Fluid management for the prevention and attenuation of acute kidney injury

John R. Prowle, Christopher J. Kirwan and Rinaldo Bellomo

Abstract | In patients with acute kidney injury (AKI), optimization of systemic haemodynamics is central to the clinical management. However, considerable debate exists regarding the efficacy, nature, extent and duration of fluid resuscitation, particularly when the patient has undergone major surgery or is in septic shock. Crucially, volume resuscitation might be required to maintain or restore cardiac output. However, resultant fluid accumulation and tissue oedema can substantially contribute to ongoing organ dysfunction and, particularly in patients developing AKI, serious clinical consequences. In this Review, we discuss the conflict between the desire to achieve adequate resuscitation of shock and the need to mitigate the harmful effects of fluid overload. In patients with AKI, limiting and resolving fluid overload might prompt earlier use of renal replacement therapy. However, rapid or early excessive fluid removal with diuretics or extracorporeal therapy might lead to hypovolaemia and recurrent renal injury. Optimal management might involve a period of guided fluid resuscitation, followed by management of an even fluid balance and, finally, an appropriate rate of fluid removal. To obtain best clinical outcomes, serial fluid status assessment and careful definition of cardiovascular and renal targets will be required during fluid resuscitation and removal.

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Introduction

Fluid therapy is a key intervention in the prevention and treatment of acute kidney injury (AKI) in critical illness and is considered vital for the maintenance of glomerular filtration and renal oxygen delivery. However, this view fails to reflect the complex and multi-factorial aetiology of AKI.[1–3] Multiple inflammatory mechanisms are involved in the pathogenesis of AKI. These include direct cellular injury and inflammation-induced injury, and malfunction of the microcirculatory system, potentially contributing to local tissue ischaemia.[4] However, how global renal ischaemia contributes to AKI is unclear.[2] Almost complete occlusion of renal circulation does not seem to be sufficient to cause sustained AKI,[5] although in experimental models, increased renal blood flow (RBF) can occur in animals developing AKI.[6] In established AKI, RBF reduction can be observed,[7] but this seems to be independent of systemic haemodynamics and occurs as a consequence, rather than a cause, of tubular injury.[8] Inflammation (both local and systemic), alterations in intrarenal blood flow, microcirculatory dysfunction and changes to glomerular haemodynamics might all contribute to impaired kidney function in AKI. Such processes might not be easily reversed or attenuated by systemic circulation manipulation simply targeted at increasing calculated renal oxygen delivery.

Kidney-targeted fluid therapy

A net pressure gradient between the glomerular capillary and Bowman's space drives glomerular filtration. In AKI, the rationale of fluid therapy is to restore mean arterial pressure (which determines renal perfusion pressure) and cardiovascular output (required for adequate RBF). Unfortunately, routine haemodynamic measurements (such as, heart rate, blood pressure and central venous pressure) are poorly predictive of cardiovascular function and adequate RBF. Moreover, fluid therapy will only effectively treat systemic hypotension that arises following hypovolaemic shock.[9–11] Furthermore, acute illness, chronic disease and drug therapy can all alter the response of the cardiovascular system to fluid therapy in an unpredictable manner. This response is modified by diverse factors including myocardial performance,[12–14] vascular tone, regional blood flow distribution,[15,16] venous reservoir capacity and capillary permeability.[17] Such modifiers mean that assessment of the effect and adequacy of volume replacement is challenging and this uncertainty leads to considerable variation of treatment in clinical practice.

For instance, central venous pressure is still widely used to guide fluid resuscitation despite a lack of evidence for its accuracy in predicting fluid responsiveness in critical illness or operative settings.[18] Similarly, adequate systemic oxygen delivery indicators, such as normalization of arterial lactate, have been proposed.[19,20] However, in sepsis, the most common setting for AKI, arterial lactate might be more a marker of disease severity than an indication of anaerobic metabolism,[21] suggesting that fluid therapy to increase calculated oxygen delivery might not be an appropriate response in this setting. Actual cardiac output measurements do provide some information on global perfusion and oxygen delivery

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The authors declare no competing interests.

Key points

- In patients who are critically ill, adequate resuscitation of shock and the need to mitigate the harmful effects of fluid overload must both be considered
- Patients developing acute kidney injury (AKI) are at particular risk of fluid overload
- Fluid overload is associated with adverse clinical outcomes and might also directly contribute to the persistence of AKI
- Optimal fluid management in critical illness and AKI might involve early, targeted resuscitation, followed by active management of an even fluid balance and, finally, an appropriate rate of fluid removal
- In AKI, renal replacement therapy might be indicated for fluid balance management before conventional indications
- To obtain best clinical outcomes, serial fluid status assessment and careful definition of cardiovascular and renal targets will be required throughout critical illness

and allow the dynamic use of fluid and other haemodynamic therapies to be titrated against cardiac response. However, maximizing cardiac output with unrestricted intravenous fluid might not benefit the patient. For example, in a sheep model, administration of intravenous fluid achieves short-lived increases in cardiac output and blood pressure,[22] but no change in renal oxygen delivery. Similarly, in a rat model of haemorrhagic shock, fluid resuscitation that restored systemic blood pressure had no effect on renal microvascular oxygenation.[23] Although the physiological benefits of fluid resuscitation might be unreliable and transient, one consequence is predictable from knowledge of the short-lived intravascular effect of fluid therapy—repeated fluid boluses will lead to a positive fluid balance.[22,24] Thus, cardiac output monitoring might be required both to ensure adequate volume expansion in hypovolaemia, and to prevent excessive fluid administration when oxygen delivery is adequate.

