

# Review Article

## Peri-operative renal dysfunction: prevention and management

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### Summary

Postoperative increases in serum creatinine concentration, by amounts historically viewed as trivial, are associated with increased morbidity and mortality. Acute kidney injury is common, affecting one in five patients admitted with acute medical disease and up to four in five patients admitted to intensive care, of whom one in two have had operations. This review is focused principally on the identification of patients at risk of acute kidney injury and the prevention of injury. In the main, there are no interventions that directly treat the damaged kidney. The management of acute kidney injury is based on correction of dehydration, hypotension, and urinary tract obstruction, stopping nephrotoxic drugs, giving antibiotics for bacterial infection, and commencing renal replacement therapy if necessary.

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### Introduction

Renal dysfunction is associated with increased postoperative morbidity and mortality [1, 3]. Importantly, this association is not restricted to patients who require renal replacement therapy, but applies across the range of kidney disease. In routine orthopaedic surgery, for example, the estimated glomerular filtration rate (eGFR) associated with excess morbidity was less than  $50 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , classified as stage 3a chronic kidney disease [2]. The prevalence of chronic kidney disease (eGFR  $< 90 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) is approximately 1 in 11 in the UK adult population. In this review, we will concentrate on acute changes in renal function rather than the management of patients with chronic renal failure.

The definition of acute kidney injury is based on changes in serum creatinine and urine production

(Table 1) [4]. Some of the increases in serum creatinine appear trivial, but are associated with worse outcomes. For example, a rise in creatinine of  $44 \mu\text{mol} \cdot \text{l}^{-1}$  has been associated with an odds ratio of 6.5 for death and an expensive 3.5 day increase in the length of hospital stay [5]. Most peri-operative studies of renal dysfunction have been in cardiac surgical patients, but similar associations of renal dysfunction with increased cardiovascular morbidity and mortality have been observed after non-cardiac surgery [6]. Renal dysfunction is not necessarily the cause of poor outcomes, as renal injury is often one sign of an underlying multifactorial process. However, renal injury and dysfunction cause specific complications that, in turn, may worsen outcomes. Hyperkalaemia and metabolic acidosis require urgent action as they can be life-threatening. The cognitive dysfunction and retention of fluid

**Table 1** The KDIGO Classification criteria for acute kidney injury.

Stage	Serum [creatinine] increase	Urine output
1	1.5–1.9 times baseline or $\geq 26.5 \mu\text{mol.l}^{-1}$ (0.3 mg.dl <sup>-1</sup> )	$< 0.5 \text{ ml.kg}^{-1}.\text{h}^{-1}$ for 6–12 h
2	2.0–2.9 times baseline	$< 0.5 \text{ ml.kg}^{-1}.\text{h}^{-1}$ for $\geq 12$ h
3	3.0 times baseline or $\geq 353.6 \mu\text{mol.l}^{-1}$ (4.0 mg.dl <sup>-1</sup> )	$< 0.3 \text{ ml.kg}^{-1}.\text{h}^{-1}$ for $\geq 24$ h or anuria $\geq 12$ h

that are associated with uraemia are insidious; despite being associated with significant morbidity and mortality, they may not be recognised or trigger intervention [7–9]. The peri-operative physician must be aware of patients at risk of acute kidney injury to try and prevent and ameliorate postoperative harm.

