Anaesthesia 2016, 71 (Suppl. 1), 51–57 doi:10.1111/anae.13313

Review Article

Peri-operative renal dysfunction: prevention and management

D. Golden,[1] J. Corbett[1] and L. G. Forni[1,2]

1 Consultant, Department of Intensive Care Medicine, Royal Surrey County Hospital, Guildford, Surrey, UK
2 Consultant, Surrey Peri-operative Anaesthesia and Critical Care Collaborative Research Group and Faculty of Health Care Sciences, University of Surrey, Guildford, Surrey, UK

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.

Correspondence to: L. G. Forni
Email: luiforni@nhs.net
Accepted: 5 October 2015

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 $ml.min^{-1}.1.73\ m^{-2}$, classified as stage 3a chronic kidney disease [2]. The prevalence of chronic kidney disease ($eGFR < 90\ ml.min^{-1}.1.73\ m^{-2}$) 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 $\mu mol.l^{-1}$ 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 μmol.l^{-1} (0.3 mg.dl^{-1})	< 0.5 ml.kg^{-1}.h^{-1} for 6–12 h
2	2.0–2.9 times baseline	< 0.5 ml.kg^{-1}.h^{-1} for $\geq$ 12 h
3	3.0 times baseline or $\geq$ 353.6 μmol.l^{-1} (4.0 mg.dl^{-1})	< 0.3 ml.kg^{-1}.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 ml.min^{-1}.1.73 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 ml.min^{-1}.1.73 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 post-operative 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 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.

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	
Peripheral arterial		Nephrotoxic drugs
Obstructive pulmonary		ACEi
Diabetes mellitus		ARB
Alcoholism		Diuretics
Male		Radio-opaque intravenous contrast
Obesity		
Age (particularly > 65 years)		

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

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 $ml.day^{-1}$ 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 $ml.kg^{-1}.h^{-1}$ 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.

References

1. Kellum JA. Acute kidney injury. *Critical Care Medicine* 2008; **36**(4 Suppl.): S141–5.
2. Ackland GL, Moran N, Cone S, Grocott MP, Mythen MG. Chronic kidney disease and postoperative morbidity after elective orthopedic surgery. *Anesthesia and Analgesia* 2011; **112**: 1375–81.
3. Gajdos C, Hawn MT, Kile D, Robinson TN, Henderson WG. Risk of major nonemergent inpatient general surgical procedures in patients on long-term dialysis. *Journal of the American Medical Association Surgery* 2013; **148**: 137–43.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney International* 2012; **2** (Suppl.): 1–138.
5. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *Journal of the American Society of Nephrology* 2005; **16**: 3365–70.
6. Biteker M, Dayan A, Tekkeşin Aİ, et al. Incidence, risk factors, and outcomes of peri-operative acute kidney injury in noncardiac and nonvascular surgery. *American Journal of Surgery* 2014; **207**: 53–9.
7. Prowle JR, Liu YL, Licari E, et al. Oliguria as predictive biomarker of acute kidney injury in critically ill patients. *Critical Care* 2011; **15**: R172.
8. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Critical Care* 2008; **12**: R74.
9. Grams ME, Estrella MM, Coresh J, et al. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clinicial Journal of the American Society of Nephrology* 2011; **6**: 966–73.
10. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. 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. *Critical Care* 2004; **8**: R204–12.
11. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clinical Chemistry* 1992; **38**: 1933–53.
12. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function – measured and estimated glomerular filtration rate. *New England Journal of Medicine* 2006; **354**: 2473–83.
13. Lai CF, Wu VC, Huang TM, et al. Kidney function decline after a non-dialysis-requiring acute kidney injury is associated with