Given the uncertainties regarding the end points of fluid resuscitation, protocolized haemodynamic resuscitation has been developed. This goal-directed therapy (GDT) approach uses intensive monitoring, including some measure of cardiac output or tissue oxygen delivery. GDT incorporates specific haemodynamic targets to guide fluid and/or vasoactive drug administration, and fluid challenges are given to achieve minimum haemodynamic targets with an assessment of response.[25] Use of GDT has been associated with decreased perioperative complications,[25–28] including the risk of renal dysfunction,[29] and improved survival and decreased organ dysfunction in critical illness, including sepsis.[30–32]

In many perioperative protocols, fluid therapy is optimized by short-duration use of inotropic drugs to augment cardiac output, which might limit the volume of fluid required and has been associated with improved outcomes.[33] Unfortunately, evidence for the efficacy of GDT only comes from small, largely single-centre studies, almost all in the setting of elective surgery, which employed different monitoring, haemodynamic goals, therapies and end points,[34] making it difficult to provide specific recommendations for therapy. However, one common factor is the short duration of protocolized resuscitation. Open-ended application of fluid and haemodynamic therapy to supra-physiological targets in critical illness conveys no benefit,[35] and is even harmful.[36]

The early and limited duration of modern GDT is thus a key feature of these protocols.

Fluid therapy and renal function

In a systematic meta-analysis of goal-directed haemodynamic optimization during surgery, we identified 24 trials reporting protocolized perioperative resuscitation, renal outcome and fluid balance.[37] GDT use was associated with a significantly lower incidence of AKI. However, this benefit was only apparent in those trials where GDT resulted in no greater overall quantity of fluid administration in the GDT group compared to the control group. In addition, only in studies that incorporated inotropic drugs in GDT was there a statistically significant reduction in postoperative AKI.[37] These data suggest that resuscitation of cardiac output is important in avoiding or attenuating AKI at a time of physiological demand, but that simultaneous avoidance of fluid loading might be of equal importance. Using inotropes for a short duration might meet the acute demand for oxygen delivery while limiting inappropriate fluid administration.[37] In contrast to surgery, much less data are available on GDT effects in the renal system during sepsis. Protocolized resuscitation, targeting central venous oxygen saturation, improved survival in a randomized study of early GDT in children with septic shock, and was associated with a significant reduction in AKI incidence.[31] Although fluid administration was higher in the treatment group from 0–6 h, it was not substantially different between the groups in the initial 72 h. In adults with septic shock and treated with early GDT, similar results have been reported.[32] Taken together, these studies suggest that prompt, targeted resuscitation can protect from AKI and spare unwarranted fluid therapy.

Fluid overload and the kidney

Clinically, fluid overload will manifest as an expansion of the interstitial space and increased venous pressure. The kidney is particularly affected by congestion and increased venous pressure, which lead to increased renal subcapsular pressure and lowered RBF and glomerular filtration rate (GFR).[38] At their most extreme, these effects manifest in the well-described association between fluid overload, the development of the abdominal compartment syndrome (ACS) and the occurrence of AKI.[39] In ACS, increased pressure in the abdomen elevates renal venous pressure, which in turn lowers RBF and increases pressure in Bowman's space.[40] Positive fluid balances are associated with increased risk of intra-abdominal hypertension in patients in intensive care units, which in turn is strongly associated with the development of AKI.[41–43] However, evidence suggests that the effects of fluid overload and venous congestion remain important in less-extreme situations. Observational studies in patients with chronic cardiac failure have shown that high central venous pressure independently predicts worsening renal function.[44,45] A raised venous pressure might reduce RBF by lowering the renal artery–vein pressure gradient and inducing renal congestion. Experimentally, increased renal

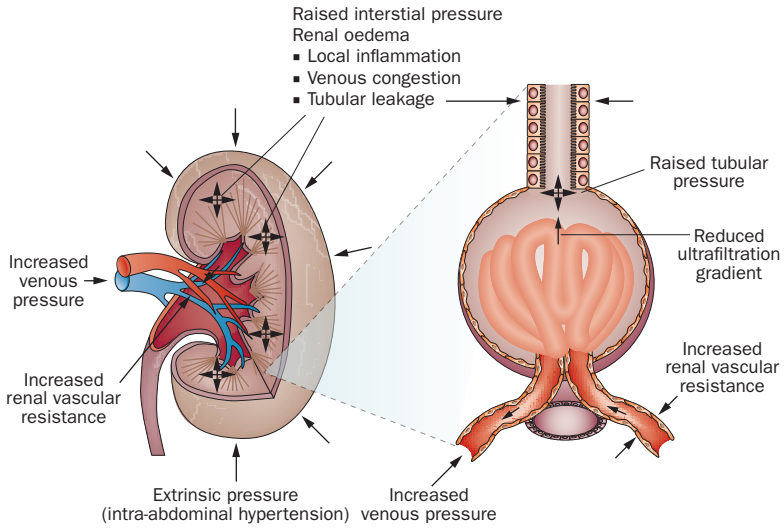

Figure 1 | Fluid overload and interstitial oedema can contribute to the maintenance of AKI. In established AKI, renal dysfunction (reduced GFR) persists despite resuscitation of systemic blood pressure and cardiac output. Increased renal venous pressure reduces the transrenal pressure gradient for RBF. Increased interstitial and tubular pressure might reduce or abolish the net glomerular filtration pressure gradient. Increased preglomerular resistance, in response to tubular injury, further reduces RBF and glomerular capillary hydrostatic pressure, hyperchloraemia might contribute to this effect.[49] Development of intra-abdominal hypertension restricts venous drainage and extrinsically compresses the kidney. Abbreviations: AKI, acute kidney injury; GFR, glomerular filtration rate; RBF, renal blood flow.