## Defining renal dysfunction

The standard definitions now used for acute kidney injury have been both accepted and applied directly in clinical research [4, 10]. Initially, the Acute Dialysis Quality Initiative (ADQI) proposed the ‘risk, injury, failure, loss of kidney function and end-stage renal disease’ (RIFLE) criteria, which have evolved into the criteria for acute kidney injury proposed by KDIGO (Table 1), but which are not diagnostic of any particular pathology. Serum creatinine concentrations may inadequately reflect renal function, which is why surveillance of chronic kidney disease uses the glomerular filtration rate, estimated from the serum creatinine (eGFR) and age, sex and race [11]. There are a number of different equations for the eGFR that include the ‘modified diet in renal disease’ (MDRD) and the ‘chronic kidney disease-epidemiology collaboration’ (CKD-EPI) [12–14]. The chronicity required to diagnose chronic kidney disease is based on eGFR values ( $< 90 \text{ ml.min}^{-1}.1.73 \text{ m}^{-2}$ ) calculated from two or more creatinine concentrations measured at least 90 days apart; shorter episodes of renal dysfunction are ‘acute kidney disease’ that might presage chronic disease, even if the eGFR subsequently exceeds  $90 \text{ ml.min}^{-1}.1.73 \text{ m}^{-2}$  [15]. Acute kidney injury and subsequent disease should not be considered benign;

both should precipitate attempts to avoid progression to chronic kidney disease.

## Defining renal dysfunction in the peri-operative period

The diagnosis of acute postoperative kidney injury cannot be made without the pre-operative creatinine concentration. Calculations that estimate the pre-operative creatinine concentration overestimate the prevalence of postoperative acute kidney injury [16]. The diagnosis of acute kidney injury is less reliable than the staging of chronic kidney disease; acute changes in serum creatinine concentrations inaccurately convert to eGFR. Critically ill patients have reduced muscle bulk. Septic patients account for nearly half the cases of acute kidney injury and septic patients generate less creatinine [17–20]. The glomerular filtration rate will be overestimated in these patients by standard equations [21]. Another problem is that kidney injury precedes increases in creatinine concentration. The prognostic interpretation of changing serum creatinine concentration is context-sensitive; a fall in creatinine was associated with poor outcomes in postoperative cardiothoracic patients [22].

The diagnosis of acute postoperative kidney injury also incorporates the urine output, which has been ignored by many studies. Patients who meet both criteria for acute kidney injury do worse than patients who are not oliguric [23]. However, in the postoperative period, oliguria is often secondary to the normal physiological retention of salt and water in response to tissue damage, pain and mild degrees of hypovolaemia or hypotension. Few prospective studies have examined the contribution of oliguria to postoperative prognosis, in particular the ability of oliguria to predict subsequent creatinine changes. A study of critically ill patients reported that oliguria was not a useful predictor of subsequent increases in creatinine, without a consistent relationship between the duration of oliguria and acute kidney injury (RIFLE criteria) [7]. This study confirmed that oliguria is common but it is not usually followed by raised creatinine. The authors suggested that the relationship between oliguria and renal failure should be researched, when adjusted for cardiovascular support and haemodynamic instability.

## Pathophysiology of renal dysfunction in the peri-operative period

Multiple factors are associated with most cases of peri-operative renal dysfunction. Arterial hypotension reduces the normal net pressure of 25 mmHg that drives ultrafiltrate through the glomerulus, the quantity of which decreases with lower cardiac output. Reduced ultrafiltration is rarely the sole cause of acute kidney injury; inflammation, direct vascular injury, or tubular obstruction, for instance from cholesterol emboli or rhabdomyolysis, usually accompany peri-operative kidney injury. Subsequent disruption of intercellular tight junctions leads to the shedding of cells into the tubular lumen as well as loss of transmembrane ion channel polarity. It is unsurprising that, in many cases, simple restoration of the circulating volume does not improve outcomes and might be counterproductive. Elevated intratubular pressure decreases glomerular filtration and activation of tubule-glomerular feedback, with consequent pre-glomerular vasoconstriction, leading to further reduction in glomerular filtration. The aetiology of peri-operative renal dysfunction is complex, an improved understanding of which could lead to treatment that reduces subsequent harm [24, 25].

