Update in
Anaesthesia

# Perioperative acute kidney injury

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**Key points**

Acute kidney injury (AKI) is a common problem in the perioperative period and an independent contributor to morbidity and mortality.

Newer diagnostic criteria based on changes in serum creatinine and decreased urine output have improved earlier detection of AKI but are neither fully sensitive nor specific.

Tubular injury results from a complex interaction between baseline predisposition, haemodynamic disturbances, nephrotoxic insults and inflammatory responses.

Striking a careful balance between fluid under- and over-resuscitation, maintaining adequate systemic arterial pressure and avoidance of nephrotoxins are the cornerstones to preventing or halting the progression of kidney disease.

Cardiopulmonary bypass and IV contrast are additional factors contributing to AKI in cardiac and endovascular surgery respectively.

## INTRODUCTION

Acute kidney injury (AKI) is a syndrome of abrupt decline in renal excretory and homeostatic function. This results in bloodstream accumulation of products of nitrogenous metabolism and failure to regulate body fluid volume, electrolyte concentrations and acid–base balance. Although the incidence of AKI varies according to the sensitivity of definition, some form of renal dysfunction can be observed in about 10% of all acute care hospitalisations[1] and more than 50% of patients admitted to intensive care units (ICUs). In a large study of patients with normal renal function undergoing non-cardiac surgery, the incidence of AKI using sensitive modern definitions was 7.5%.[2] AKI is both a sensitive marker of physiological distress and an independent contributor to morbidity and mortality and even mild transient renal dysfunction has been associated with increased risk of death[1,2] and health care costs.[1] In addition, it is now recognised that, in survivors, recovery from AKI is often incomplete and episodes of AKI are a significant risk factor to development or worsening of chronic kidney disease (CKD).[3] Therefore, high-quality perioperative care should focus on evaluation of risk, early detection of renal dysfunction and appropriate supportive management of AKI in order to improve patient outcomes.

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## DIAGNOSIS OF AKI

The term AKI has replaced the term 'acute renal failure' as it best describes a clinical spectrum of disease of differing severity rather than an all-or-none phenomenon of organ failure. This change has been accompanied by the realisation that serum creatinine (SCr) has many limitations for the diagnosis of acute renal dysfunction. SCr is a product of muscle breakdown and therefore depends on age, gender, nutrition and muscle mass. Creatinine values thus have to be placed in the context of the individual patient and point in the time-course of AKI. At steady state, SCr is reciprocally related to glomerular filtration rate (GFR), but starts to increase significantly only when about 50% of glomerular filtration has been lost (Figure 1). In addition, baseline SCr values will imply very different GFR depending on age, sex and race (Figure 2). Therefore, it is possible that early renal dysfunction may often go undetected.

The development of the Risk, Injury, Failure, Loss, End Stage (RIFLE) classification of AKI in 2004 refocused approaches to AKI.[4] These criteria have most recently been updated in the 2012 Kidney Disease Improving Global Outcomes (KDIGO) criteria for the diagnosis and management of AKI (Table 1).[5] This diagnostic classification of AKI emphasises relative

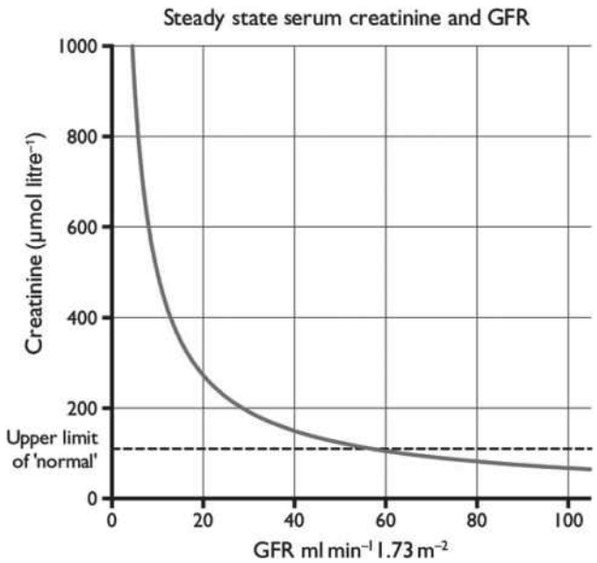


**Figure 1.** *Steady-state SCr plotted versus GFR in a 70-year-old white male. Large changes in GFR can be associated with small changes in SCr in and just above the 'normal range'.*