venous pressure leads to decreased RBF and GFR, with increased plasma renin activity, serum aldosterone, and urinary protein leak.[46] Similarly, in an experimental model of ischaemia reperfusion injury, clamping of the renal vein induced more rapid AKI and persistently decreased RBF than clamping of the renal artery or both artery and vein, suggesting an independent role for venous congestion in the pathophysiology of AKI.[47] In a rat ischaemia reperfusion model, AKI was associated with large (up to sevenfold) elevations of renal subscapular pressure, proportional to the severity of AKI.[48] Furthermore, renal decapsulation improved RBF, GFR and histological injury, suggesting that inflammatory oedema-related increase in renal parenchymal pressure might have a mechanistic role in the persistence of AKI.[48] These findings recapitulate the findings of historical clinical studies in patients, in whom renal decapsulation prevented AKI in patients with haemorrhagic shock who needed substantial resuscitation.[75] Increased intrarenal pressure would be expected to increase intratubular pressure, reducing or abolishing the glomerular ultrafiltration gradient. During the maintenance phase of AKI, elevated tubular pressure might be the principal factor in the continued loss of renal function.[76] Importantly, administration of modest volumes of intravenous fluid to patients significantly increases renal volume by MRI.[49] Further studies are required to assess the effect of renal volume changes on intrarenal pressure, which might be large given the non-compliant renal capsule. Both renal venous congestion and renal interstitial oedema are, therefore, important factors that may initiate and maintain AKI. Fluid overload is likely to exacerbate these effects by increasing venous pressure and renal volume. Fluid overload, increased venous pressure and renal interstitial oedema might, therefore, have a causative role in the development and prolongation of AKI, instead of merely being markers for illness severity or reduced salt and water excretion (Figure 1).

Fluid overload in AKI

Over the past 5 years, the interaction between fluid overload, AKI and adverse outcomes during and after critical illness has been explored in many large observational studies (Table 1). Positive fluid balance was associated with increased AKI risk in an observational study of critically ill patients in Europe,[50] a similar study also associated positive fluid balance in AKI with non-recovery of renal function.[51] A positive fluid balance at the development of AKI was associated with increased mortality in both studies, a finding subsequently confirmed by other authors.[52] However, observational data makes it difficult to separate indirect associations of fluid overload as a marker of physiological instability, from a direct causative role in AKI that might be modifiable by limiting fluid accumulation. Some investigators have found fluid overload remained independently associated with adverse outcomes in AKI after accounting for the confounding effects of illness severity and haemodynamic instability.[53–57] In addition, fluid overload seems to be important in AKI pathogenesis at all stages of its clinical course. For instance, early positive fluid balance can also predict the occurrence of AKI after cardiac surgery.[58,59] Furthermore, fluid overload when commencing renal replacement therapy (RRT) in the intensive care unit has been associated with increased risk of death in both adults[57] and children,[56,60] and impaired recovery of renal function in survivors.[61] Finally, a negative fluid balance achieved during RRT has been significantly associated with increased RRT-free days.[62] By contrast, in a previous review, we could not identify any studies in the intensive care unit or perioperative setting that showed that fluid liberal strategies led to improved renal outcomes.[63] In particular, the results of the Fluid and Catheter Treatment Trial (FACTT),[64] which enrolled patients with an acute lung injury, support a conservative fluid balance approach after the initial resuscitation phase of critical illness. In FACTT, fluid removal to achieve an even fluid balance was compared with a more-conventional liberal fluid strategy, which was associated with fluid accumulation (median 7 l positive by day 7). The conservative fluid strategy was associated with a trend towards a reduced requirement for RRT,[64] and an apparent lower incidence of AKI when attempting to account for fluid balance on creatinine-based AKI diagnosis.[65] Importantly, a positive fluid balance was strongly associated with mortality, and diuretic treatment associated with improved survival in patients who developed AKI during the course of the study.[55]

Fluid composition

Colloid solutions are commonly used for fluid resuscitation and are intended to provide greater magnitude and

