacological therapy has consistently been shown to limit the progression of or speed up the recovery from acute kidney injury and some drugs may be harmful (*Table 3*). Multicentre clinical trials with adequate statistical power are urgently needed to find effective therapies that will improve outcomes. BJHM

Table 3. Strategies used in prevention of acute kidney injury

Strategies recommended to prevent acute kidney injury	Intravenous isotonic hydration
	Maintenance of 'adequate' mean arterial pressure
	Minimizing nephrotoxin exposure
	Once-daily dosing of aminoglycosides
	Use of lipid formulations of amphotericin B
	Use of low-volume non-ionic iso-osmolar contrast media
	Allopurinol or rasburicase to prevent tumour lysis syndrome
Strategies that may help prevent contrast nephropathy	N-acetylcysteine
	Hydration with sodium bicarbonate
Strategies that require further evaluation	Low-dose human recombinant atrial natriuretic peptide (in cardiac surgical patients)
	Low-dose fenoldopam (in critically ill and cardiac surgical patients)
	Theophylline (in prevention of contrast nephropathy)
Strategies that have no role in the prevention of acute kidney injury (and may be harmful)	Loop diuretics
	Low-dose dopamine
	Atrial natriuretic peptide
	Fenoldopam (in prevention of contrast nephropathy)
	N-acetylcysteine (in cardiac surgical patients)

adapted from Venkataramam (2008)

Conflict of interest: In the past five years Dr Hilton has received travel bursaries from Roche and Astellas, speaker's honoraria from Roche and has served as a consultant to Roche and Novartis.

KEY POINTS

- Acute kidney injury is common, particularly in older patients, patients with diabetes, hypertension or vascular disease, patients with pre-existing renal impairment and critically ill patients.
- Acute kidney injury in hospital most often results from many insults such as sepsis, hypotension and use of nephrotoxic drugs.
- Even mild acute kidney injury is associated with an increase in mortality.
- Many cases of acute kidney injury can be prevented by replacing volume, treating infection, and stopping nephrotoxic medications such as non-steroidal anti-inflammatory agents, diuretics and antihypertensive agents.
- No pharmacological therapy has consistently been shown to limit the progression of or speed up the recovery from acute kidney injury and some drugs may be harmful.

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