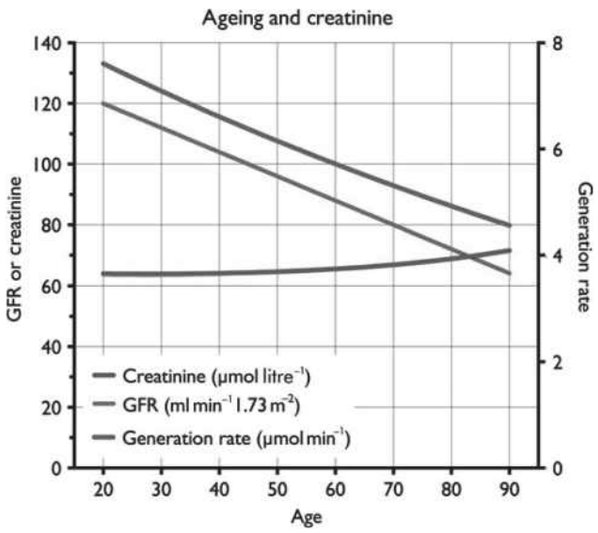


**Figure 2.** *Predicted change in normal GFR and SCr with age in a white female. The same creatinine is associated with very different GFR at different ages. Creatinine generation and GFR decline in parallel with age.*

**Table 1.** *KDIGO clinical practice guideline for AKI: staging of AKI*[15]

| Stage | Serum creatinine | Urine output |
|---|---|---|
| 1 | 1.5–1.9 × baseline<br>or<br>≥ 0.3 mg dL$^{-1}$ (≥ 26.5 μmol L$^{-1}$) increase within 48 hours | ≤ 0.5 mL kg$^{-1}$ h$^{-1}$ for 6–12 hours |
| 2 | 2.0–2.9 × baseline | ≤ 0.5 mL kg$^{-1}$ h$^{-1}$ for 12 hours |
| 3 | 3.0 × baseline<br>or<br>Increase in serum creatinine to 4.0 mg dL$^{-1}$ (≥ 353.6 μmol L$^{-1}$)<br>or<br>Initiation of renal replacement therapy<br>or<br>In patients < 18 years, decrease in eGFR to < 35 mL min$^{-1}$ per 1.73 m$^2$ | ≤ 0.3 mL kg$^{-1}$ h$^{-1}$ for 24 hours<br>or<br>Anuria for 12 hours |

ACEI, angiotensin-converting enzyme inhibitor; A2RB, angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drug; CKD, chronic kidney disease.

increases in SCr from baseline as a more accurate marker of worsening glomerular function than actual SCr values alone. However, in the dynamic situation of individuals with acute illness, applying these definitions can be more difficult as there is often a time lag between an acute decrease in GFR and an increase in SCr to a new steady state, which itself may be further delayed by changes in volume of distribution and creatinine generation rate. In recognition of this, urine output criteria have been incorporated into standardised AKI definitions. Sustained oliguria (> 12 hours) is a highly specific marker of AKI; however, it is insensitive as significant reduction in GFR can occur in the absence of oliguria. Conversely, shorter periods of low urine output are less specific in the perioperative situation as they may merely reflect response to physiological stress and transient haemodynamic changes in the absence of worsening kidney function.[6]

## AKI PATHOPHYSIOLOGY

The aetiology of AKI is traditionally classified into pre-renal, intrinsic and post-renal causes (Table 2). However, while the identification of obstruction and intrinsic kidney diseases (such as interstitial