Table 1 | Studies relating fluid balance to outcomes in AKI since 2008

Study	Setting	*n*	Design	Findings
Teixeira *et al.* (2013)[52]	Critically ill adults	601	Secondary analysis of a multicentre observational study	In AKI, higher fluid balance and lower urine volume independently associated with 28-day mortality
Askenazi *et al.* (2013)[130]	Near-term/term sick neonates	58	Prospective single-centre observational study	AKI associated with a net-positive fluid balance and higher mortality
Basu *et al.* (2013)[53]	Paediatric patients undergoing arterial switch operation	92	Retrospective single-centre observational study	AKI associated with higher postoperative day 1 fluid balance and independently associated with prolonged duration of ventilation and hospitalization
Hazle *et al.* (2013)[131]	Infants undergoing congenital heart surgery	49	Prospective single-centre observational study	Fluid overload might be an important risk factor for morbidity at all severities of AKI
Vaara *et al.* (2012)[57]	Critically ill adults with AKI requiring RRT	283	Prospective multicentre observational study	Fluid overload at RRT initiation doubled crude 90-day mortality and remained a significant risk for death after adjustment for demographics and illness severity
Prowle *et al.* (2012)[37]	Studies of perioperative GDT reporting AKI outcomes	24 RCTs	Meta-analysis	GDT significantly reduced risk of postoperative AKI. However, only GDT protocols that were overall fluid neutral were associated with a beneficial renal outcome
Selewski *et al.* (2012)[132]	Paediatric ICU patients requiring ECMO and RRT	53	Retrospective single-centre observational study	Fluid overload at RRT initiation significantly lower in survivors. Correction of fluid overload after initiation of RRT did not improve outcome
Bellomo *et al.* (2012)[62]	Critically ill patients requiring RRT for AKI in the RENAL study	1,453	Retrospective analysis of a multicentre RCT	Negative mean daily fluid balance on RRT consistently associated with risk of death, survival time, RRT-free days, and ICU and hospital-free days
Dass *et al.* (2012)[58]	Cardiovascular surgery patients	94	Retrospective analysis of a single-centre RCT	Positive fluid balance >849 ml in early postoperative period associated with significantly elevated AKI risk
Kambhampati *et al.* (2012)[59]	Adult patients undergoing cardiovascular surgery	100	Prospective single-centre observational study	Progressive severity of positive fluid balance associated with increased AKI risk
Heung *et al.* (2012)[61]	Patients with AKI requiring initiation of RRT	170	Retrospective single-centre observational study	High fluid overload at RRT initiation predicted worse renal recovery at 1 year
Selewski *et al.* (2011)[133]	Critically ill children requiring RRT	113	Retrospective single-centre observational study	Fluid overload at initiation of RRT significantly greater in non-survivors
Grams *et al.* (2011)[55]	Critically ill patients with lung injury enrolled into FACTT	1,000	Retrospective analysis of multicentre RCT	A positive fluid balance after AKI strongly associated with mortality in crude and adjusted analyses; post-AKI diuretic therapy associated with 60 day survival
Fülöp *et al.* (2010)[54]	Critically ill adults with AKI requiring RRT	81	Retrospective single-centre observational study	Volume related weight gain ≥10% and oliguria significantly associated with mortality in multivariable models adjusting for illness severity and diagnosis
Sutherland *et al.* (2010)[56]	Critically ill children with AKI requiring RRT	297	Prospective observational study	≥20% fluid overload at CRRT initiation associated with higher mortality than 10–20% fluid overload, in turn associated with higher mortality than <10% fluid overload; association between degree of fluid overload and mortality remained after adjusting for intergroup differences and severity of illness
Bouchard *et al.* (2009)[51]	Critically ill adults with AKI	618	Secondary analysis of a prospective multicentre observational study	In patients with AKI >10% fluid overload independently associated with 60-day mortality; >10% fluid overload at peak serum creatinine associated with non-recovery of renal function
Payen *et al.* (2008)[50]	Patients enrolled in the SOAP study	3,147	Secondary analysis of a prospective multicentre observational study	Fluid overload an independent risk factor for 60-day mortality in AKI; patients not developing AKI achieved a mean neutral to negative daily fluid balance; AKI associated with daily fluid accumulation

Abbreviations: AKI, acute kidney injury; CRRT, continuous RRT; ECMO, extra-corporeal membrane oxygenation; GDT, goal-directed therapy; ICU, intensive care unit; RCT, randomized controlled trial; RRT, renal replacement therapy.

duration of plasma expansion than a similar volume of infused crystalloid.[66] As such, colloids are superficially attractive for the limitation of fluid overload. However, commonly used colloids, such as medium molecular weight (6%, 130 kDa) hydroxyethyl starch solutions and gelatins, are lost from the circulation within 4–6 h.[67] Despite the increases in transcapillary albumin leakage during systemic inflammation,[17] much of the total body albumin (up to 60%) is found in extravascular compartments.[68] Thus, most iso-oncotic colloid solutions leak into the extravascular compartment, and may have limited advantage over crystalloids in limiting the total quantity of administered fluid.[69–73] The Crystalloid Versus Hydroxyethyl Starch Trial (CHEST),[70] and the Scandinavian Starch for Severe Sepsis/Septic Shock Trial (6S),[71] compared outcomes of resuscitation with hydroxyethyl starch or crystalloid solutions. CHEST enrolled >7,000 patients in intensive care units and found that severe AKI or use of RRT was associated with hydroxyethyl starch use for resuscitation.[70] In 6S, patients with severe sepsis were enrolled and hydroxyethyl starch use was associated with increased mortality

and use of RRT.[71] These conclusions are supported by a meta-analysis of studies using 6% 130 kDa hydroxyethyl starch for resuscitation of patients with sepsis,[74] critically ill patients requiring volume resuscitation[75] and colloids versus crystalloids for fluid resuscitation in critically ill patients.[76] Each of these analyses concluded that hydroxyethyl starch can increase AKI risk in critically ill patients, and recommended against its use in this group. These data have led to withdrawal of hydroxyethyl starch products from the UK market and severe restrictions on their use in the EU and USA.

Unlike hydroxyethyl starch, gelatin-based solutions have not been clearly associated nephrotoxicity.[77] However, there are insufficient data to support the efficacy or safety of gelatin in comparison to crystalloid or albumin.[78] Whether gelatins provides clinical benefit, and if they are toxic or neutral in terms of renal function, remain open questions. By contrast, evidence suggests that 4% albumin solutions are not nephrotoxic. The double-blind randomized controlled SAFE study[69] that was conducted in multiple centres and enrolled 6,997 patients, compared 4% albumin with 0.9% saline. The SAFE investigators reported no difference in urine output, organ failure and duration of RRT between the albumin and saline groups. In summary, starch is nephrotoxic and gelatin, which is >10 times more expensive than saline, might be nephrotoxic, while albumin seems safe from a renal perspective, but is 2–5 times more expensive again.