higher long-term mortality in critically ill survivors. *Critical Care* 2012; **16**: R123.
14. Carlier M, Dumoulin A, Janssen A, et al. Comparison of different equations to assess glomerular filtration in critically ill patients. *Intensive Care Medicine* 2015; **41**: 427–35.
15. Goldstein SL, Jaber BL, Faubel S, Chawla LS; Acute Kidney Injury Advisory Group of American Society of Nephrology. AKI transition of care: a potential opportunity to detect and prevent CKD. *Clinical Journal of the American Society of Nephrology* 2013; **8**: 476–83.
16. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. *Kidney International* 2015; **87**: 62–73.
17. Heimbürger O, Stenvinkel P, Bárány P. The enigma of decreased creatinine generation in acute kidney injury. *Nephrology Dialysis Transplantation* 2012; **27**: 3973–4.
18. Beddhu S, Samore MH, Roberts MS, Stoddard GJ, Pappas LM, Cheung AK. Creatinine production, nutrition, and glomerular filtration rate estimation. *Journal of the American Society of Nephrology* 2003; **14**: 1000–5.
19. Doi K, Yuen PS, Eisner C, et al. Reduced production of creatinine limits its use as marker of kidney injury in sepsis. *Journal of the American Society of Nephrology* 2009; **20**: 1217–21.
20. Wilson FP, Sheehan JM, Mariani LH, Berns JS. Creatinine generation is reduced in patients requiring continuous venovenous hemodialysis and independently predicts mortality. *Nephrology Dialysis Transplantation* 2012; **27**: 4088–94.
21. Schetz M, Gunst J, Van den Berghe G. The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU. *Intensive Care Medicine* 2014; **40**: 1709–17.
22. Lassnigg A, Schmidlin D, Mouhieddine M, et al. Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: a prospective cohort study. *Journal of the American Society of Nephrology* 2004; **15**: 1597–605.
23. Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G. Classifying AKI by urine output versus serum creatinine level. *Journal of the American Society of Nephrology* 2015; **26**: 2231–8.
24. Bonventre JV. Mechanisms of acute kidney injury and repair. In: Jorres A, Ronco C, Kellum J, eds. *Management of Acute Kidney Problems*. Heidelberg: Springer-Verlag Berlin, 2010: 13–20.
25. Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. *Nature Reviews Nephrology* 2011; **7**: 189–200.
26. Thakar CV. Perioperative acute kidney injury. *Advances in Chronic Kidney Disease* 2013; **20**: 67–75.
27. Calvert S, Shaw A. Perioperative acute kidney injury. *Perioperative Medicine* 2012; **1**: 6.
28. Englberger L, Suri RM, Li Z, et al. Validation of clinical scores predicting severe acute kidney injury after cardiac surgery. *American Journal of Kidney Diseases* 2010; **56**: 623–31.
29. Brown JR, Kramer RS, MacKenzie TA, Coca SG, Sint K, Parikh CR. Determinants of acute kidney injury duration after cardiac surgery: an externally validated tool. *Annals of Thoracic Surgery* 2012; **93**: 570–6.
30. Kiers HD, van den Boogaard M, Schoenmakers MC, et al. Comparison and clinical suitability of eight prediction models for cardiac surgery-related acute kidney injury. *Nephrology Dialysis Transplantation* 2013; **28**: 345–51.