**Table 2.** *Aetiological classification of AKI*

| Haemodynamic 'pre-renal' | Intrinsic renal disease | Post-renal |
|---|---|---|
| *Hypovolaemia*<br>• Bleeding<br>• Dehydration<br>• Extravasation<br><br>*Vasodilatory hypotension*<br>• Sepsis<br><br>*Low cardiac output states*<br><br>*Acute and chronic heart failure*<br><br>*Locally impaired renal circulation*<br>• Medication (ACEI, A2RB, NSAIDs)<br>• Renovascular disease<br>• CKD<br>• Chronic liver disease<br>• Abdominal compartment syndrome | *Acute tubular injury*<br>Multifactorial aetiology with common inflammatory pathogenesis<br><br>Causes include:<br>Systemic inflammation<br>• Sepsis, major surgery, cardiopulmonary bypass, etc.<br>Prolonged or total ischaemia<br>• Unresolved haemodynamic factors<br>Exogenous nephrotoxins<br>• Aminoglycosides<br>• Radiological contrast etc.<br><br>*Pigment nephropathy*<br>• Rhabdomyolysis, haemolysis including cardiopulmonary bypass<br><br>*Metabolic syndromes*<br>• Hypercalcaemia<br>• Hyperuricaemia<br><br>*Autoimmune/inflammatory*<br>• Glomerulonephritis<br>• Vasculitis<br>• Thromobotic microangiopathies<br>• Interstitial nephritis | *Obstruction*<br>• Prostatic hypertrophy<br>• Nephrolithiasis<br>• Retroperitoneal fibrosis<br>• Pelvic masses<br>• Bladder tumours, etc. |

nephritis) is important, these diagnoses account for only a small proportion of cases of postoperative AKI, the majority of which are related to tubular injury of have a multifactorial aetiology.

In true pre-renal AKI, haemodynamic compromise and neuro-endocrine responses result in decreased GFR and oliguria that is fully reversible with correction of haemodynamic disturbances. In reality, there is usually significant overlap with tubular injury triggered by prolonged haemodynamic disturbance, and so clinical efforts to distinguish pre-renal AKI from intrinsic tubular injury are rarely successful or helpful. The pathogenesis of tubular injury after major surgery is a result of complex interaction between baseline predisposition, haemodynamic disturbances, nephrotoxic insults and inflammatory responses. Inflammatory mechanisms play a central role, causing both direct cellular injury and inflammation-induced microcirculatory dysfunction contributing to local tissue ischaemia.

Thus, AKI is often one expression of the inflammatory processes that underlies general multi-organ dysfunction in critical illness. Tissue ischaemia is likely to play an important role in the initiation of perioperative AKI; however, renal injury may persist because of ischaemia-induced inflammation and local alterations in microvascular perfusion. Preglomerular resistance may in turn be increased in response to tubular injury, reducing renal perfusion that is independent of systemic haemodynamics. Thus, once established, these processes may not be readily reversed by manipulation of the systemic circulation aimed at maximising global renal oxygen delivery. Recognition of stage in the pathophysiology of AKI is therefore essential in selecting appropriate likely clinical progress and appropriate management (Figure 3).

## PREOPERATIVE: ASSESSMENT AND PLANNING

Preoperative assessment should aim to identify those at greatest risk of AKI, allowing pre-optimisation and planning for higher level postoperative care and monitoring in the most vulnerable. Risk factors can be divided into patient, operative, and pharmacological factors (Table 3). Although many patient risk factors are unmodifiable, efforts should be made to optimise cardiorespiratory status,