This information leaves crystalloids as potentially the best fluids for resuscitation of patients in the intensive care unit. However, for 0.9% saline there is concern that excess levels of chloride might have adverse effects in acid–base homeostasis and renal function.[79] In blinded and randomized studies, saline delayed time to first micturition, and lowered urine output and sodium excretion compared with buffered solutions, with chloride concentrations closer to normal physiological levels.[80] A 2012 study[81] used a large clinical database (covering 20% of all hospital discharges in the USA) to retrospectively compare patients who had surgery and were treated only with a balanced solution, Plasma-Lyte® (Baxter International Inc., Morton Grove, IL, USA) to those treated with saline. In a propensity analysis, saline treatment was associated with increased risk of adverse clinical outcomes including the need for RRT. In a double-blind, randomized cross-over volunteer study,[49] comparing saline with Plasma-Lyte®, increased time to first micturition, decreased postinfusion urinary volume and reduced cortical perfusion were all seen with 2 l of saline therapy. These studies suggest that excessive administration of chloride might adversely affect renal function. This notion is supported by other experimental work.[79,82] In an observational study examining the effect of a change from a chloride-liberal fluid infusion policy to a chloride-restrictive approach in critically ill patients, a significant reduction in the incidence of hyperchloraemia and metabolic acidosis was achieved.[83] Furthermore, this intervention led to a significant decrease in AKI incidence and need for RRT.[84] In light of previous observations, these data suggest that high chloride fluids might adversely affect kidney function.

Fluid administration or alternatives

Although evidence indicates that over-zealous fluid resuscitation is harmful, some data suggest that vasopressor therapy to maintain systemic blood pressure can have a beneficial effect on renal physiology. Vasopressor therapy is commonly used in hyperdynamic septic shock. Vasoconstrictors have been regarded as potentially harmful to an ischaemic kidney; however, most available evidence favours moderate vasopressor use in vasodilatory shock. Use of noradrenaline has been shown to improve RBF and GFR in experimental models of AKI[85,86] and to restore urine output in clinical septic shock complicated by oliguria.[87] It seems that systemic vasoconstrictors have a greater positive effect in raising renal perfusion pressure by increasing systemic blood pressure than a negative effect by increasing renal vascular resistance, an effect than might be mitigated by reductions in renal sympathetic tone as systemic blood pressure is restored.[85] Increasing mean arterial pressure up to 75 mmHg increases renal oxygen delivery and GFR during AKI in adults[88] and a persistently lower blood pressure has been associated with persistence or worsening of AKI during sepsis.[89] Consideration should be given to a patient's baseline blood pressure when selecting blood pressure targets because relative hypotension in comparison to patient-normal blood pressure has been associated with development of AKI in hospital.[90] Early consideration should, therefore, be given to intensive care unit admission for vasopressor use in patients with persistent hypotension, unresponsive to initial fluid resuscitation. Such an approach might protect renal function and prevent unnecessary fluid administration. However, vasopressor therapy should not be the sole therapy for hypotension in the context of a low cardiac output and blood pressure targets need to be tailored according to clinical context. In the sickest patients, haemodynamic management should target adequate vital organ perfusion with the least harm to the patient. Often early recourse to RRT might be the best option to control fluid balance in the sickest patients with AKI.

Fluid therapy in transplantation

Renal transplant recipients form an important subgroup of surgical patients, who are at increased risk of AKI in the form of delayed graft function and are, understandably, of special interest to the nephrologist. The high rates of cardiovascular disease in patients with end-stage renal disease (ESRD), uncertain preoperative fluid status in patients with ESRD, donor factors, immunological modulation associated with delayed graft function and the de-innervated renal allograft all make haemodynamic management in these patients complex and controversial.[91,92] However, many factors are common to the haemodynamic management of AKI in critical illness and major surgery including the deleterious effect of fluid overload, which is often under-appreciated in these patients.

Table 2 | Methods to assess fluid responsiveness and overload in critically ill patients with or at risk of AKI

Measure	Interpretation	Limitations
Fluid responsiveness		
Stroke volume and pulse pressure variation	Significant variation with respiratory cycle implies fluid responsiveness	Requires mandatory mechanical ventilation Indicates position on Frank–Starling curve, not extent of tissue fluid overload
Echocardiography	Subjective impression of right ventricular filling and inferior vena cava collapse	Requires technical expertise Poor windows in critically ill
Passive straight leg raise	Provides impression of fluid responsiveness without requirement for fluid challenge	Difficult or impossible in some patients
Stroke volume or other haemodynamic response to fluid challenge	Direct assessment of bolus fluid responsiveness	Requires administration of fluid Positive response does not imply that fluid is clinically indicated, or that response will be sustained
Central venous or pulmonary artery wedge pressure	Very low values might imply that right ventricular preload could be increased with fluid therapy	No evidence that absolute values or relative changes correlate with cardiac output or fluid responsiveness
Blood volume monitoring (continuous haematocrit)	Measurement of vascular refilling during fluid removal that may predict haemodynamic instability	Currently available during haemodialysis only Might be too imprecise to pre-empt hypotension during ultrafiltration in critically ill patients
Fluid overload		
Clinical examination	Physical exam for signs of peripheral or pulmonary oedema	Volume overload can occur without oedema Oedema and intravascular volume depletion might coexist Wide range of additional contributing factors
Serial weight	Quantifies extent of fluid overload	Difficult to perform in critically ill patients Loss of muscle and fat mass might mask fluid gain
Cumulative fluid balance	Quantifies extent of fluid overload	Often imprecisely recorded Difficult to account for insensible losses
Chest X-ray	Radiological assessment of pulmonary oedema and pulmonary venous congestion	Only gives indication of pulmonary oedema Wide differential diagnosis
Oxygenation indices and ventilatory requirements	Impaired gas exchange that might be attributable to pulmonary oedema	Nonspecific for fluid overload depending on clinical context
Lung ultrasound	Sonographic assessment of pulmonary venous congestion that may precede chest X-ray, oxygenation and symptomatic changes[134]	Requires technical expertise Might be confounded by other pulmonary pathology
Echocardiography	Subjective impression of right ventricular or inferior vena cava distension	Requires technical expertise Poor windows in critically ill patients
Intra-abdominal pressure	Bladder catheter measure of intra-abdominal hydrostatic pressure	Only significant if abnormal Cause might be primary or secondary (fluid overload)
Bioimpedance analysis of body composition	Non-invasive technique that enables separate estimate of extracellular volume over hydration and intracellular (muscle) volume	Methodology not validated in critically ill Might be difficult to perform good-quality measurements at bedside in intensive care unit Requires accurate weight measurement Range of algorithms to calculate volume measurements, which are device specific, may not be applicable to critically ill

Abbreviation: AKI, acute kidney injury.