## Predicting peri-operative renal dysfunction

One in three cases of acute kidney injury occurs peri-operatively [26, 27]. Studies of factors associated with peri-operative acute kidney injury have been hampered by inconsistent outcomes. For example, some studies have defined acute kidney injury as a doubling of creatinine, some a pre-designated creatinine value and others the need for renal replacement therapy [28–30]. More recently, scores have been devised adopting the KDIGO definitions of kidney injury, mainly in cardiothoracic patients [31–33]. The models used by these studies reasonably predicted the severity of kidney injury, rather than just the need for dialysis [31]. Prediction models from some studies of non-cardiac patients might not be generally applicable as they focused on specific populations [34–36]. Table 2 outlines common risk factors, related to the patient, procedure or other factors [37]. Recently, there has been considerable interest in functional assessment before major surgery to further stratify risk [38, 39]. There is

**Table 2** Major risk factors for the development of peri-operative acute kidney injury.

Patient	Surgery	Other
Chronic diseases	Emergency	Acute illness
Kidney	Non-renal solid organ transplant	Sepsis
Heart failure	Cardiac bypass time	Multi-organ dysfunction
Hypertension	Aortic cross clamp	Nephrotoxic drugs
Peripheral arterial		ACEi
Obstructive pulmonary		ARB
Diabetes mellitus		Diuretics
Alcoholism		Radio-opaque intravenous contrast
Male		
Obesity		
Age (particularly > 65 years)		

ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

little evidence to suggest that results of functional testing, such as cardiopulmonary exercise testing, are independently predictive of peri-operative acute kidney injury. However, the results of these tests are independently associated with mortality, which in turn exhibits a similar risk profile to significant morbidity, so it is possible that unfit patients may be more likely to suffer kidney injury, independent of pre-operative renal function and other factors.

## Preventing peri-operative renal dysfunction

### *Before surgery*

Risk factors for kidney injury include chronic hypertension, poor diabetic control and nephrotoxic drugs, which could be modified to reduce individual risk [40, 41]. Pre-operative exercise programmes can improve cardiovascular fitness and might improve outcomes, which one could speculate would include renal dysfunction [42–44]. Enhanced recovery protocols should deliver a hydrated euvolaemic patient to theatre.

### *During surgery*

The maintenance of cardiac output and renal perfusion may reduce peri-operative renal injury [45]. The

duration of intra-operative hypotension (particularly relative to a patient's 'normal' blood pressure), including brief episodes of mean arterial pressures less than 55 mmHg, has been associated with kidney injury [46]. The judicious maintenance of cardiovascular stability, including the infusion of fluids, throughout this period, is vital to protect renal perfusion, while avoiding volume overload. Goal-directed infusion of fluids, packed red cells and inotropes to reach predetermined target haemodynamic goals, whether given before, during or after surgery, may prevent postoperative organ dysfunction [47–50]. Which intravenous fluid should be infused remains controversial [51, 52]. Semi-synthetic colloids cause renal injury and are more expensive than crystalloids, but 0.9% saline promotes hyperchloraemic acidosis [52]. There is no evidence from adequately powered randomised trials that different crystalloids cause different outcomes. Observational propensity-matched studies and historical-control studies suggest that balanced solutions may result in less kidney injury than fluids with higher chloride concentrations, such as normal saline [53–55]. High chloride concentrations cause renal vasoconstriction in dogs, which reduces the glomerular filtration rate [56]. In human volunteers, chloride fluids reduce renal perfusion on magnetic resonance imaging [57].

### **After surgery**

Postoperative oliguria may or may not signal acute kidney injury; intravenous infusions of fluid given in response to oliguria may be unnecessary or harmful. Intra-abdominal hypertension during laparoscopic surgery, positive end-expiratory pressure mechanical ventilation, as well as pain and surgical stress, all release antidiuretic hormone. The most likely causes of postoperative kidney injury are impaired perfusion and outflow obstruction. If hypoperfusion is suspected, the response to a fluid bolus should be assessed. Ultrasonography can diagnose most causes of obstruction, although occasionally an obstructed urinary tract is not dilated [58]. Intra-abdominal pressure can be raised by ascites, blood, fluid overload, oedematous bowel, and intra-abdominal sepsis [59, 60]. Intra-abdominal hypertension is a pressure more than 12 mmHg and abdominal compartment syndrome is a pressure more than 20 mmHg with new organ failure

[61]. Pressures should be monitored four-hourly for those at risk of developing abdominal compartment syndrome using a trans-bladder technique. Rate of increase in pressure can be limited by avoiding fluid overload and by adequately sedating the critically ill.