31. Birnie K, Verheyden V, Pagano D, et al. Predictive models for kidney disease: improving global outcomes (KDIGO) defined acute kidney injury in UK cardiac surgery. *Critical Care* 2014; **18**: 606.
32. Duthie FA, McGeehan P, Hill S, et al. The utility of the additive EuroSCORE, RIFLE and AKIN staging scores in the prediction and diagnosis of acute kidney injury after cardiac surgery. *Nephron Clinical Practice* 2014; **128**: 29–38.
33. Bang JY, Lee JB, Yoon Y, Seo HS, Song JG, Hwang GS. Acute kidney injury after infrarenal abdominal aortic aneurysm surgery: a comparison of AKIN and RIFLE criteria for risk prediction. *British Journal of Anaesthesia* 2014; **113**: 993–1000.
34. Xing XZ, Wang HJ, Huang CL, et al. Two acute kidney injury risk scores for critically ill cancer patients undergoing non-cardiac surgery. *World Journal of Emergency Medicine* 2012; **3**: 278–81.
35. Chang CH, Fu CM, Yang CH, et al. Society of Thoracic Surgeons score predicts kidney injury in patients not undergoing bypass surgery. *Annals of Thoracic Surgery* 2015; **99**: 123–9.
36. Cho E, Kim SC, Kim MG, Jo SK, Cho WY, Kim HK. The incidence and risk factors of acute kidney injury after hepatobiliary surgery: a prospective observational study. *BMC Nephrology* 2014; **15**: 169.
37. Kheterpal S, Tremper KK, Heung M, et al. Development and validation of an acute kidney injury risk index for patients undergoing general surgery: results from a national data set. *Anesthesiology* 2009; **110**: 505–15.
38. Hennis PJ, Meale PM, Grocott MP. Cardiopulmonary exercise testing for the evaluation of peri-operative risk in non-cardiopulmonary surgery. *Postgraduate Medical Journal* 2011; **87**: 550–7.
39. Colson M, Baglin J, Bolsin S, Grocott MP. Cardiopulmonary exercise testing predicts 5 yr survival after major surgery. *British Journal of Anaesthesia* 2012; **109**: 735–41.
40. Josephs SA, Thakar CV. Perioperative risk assessment, prevention, and treatment of acute kidney injury. *International Anesthesiology Clinics* 2009; **47**: 89–105.
41. Thakar CV, Kharat V, Blanck S, Leonard AC. Acute kidney injury after gastric bypass surgery. *Clinical Journal of the American Society of Nephrology* 2007; **2**: 426–30.
42. Kothmann E, Batterham AM, Owen SJ, et al. Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms: a pilot study. *British Journal of Anaesthesia* 2010; **103**: 505–10.
43. Dronkers JJ, Lamberts H, Reutelingsperger IM, et al. Preoperative therapeutic programme for elderly patients scheduled for elective abdominal oncological surgery: a randomized controlled pilot study. *Clinical Rehabilitation* 2010; **24**: 614–22.
44. West MA, Loughney L, Lythgoe D, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *British Journal of Anaesthesia* 2015; **114**: 244–51.
45. Brienza N, Giglio MT, Marucci M. Preventing acute kidney injury after noncardiac surgery. *Current Opinion in Critical Care* 2010; **16**: 353–8.
46. Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. *Anesthesiology* 2013; **119**: 507–15.
47. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial. *Critical Care* 2005; **9**: R687–93.
48. Shoemaker WC, Appel PL, Kram HB. Hemodynamic and oxygen transport responses in survivors and nonsurvivors of high-risk surgery. *Critical Care Medicine* 1993; **21**: 977–90.