Recipients of a renal transplant rarely experience substantial blood losses compared with patients undergoing major intraperitoneal surgery,[93] thereby placing them at increased risk of intraoperative fluid overload. Intraoperative fluid therapy is often required to counteract the effects of venodilation during general anaesthesia in patients with poor cardiovascular reserve, further exacerbating postoperative fluid overload.[91] The need for fluid administration might be limited by avoiding fluid removal if haemodialysis is required on the day of surgery, and postoperative fluid status should be referenced by comparison to postdialysis target 'dry weight' and any degree of pre-existing chronic fluid overload. Overall, there is little evidence to suggest that fluid therapy has a beneficial effect on short-term or long-term graft function. In a retrospective case series of 1,966 recipients of a renal allograft, perioperative fluid administration of >2,500 ml or central venous pressure >11 mmHg was associated with poorer long-term renal transplant outcomes than those with lower fluid administration or central venous pressure.[94] Similarly, targeting a high central venous pressure with fluid therapy after renal transplant in this group had no effect on the incidence of delayed graft function and was potentially detrimental,[95] while low systemic blood pressure but not low central venous pressure was associated with delayed graft function in a further case series.[96] Overall, we believe renal transplant recipients should not be

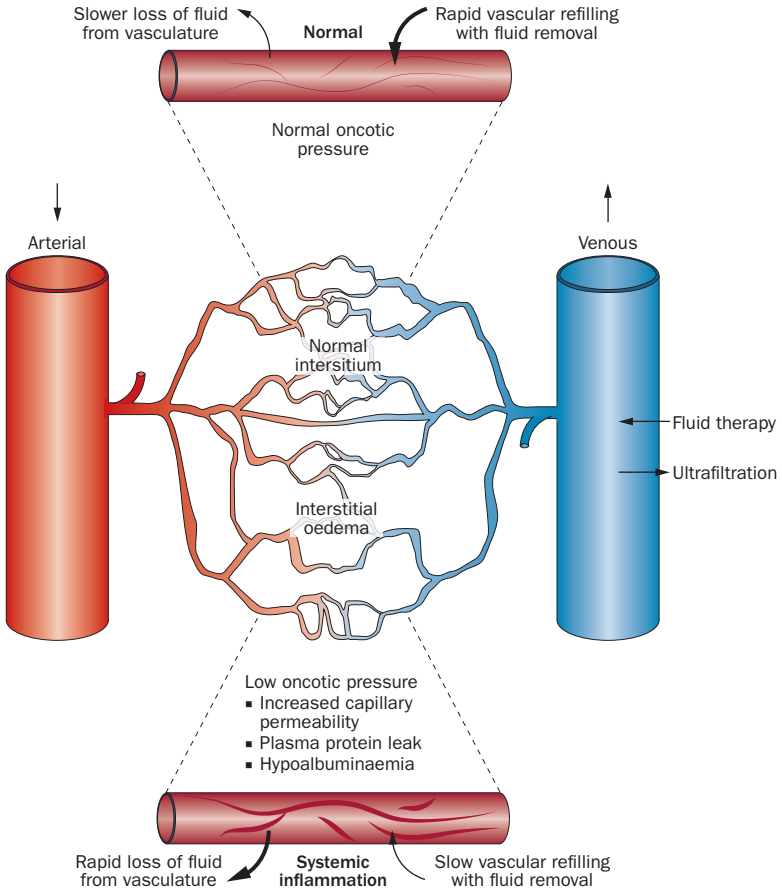

Figure 2 | Systemic inflammation leads to increased capillary permeability and loss of colloid osmotic gradient, exacerbated by hypoalbuminaemia of acute illness. Consequently, exogenous fluid is more-rapidly lost to the extracellular compartment, while interstitial fluid will more-slowly refill the vascular compartment during ultrafiltration.

considered to be different to general surgical patients with regard to the limited benefits and significant hazards of fluid therapy.

The denervated transplant kidney adds complexity to blood pressure management in the perioperative period.[97,98] Care must be taken when using vasopressors as their effects on renal vascular resistance can be exaggerated by sympathetic denervation.[98,99] However, judicious use of vasopressors to augment systemic blood pressure in the context of high cardiac output is probably safe, although there should be a low threshold for the application of cardiac output monitoring to guide therapy.