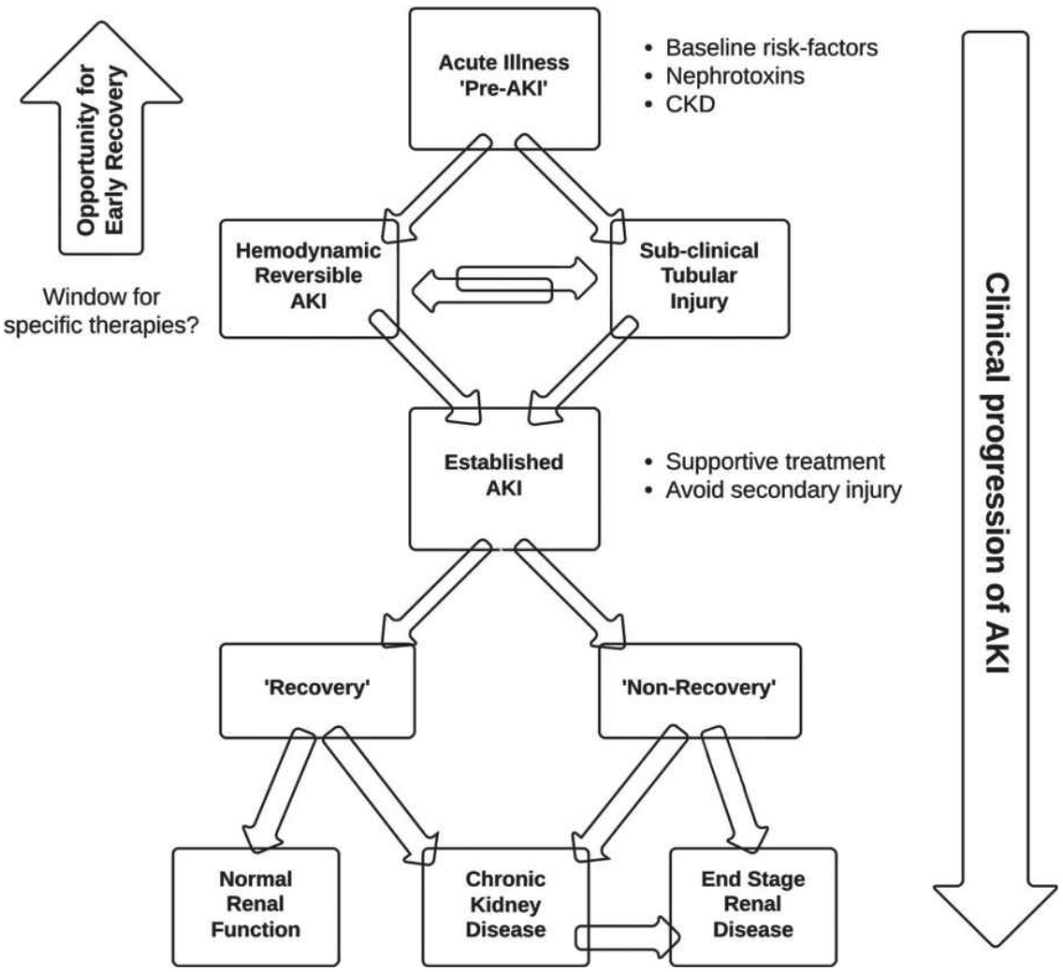


**Figure 3**. *Clinical course of AKI. Initiation of AKI can involve haemodynamic changes in GFR, subclinical tubular injury or both processes occurring simultaneously. A short window may exist when specific therapy might reverse AKI; however, this treatment may need to be tailored to the nature of the injury. Recovery from established AKI takes days to weeks; the emphasis in this case should be on supportive therapy and the avoidance of secondary renal injury that may result in non-recovery of renal function or CKD. Reproduced with permission from Prowle JR. Acute kidney injury: an intensivist's perspective.* Pediatric Nephrology *2014;* ***29****: 13–21.*