### **Drugs**

No drugs prevent acute kidney injury, despite which, both dopamine and fenoldopam continue to be used, particularly in cardiothoracic patients. Diuretics increase urine output, but do not decrease chronic renal dysfunction or mortality.

### **Renal replacement therapy**

Hyperkalaemia, hyperuraemia, metabolic acidosis, and fluid overload are indications for renal replacement, but it is uncertain what values should precipitate treatment [62, 63]. It is also unclear when renal replacement therapy should be stopped. Observational studies suggest that urine output is a reasonable sign of adequate renal function: 79% of patients who produced more than 400 ml.day<sup>-1</sup> urine without diuretic drugs did not require renal support to be restarted within one week of its discontinuation [64, 65]. Restarting renal replacement is associated with increased mortality, which is probably not a causative association [65].

There is no evidence that one replacement technique is superior to another. Techniques are broadly grouped into: continuous therapies; intermittent therapies; and a mixture of these, termed prolonged intermittent renal replacement therapy. Continuous therapies are less likely to compromise haemodynamically unstable patients, and intermittent treatments may be more suitable in other circumstances [4]. In practice, the technique used is governed by familiarity and availability.

The recommended dose is in the range of 20–30 ml.kg<sup>-1</sup>.h<sup>-1</sup> for continuous therapies [4]. Future research should assess whether tailoring the delivered dose alters outcome. For example, the postoperative, catabolic septic patient may initially need aggressive treatment and a higher delivered dose than when they are recovering and less catabolic.

### **The future: earlier detection?**

Acute kidney injury is currently defined by changes in serum creatinine, with the caveats noted above, and

the presence of oliguria. Changes in serum creatinine lag changes in renal function by 12–24 h, while oliguria has poor predictive values. A number of possible biochemical markers of early renal dysfunction have been studied [66]. Their performance is hampered by a lack of sensitivity, which, in part, reflects the varied aetiology of acute kidney injury, and lack of specificity, which reflects various causes for changes in biochemical concentration. Studies with the most promising results have often included a kidney injury that has a nature and time that are well-defined, such as patients receiving radiocontrast or after particular operations [67–69]. In more heterogeneous populations, where the timing of the renal injury is variable, biomarkers perform less well. The performance of biomarkers for acute kidney injury is impaired by the presence of chronic kidney disease or other comorbidities [70, 71]. The indiscriminate and frequent use of poorly prognostic biomarkers may distract from adequate clinical evaluation, potentially worsening patient outcomes. Nevertheless, biomarkers associated with acute kidney injury have informed us of the processes involved in its development. Some studies have examined cell cycle arrest proteins as biomarkers for acute kidney injury, for instance ‘tissue inhibitor of metalloproteinase 2’ and ‘insulin growth factor binding protein 7’ [72, 73]. Studies of cardiac surgery patients show changes in the concentrations of these markers before changes in serum creatinine or urine output occur [74, 75]. Cell cycle arrest may be a common measurable response to renal tubular injury [24, 76]. The main value of an additional 12 h’ warning, that biomarkers of renal injury might give the peri-operative clinician, is to precipitate interventions that prevent or mitigate further renal injury. We therefore need to know which interventions to use, how to use them and when.

## Conclusions

There is consensus on how to classify acute kidney injury, but there is little evidence on how to treat it. We now have some idea about which patients are most likely to develop peri-operative kidney injury, upon which prophylactic measures can be concentrated. Patients should be fed and hydrated before surgery, with peri-operative fluid infusions being titrated to achieve clear cardiovascular goals. Nephrotoxic

agents and fluid overload should be avoided. Postoperative oliguria should be observed closely but treated cautiously. In the future, early detection of renal injury may enable its earlier treatment. However, the prevention of injury through careful attention to detail is likely to prove the best medicine.

## Competing interests

No external funding and no competing interests declared.

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