Fluid balance management

Even when employing protocol-guided fluid resuscitation and early use of vasopressors to treat vasodilatory hypotension, acute resuscitation of critical illness almost inevitably leads to a positive fluid balance and tissue oedema. As patients who are critically ill have high mandatory water and sodium intake from medication and feeding, in the presence of impaired excretion, early attention to fluid removal is required to prevent progressive worsening of an already positive fluid balance. In patients who are acutely ill, a neutral or negative fluid balance can be problematic to achieve, even with the aid of medication or technology. A range of methods are available to assess fluid overload or fluid responsiveness; however, all have limitations and many are difficult to interpret in critical illness (Table 2). A corollary of the rapid distribution of fluid administered into the extravascular compartment in critical illness is that fluid removed from the vascular compartment will be replaced by refilling from the extravascular fluid slowly, because capillary leak and hypoalbuminaemia encourage the accumulation and retention of fluid outside the vasculature (Figure 2).[66]

Any process of fluid removal, by diuretic therapy or RRT, risks transient hypovolaemia even when extravascular whole-body salt and water overload persists. In patients with AKI, uraemia can be made worse by diuretic therapy.[100] Indeed, diuretics do not improve the clinical outcomes of AKI[101] or expedite recovery.[102] Maintaining a neutral fluid balance without additional complications might require initiation of RRT. Our suggested clinical management of fluid balance in established critical illness emphasizes the prevention and resolution of fluid overload, while appropriately monitoring for hypovolaemia (Figure 3). Beyond the initial 24 h of critical illness, maintenance of fluid balance has logical consistency over prolonged attempts to optimize preload or serially assess for fluid responsiveness to (transiently) augment cardiac output in the absence of clear indications. However, the choice of minimal criteria for adequate systemic perfusion is complex and situation-dependent, and there is little evidence to guide fluid management in this period after the initial resuscitation of sepsis or the immediate perioperative period.

In theory, continuous RRT has advantages in the management of fluid overload in critically ill patients with AKI;[103] continuous fluid removal permits slow fluid removal to at least match fluid inputs. By contrast, intermittent haemodialysis requires fluid removal goals to be met during a 4–6 h therapy, which is likely to lead to transient intravascular under-filling, intradialytic hypotension and associated recurrent renal injury.[104,105] In the intensive care unit, intermittent haemodialysis use has been associated with progressively positive fluid balances, whereas continuous RRT enables net fluid removal,[51] despite being used in patients who are haemodynamically unstable. Similarly, in a systematic review of 16 observational studies examining RRT for AKI, the use of intermittent therapy as first RRT was associated with a twofold increase in relative risk of non-recovery of renal function than continuous RRT.[106] Data analysis from seven randomized trials comparing intermittent haemodialysis with continuous RRT failed to confirm these observations. However, these studies showed a similar trend, were underpowered and notably excluded patients who were haemodynamically unstable and/or used multiple measures to maintain blood pressure on intermittent haemodialysis, such as use of higher sodium dialysate, that may worsen fluid overload.[107] Extended duration intermittent therapies,

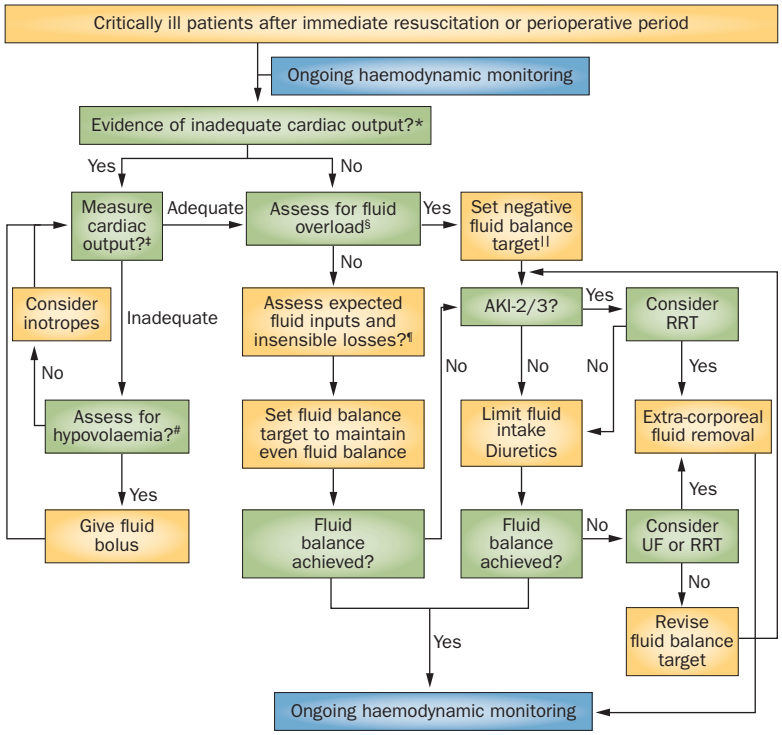

Figure 3 | Fluid and haemodynamic management after the initial phase of critical illness. Throughout this pathway a clinically appropriate arterial blood pressure is targeted using vasopressors, if required. In addition to fluid overload, in AKI, RRT may be required for other indications including hyperkalaemia, acidaemia, or severe uraemia. *Increased vasopressor requirement, new or worsening organ dysfunction, tachycardia, lactic acidosis or clinical examination. ‡Measure cardiac index, stroke volume, ejection volume, oxygen delivery or venous saturation of oxygen. Ensure oxygen delivery is adequate to clinical need. §Clinical examination, serial weights, cumulative fluid balance, chest X-ray or ventilation parameters. Lung ultrasound, echocardiography, abdominal pressure measurements and bioimpedance analysis may provide added information. ||Based on relative fluid overload, haemodynamic stability and expected speed of vascular refilling. ¶Maintenance intravenous fluid is rarely needed where no large ongoing fluid losses are present and feeding established. Replacement should be titrated to volume and expected composition of fluid losses. #Interpretation of stroke volume, pulse pressure, corrected aortic systolic flow time, intrathoracic blood volume index, low central venous or pulmonary artery pressure, echocardiography, or fluid responsiveness to passive leg raises or fluid challenges. Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy; UF, ultrafiltration.