**Table 3**. *Risk factors for perioperative AKI*

| Patient | Operative | Pharmacological |
|---|---|---|
| Age | Emergency surgery | Non-steroidal anti-inflammatory agents |
| Male sex | Cardiac surgery | Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers |
| CKD | Liver transplant surgery | |
| Chronic cardiac failure | Vascular surgery | Antibiotics (aminoglycosides, glycopeptides, etc.) |
| Hypertension | Intraperitoneal surgery | Immunosuppressive drugs (calcineurin inhibitors) |
| Chronic liver disease | Duration of surgery | Hydroxyethylstarch solutions |
| Diabetes mellitus | Major haemorrhage | Radiological contrast |
| Sepsis | Blood transfusion | |
| Limited cardiorespiratory reserve | Intraoperative hypovolaemia and hypotension | |

nutrition and glycaemic control and to minimise nephrotoxin exposure. Cardiopulmonary exercise testing can be used to better define cardiorespiratory reserve to aid risk stratification. Those with known CKD are at highest risk for AKI and require most careful attention to arterial pressure and fluid balance. The need for nephrotoxic medication, such as NSAIDs, should be balanced against risk of AKI and such medication should be avoided in patients with significant risk factors. Antibiotics with nephrotoxic properties, such as aminoglycosides, should be judiciously considered, taking into account the degree and likelihood of microbial contamination or active infection and likely sensitivities to the antibiotics in question.

Sepsis is the leading cause of AKI in the ICU and concerns about nephrotoxicity should not prevent adequate treatment of infection, providing dosing and monitoring for level of renal function is appropriate. The need for regular antihypertensive medication in the perioperative period should also be reviewed considering the likelihood of postoperative vasodilatory hypotension and additional risk factors such as epidural anaesthesia. In particular, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers will selectively reduce glomerular perfusion pressure and systemic arterial pressure. Although clinical trials showing a clear benefit of omission of these agents during the perioperative phase are lacking, it is suggested that for high-risk patients and those with limited cardiovascular reserve, they should not be given on the day of surgery and not recommenced until after recovery from the acute effects of surgery.

## PERIOPERATIVE MANAGEMENT

### Haemodynamic management and fluid therapy

Targeted approaches to perioperative haemodynamic management have been shown to improve patient and renal outcomes after high-risk surgery and we suggest that goal-directed perioperative fluid management should be considered in patients deemed at high risk of AKI and all patients undergoing high-risk surgery. Such goal-directed therapy (GDT) strategies involve titrating fluid boluses and/or inotropic drugs to endpoints such as cardiac output (as provided by oesophageal Doppler, pulse contour waveform analysis or dilutional techniques) or markers of end-organ perfusion (such as arterial lactate).

Adequate monitoring of fluid resuscitation is essential in at-risk patients as there is often a fine balance to be met between resuscitating to achieve an adequate cardiac output (to prevent renal ischaemia) and avoidance of fluid overload, which is associated with adverse postoperative outcomes. Several lines of evidence suggest that fluid overload may worsen AKI,[7] decrease survival in those developing AKI and is associated with impaired recovery of renal function in patients surviving critical illness.[8] Timing of fluid resuscitation may also be crucial and experimental evidence suggests that early compared with late systemic resuscitation in systemic inflammatory states reduces renal inflammation and improves microvascular perfusion.[9] Therefore, GDT protocols may afford the best method of minimising risk of hypovolaemia, delayed resuscitation and fluid overload. A recent meta-analysis not only demonstrated a reduction in AKI with the use of perioperative GDT, but also showed that overall, the amount of fluid given in the GDT group was similar to the non-GDT group.[10] This suggests that the timing and appropriate targeting of fluid therapy is the important factor and is unlikely to contribute to fluid overloaded states.

Composition of resuscitation fluid remains an area of controversy. Evidence of increased harm with starches and lack of clear benefit compared with crystalloids or albumin led to its withdrawal in June 2013. However, there is currently no clear consensus on superiority of albumin or crystalloids. For crystalloids, there is evidence that balanced salt solutions should be given in preference to 0.9% saline, which has been associated with development of hyperchloraemic acidosis, decreased renal blood flow (RBF) and increased risk of AKI.[11]

### Vasopressors

Maintaining an adequate mean arterial pressure (MAP) is essential to preserving renal function, both to ensure adequate renal perfusion pressure and to maintain the transglomerular pressure gradient for ultrafiltration. Hypotension related to systemic vasodilation, as a consequence of systemic inflammatory response to surgical trauma or sepsis, or the effects of medication and neuroaxial block is common in postoperative settings. Vasodilatory hypotension is unlikely to respond to fluid therapy and over-reliance on IV fluids in these settings is likely to lead to prolonged hypotension and fluid overload.