49. Huddart S, Peden CJ, Swart M, et al. Use of a pathway quality improvement care bundle to reduce mortality after emergency laparotomy. *British Journal of Surgery* 2015; **102**: 57–66.
50. Brienza N, Giglio MT, Marucci M, Fiore T. Does peri-operative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Critical Care Medicine* 2009; **37**: 2079–90.
51. Joannidis M, Druml W, Forni LG, et al. Prevention of acute kidney injury and protection of renal function in the intensive care unit. Expert opinion of the Working Group for Nephrology, ESICM. *Intensive Care Medicine* 2010; **36**: 392–411.
52. Severs D, Hoorn EJ, Rookmaaker MB. A critical appraisal of intravenous fluids: from the physiological basis to clinical evidence. *Nephrology Dialysis Transplantation* 2015; **30**: 178–87.
53. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. *Annals of Surgery* 2012; **255**: 821–9.
54. Yunos NM, Bellomo R, Glassford N, Sutcliffe H, Lam Q, Bailey M. Chloride-liberal vs. chloride-restrictive intravenous fluid administration and acute kidney injury: an extended analysis. *Intensive Care Medicine* 2015; **41**: 257–64.
55. 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. *Journal of the American Medical Association* 2012; **308**: 1566–72.
56. Wilcox CS. Regulation of renal blood flow by plasma chloride. *The Journal of Clinical Investigation* 1983; **71**: 726–35.
57. Chowdhury AH, Cox EF, Francis ST, Lobo DN. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte® 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Annals of Surgery* 2012; **256**: 18–24.
58. Kulkarni S, Jayachandran M, Davies A, Mamoun W, Al-Akraa M. Non-dilated obstructed pelvicalyceal system. *International Journal of Clinical Practice* 2005; **59**: 992–4.
59. Sugrue M, Jones F, Deane SA, Bishop G, Bauman A, Hillman K. Intra-abdominal hypertension is an independent cause of postoperative renal impairment. *Archives of Surgery* 1999; **134**: 1082–5.
60. Malbrain ML, Chiumello D, Pelosi P, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Critical Care Medicine* 2005; **33**: 315–22.
61. Ameloot K, Gillebert C, Desie N, Malbrain ML. Hypoperfusion, shock states, and abdominal compartment syndrome (ACS). *Surgical Clinics of North America* 2012; **92**: 207–20.
62. Ronco C, Ricci Z, De Backer D, et al. Renal replacement therapy in acute kidney injury: controversy and consensus. *Critical Care* 2015; **19**: 146.
63. Joannidis M, Forni LG. Clinical review: timing of renal replacement therapy. *Critical Care* 2011; **15**: 223.
64. Wu VC, Ko WJ, Chang HW, et al. Risk factors of early redialysis after weaning from postoperative acute renal replacement therapy. *Intensive Care Medicine* 2008; **34**: 101–8.
65. Uchino S, Bellomo R, Morimatsu H, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. *Critical Care Medicine* 2009; **37**: 2576–82.
66. Ostermann M, Philips BJ, Forni LG. Clinical review: biomarkers of acute kidney injury: where are we now? *Critical Care* 2012; **16**: 233.
67. Ling W, Zhaohui N, Ben H, et al. Urinary IL-18 and NGAL as early predictive biomarkers in contrast-induced nephropathy after coronary angiography. *Nephron Clinical Practice* 2008; **108**: 176–81.
68. Koyner JL, Garg AX, Shlipak MG, et al. Urinary cystatin C and acute kidney injury after cardiac surgery. *American Journal of Kidney Diseases* 2013; **61**: 730–8.
69. Liebetrau C, Dörr O, Baumgarten H, et al. Neutrophil gelatinase-associated lipocalin (NGAL) for the early detection of cardiac surgery associated acute kidney injury. *Scandinavian Journal of Clinical and Laboratory Investigation* 2013; **73**: 392–9.
70. Endre ZH, Pickering JW, Walker RJ, et al. Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. *Kidney International* 2011; **79**: 1119–30.
71. McIlroy DR, Wagener G, Lee HT. Neutrophil gelatinase-associated lipocalin and acute kidney injury after cardiac surgery: the effect of baseline renal function on diagnostic performance. *Clinical Journal of the American Society of Nephrology* 2010; **5**: 211–9.
72. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Critical Care* 2013; **17**: R25.
73. Koyner J1, Shaw AD, Chawla LS, et al. Tissue inhibitor metalloproteinase-2 (TIMP-2)IGF-binding protein-7 (IGFBP7) levels are associated with adverse long-term outcomes in patients with AKI. *Journal of the American Society of Nephrology* 2014; **26**: 1747–54.
74. Meersch M, Schmidt C, Van Aken H, et al. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. *PLoS ONE* 2014; **9**: e93460.
75. Gocze I, Koch M, Renner P, et al. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. *PLoS ONE* 2015; **10**: e0120863.
76. Bonventre JV. Maladaptive proximal tubule repair: cell cycle arrest. *Nephron Clinical Practice* 2014; **127**: 61–4.