often termed sustained low efficiency dialysis, but better described as prolonged intermittent RRT, have been proposed as an alternative to continuous RRT for use in the intensive care unit. In contrast to traditional intermittent haemodialysis, prolonged intermittent RRT administered daily for >8 h can achieve similar fluid balance control[108] and comparable patient outcomes as continuous RRT.[109] In our opinion, when fluid balance cannot be adequately controlled in patients with AKI, clinicians should consider early initiation of continuous RRT or prolonged intermittent RRT. Often this should be within 24 h of overt AKI onset, an approach that anticipates and limits the extent of fluid overload, rather than treating its consequences. Consideration should also be given to extended use of continuous modalities in fluid overloaded patients with persistent AKI. Rapid transition to intermittent haemodialysis might prejudice renal recovery and slow resolution of oedema, even when a patient has regained haemodynamic stability. For instance in the VA-NIH ATN study[110] that investigated RRT dose in the intensive care unit, 25% of AKI survivors remained on RRT at 60 days. In VA-NIH ATN, transition to intermittent haemodialysis in the intensive care unit was permitted when patients were deemed to have sufficient cardiovascular stability. By comparison in the similar RENAL trial,[111] where continuous RRT was continued, if required, until close to discharge from the intensive care unit, only 6% of survivors remained on RRT at day 90.

An important point to recognize is that dialysis independence does not equate to recovery of premorbid renal function, and the burden of chronic kidney disease after AKI is likely to be far larger than we currently estimate.[112] The effects of RRT modality and other aspects of AKI management on the development of chronic kidney disease are still not well understood and are important topics for future research.

Fluid removal in AKI

Assessment of the target fluid balance and appropriate rate of fluid removal in AKI is challenging. Absolute serum creatinine provides little information on underlying renal function in critical illness,[113–115] and almost none in patients on RRT. The development of biomarkers to indicate renal injury and identify patients with early AKI have shown promise.[116] Biomarkers might also allow detection of continued or recurrent renal injury during recovery from AKI, indicating a need for close attention to haemodynamic stability and nephrotoxic medication. In this context, higher plasma neutrophil gelatinase-associated lipocalin at commencement of RRT has been associated with increased risk of non-recovery of renal function,[117] while a panel of urine biomarkers can improve clinical risk prediction for recovery of renal function after AKI.[118] Although not yet ready for immediate clinical application, biomarkers might allow detection and limitation of recurrent renal injury associated with fluid removal during RRT or diuresis.

Real-time monitoring of plasma refilling during ultrafiltration is possible using real-time monitoring of blood haematocrit, so-called relative blood volume monitoring. To date, relative blood volume monitoring has been mainly applied to fluid removal during chronic dialysis, and its ability to predict overt intradialytic hypotension, or haemodynamic instability during acute dialysis for AKI, has been disappointing.[119,120] Thus, while conceptually attractive, relative blood volume monitoring alone seems insufficient to guide fluid removal during RRT in critical illness.

Bioimpedance analysis techniques can quantify the expansion of extracellular and intracellular fluid volume.[121] In a prospective randomized trial, monitoring of fluid status during maintenance haemodialysis using bioimpedance analysis allowed better management of long term fluid status, which was associated with regression of left ventricular mass index, decrease in blood pressure, and improvement in arterial stiffness.[122]

Importantly, by quantifying intracellular and extracellular volume, bioimpedance analysis can reveal the extent of interstitial fluid overload, which might otherwise be masked by loss of intracellular volume related to muscle mass reduction during critical illness.[123] However, although bioimpedance analysis can assess the need for fluid removal, it might be less helpful in assessing the ability to remove this fluid during acute RRT while retaining haemodynamic stability.[124] This technology now requires prospective studies of bioimpedance analysis-directed fluid targeting to better define the clinical role of this promising approach in critical illness.

Conclusions

For the clinician, fluid management in high-risk patients with or at risk of AKI requires a fine balance between restoring adequate cardiac output, which might prevent renal ischaemia, and avoiding fluid overload that might lead to adverse clinical outcomes. However, achieving such a balance is often impossible, particularly in patients with systemic inflammation and generalized capillary leakage. Indeed, in paediatric care, the degree of fluid overload has been described as an index of AKI severity.[125] Use of GDT protocols may guide initial fluid resuscitation and target treatment to those that require it. However, the small studies available do not adequately demonstrate what should be the end points for resuscitation in the setting of sepsis and systemic inflammation. Moreover, we have even less information to guide treatment much beyond the initial resuscitative period. Consequently, fluid management practices vary between clinicians and intensive care units.

Three large multicentre randomized controlled trials examining the effect of early GDT in sepsis (Process, ARISE, Promise)[126–128] and another examining perioperative GDT in high-risk surgery (OPTIMISE)[129] are approaching publication. They will provide much more high-quality evidence to guide clinicians in the fluid management in the setting of early critical illness. Based on current evidence, we believe fluid management should recognize and treat hypovolaemia quickly; however, clinicians should also strive to avoid inappropriate fluid loading. A cautious approach involving regular reassessment of patient fluid balance will, in our opinion, best optimize renal and wider clinical outcomes. Despite these measures, fluid overload will often occur as an inevitable adverse effect of appropriate early resuscitation and, in instances complicated by AKI, early use of RRT should be considered to avoid progressive worsening of fluid balance.

Review criteria

We interrogated the PubMed electronic reference database for the terms “acute kidney injury” OR “acute renal failure” AND “fluid balance” OR “fluid overload” OR “fluid resuscitation”, to identify articles published in English from June 2008 to June 2013. We included articles that reported outcomes in patients with acute kidney injury by groups differing in fluid balance.

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Author contributions
All authors contributed equally to researching data for the article, made substantial contribution to discussion of the content, wrote, reviewed and edited the manuscript before submission.