While vasoconstrictors have historically been regarded as potentially harmful to an ischaemic kidney, most available evidence favours moderate vasopressor use in vasodilatory shock. The use of noradrenaline has been shown to improve RBF, GFR and urine output in experimental models of septic AKI and clinical settings. This is because systemic vasoconstrictors have a larger positive effect in increasing renal perfusion pressure than a negative effect caused by increases in renal vascular resistance. Vasopressor management in AKI requires consideration of what MAP is normal for any individual and higher levels may need to be targeted in the elderly and chronically hypertensive. It is difficult to make specific recommendations; however, increasing MAP up to 75 mmHg has been shown to increase renal oxygen delivery and GFR during post-cardiac surgery AKI, while higher targets did compromise renal perfusion in some.[12]

### Other specific therapies

There is no evidence that renal vasodilators prevent the onset or halt the progression of AKI in clinical settings. In particular, a large randomised multicentre trial demonstrated that low-dose dopamine is ineffective in the treatment of early AKI.[13] Such agents are not recommended outside clinical trial settings.

The use of diuretics should be limited to controlling fluid balance and preventing fluid overload. Although diuretics may improve urine output, there is no evidence that they reduce the onset of AKI or alter GFR. Inappropriate diuretic use risks hypovolaemia and additional renal injury.

There is also insufficient evidence to support the use of atrial natriuretic peptide, nesiritide (recombinant human β-natriuretic peptide) or theophylline in the prevention or treatment of AKI.

## AKI IN SPECIFIC PERIOPERATIVE SETTINGS

### Cardiac surgery

Up to 50% of high-risk patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) develop some degree of postoperative AKI. Cardiac surgery-associated AKI involves several synergistically injury pathways including ischaemia–reperfusion injury, exogenous and endogenous toxins, inflammation, oxidative stress and vasodilation. The use of a CPB pump has been associated with elevation in levels of systemic inflammatory mediators and length of time on CPB is a well-recognised risk factor for the development of AKI. Oxido-inflammatory changes during CPB can be further exacerbated by haemolysis in the extracorporeal circuit with release of free haemoglobin into the circulation. Haem-induced oxidant injury is likely to be a consequence of lipid peroxidation leading to the formation of potent renal vasoconstrictors and by direct cellular injury.

Thus, in common with most forms of AKI, cardiac surgery-associated AKI is multifactorial and management involves recognition of risk, early diagnosis, and supportive haemodynamic therapy. However, there are specific nephrotoxic features of CPB surgery, and some evidence suggests that 'off-pump' surgery, where feasible, is associated with lower risk of AKI.[14]

### Endovascular surgery

Interventional procedures such as endovascular aortic repair are associated with specific risk of AKI. Mechanism of renal injury is again multifactorial with mechanisms including contrast-induced AKI (CI AKI), guidewire embolisation of atheromatous material from major vessels, perioperative hypotension and inflammation.

CI AKI can occur in as many as 25% of patients with pre-existing renal impairment or those exposed to other major risk factors. Postulated mechanisms of contrast toxicity include increased systemic vasoconstriction, decreased local prostaglandin and nitric oxide-mediated vasodilatation and a direct toxic effect on renal tubular cells. Current consensus recommendations are to use the lowest possible dose of iso- or hypo-osmolar contrast. In order to limit the cumulative dose of contrast at the time of surgery, preparative imaging should be done as far in advance as possible.

Avoidance of hypovolaemia and adequate hydration with isotonic crystalloid has been proven to reduce the risk of CI AKI. While sodium bicarbonate has theoretical benefits over isotonic saline, evidence of clinical superiority is lacking. A suggested fluid regime is $3\,mL\,kg^{-1}$ isotonic crystalloid (0.9% saline, buffered solutions or isotonic sodium bicarbonate) 1 hour before exposure, followed by $1\,mL\,kg^{-1}\,h^{-1}$ post exposure for 6–24 hours. Prophylactic fluid therapy remains the only proven intervention for the prevention of CI AKI and there is currently insufficient evidence to recommend the use of theophylline, fenoldopam or prophylactic haemodialysis or haemofiltration.

Evidence for the use of N-acetylcysteine for the prevention of CI AKI is neither consistent nor overwhelming, and recent guidelines produced by NICE[15] and the UK Renal Association, British Cardiovascular Intervention Society and the Royal College of Radiologists[16] suggest that there is no convincing benefit for prescribing oral or IV acetylcysteine or any other pharmacological agents to prevent CI AKI.

## CONCLUSIONS

AKI is associated with significant perioperative morbidity and mortality but is complex to diagnose and lacks evidence-based clinical interventions. Preventative management relies on identification of patients at risk, avoidance of nephrotoxins, optimisation of haemodynamics (including use of GDT) and assiduous monitoring during the period of risk. Current investigations for AKI have significant limitations and diagnosis is often late and imprecise. Once AKI is overt, the immediate clinical course may be unalterable and emphasis should be placed on best supportive care and avoidance of harm, including iatrogenic fluid overload, while recovery occurs.

## REFERENCES

1. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; **16**: 3365–70.
2. Abelha FJ, Botelho M, Fernandes V, Barros H. Determinants of postoperative acute kidney injury. *Crit Care* 2009; **13**: R79.
3. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and metaanalysis. *Kidney Int* 2012; **81**: 442–8.
4. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8**: R204–12.
5. Kidney Disease: Improving Global Outcomes (KDIGO). KDIGO Clinical Practice Guideline for Acute Kidney Injury. Section 2: AKI definition. *Kidney Int Suppl* 2012; **2**: 19–36.

6. Prowle JR, Liu YL, Licari E et al. Oliguria as predictive biomarker of acute kidney injury in critically ill patients. *Crit Care* 2011; **15**: R172.
7. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nature Rev Nephrol* 2010; **6**: 107–15.
8. Heung M, Wolfgram DF, Kommareddi M, Hu Y, Song PX, Ojo AO. Fluid overload at initiation of renal replacement therapy is associated with lack of renal recovery in patients with acute kidney injury. *Nephrol Dial Transplant* 2012; **27**: 956–61.
9. Legrand M, Bezemer R, Kandil A, Demirci C, Payen D, Ince C. The role of renal hypoperfusion in development of renal microcirculatory dysfunction in endotoxemic rats. *Intens Care Med* 2011; **37**: 1534–42.
10. Prowle JR, Chua HR, Bagshaw SM, Bellomo R. Clinical review: volume of fluid resuscitation and the incidence of acute kidney injury: a systematic review. *Crit Care* 2012; **16**: 230.
11. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; **308**: 1566–72.
12. Redfors B, Bragadottir G, Sellgren J, Sward K, Ricksten SE. Effects of noradrenaline on renal perfusion, filtration and oxygenation in vasodilatory shock and acute kidney injury. *Intens Care Med* 2011; **37**: 60–7.
13. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet* 2000; **356**: 2139–43.
14. Lamy A, Devereaux PJ, Prabhakaran D et al. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *NEJM* 2012; **366**: 1489–97.
15. NICE Clinical Guideline 169 (issued August 2013). Acute Kidney Injury. Prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. Available from http://guidance.nice.org.uk/cg169 (accessed 17 March 2014).
16. http://www.rcr.ac.uk/docs/radiology/pdf/2013_RA_BCIS_RCR.pdf (accessed 17 March 2014).