

# Fluid balance and acute kidney injury

John R. Prowle, Jorge E. Echeverri, E. Valentina Ligabo, Claudio Ronco and Rinaldo Bellomo

**Abstract** | Intravenous fluids are widely administered to patients who have, or are at risk of, acute kidney injury (AKI). However, deleterious consequences of overzealous fluid therapy are increasingly being recognized. Salt and water overload can predispose to organ dysfunction, impaired wound healing and nosocomial infection, particularly in patients with AKI, in whom fluid challenges are frequent and excretion is impaired. In this Review article, we discuss how interstitial edema can further delay renal recovery and why conservative fluid strategies are now being advocated. Applying these strategies in critical illness is challenging. Although volume resuscitation is needed to restore cardiac output, it often leads to tissue edema, thereby contributing to ongoing organ dysfunction. Conservative strategies of fluid management mandate a switch towards neutral balance and then negative balance once hemodynamic stabilization is achieved. In patients with AKI, this strategy might require renal replacement therapy to be given earlier than when more-liberal fluid management is used. However, hypovolemia and renal hypoperfusion can occur in patients with AKI if excessive fluid removal is pursued with diuretics or extracorporeal therapy. Thus, accurate assessment of fluid status and careful definition of targets are needed at all stages to improve clinical outcomes. A conservative strategy of fluid management was recently tested and found to be effective in a large, randomized, controlled trial in patients with acute lung injury. Similar randomized, controlled studies in patients with AKI now seem justified.

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### Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Describe the goals of vigorous fluid administration in the setting of acquired acute kidney injury (AKI).
- 2 Identify the most likely cause of AKI in the intensive care setting.
- 3 Describe complications of fluid overload in patients with AKI.
- 4 Describe options to optimize fluid replacement in the setting of AKI.
- 5 Describe biomarkers of fluid overload.

### Competing interests

The authors, the Journal Editor S. Allison and the CME questions author D. Lie declare no competing interests.

## Introduction

Appropriate management of intravenous fluid replacement is a key aspect of the treatment of acute kidney injury (AKI).<sup>1</sup> In patients with acute glomerulonephritis and other intrinsic renal diseases, there is little clinical dispute that sodium and water restriction is beneficial in the setting of impaired renal excretory function.<sup>2</sup> Conversely, in patients with AKI complicating systemic illness, supplemental intravenous fluids are considered an essential element of treatment.<sup>3</sup> These acquired forms of AKI usually have a multifactorial etiology and, in such cases, fluid therapy aims to mitigate the effects of hemodynamic and nephrotoxic renal insults that might cause tubular injury.<sup>4</sup> On the other hand, the adverse effects of fluid overload may be most pronounced in situations such as systemic sepsis, major surgery, or trauma, which predispose to acquired AKI.<sup>5–7</sup> In this Review, we focus on the dilemmas of fluid management in acquired AKI, which seeks a balance between the competing needs of adequate fluid resuscitation, the avoidance of progressively positive fluid balances with extracellular volume expansion and organ edema, and the possibility of overzealous fluid removal with the attendant risk of hypovolemic AKI.

## The rationale for fluid therapy

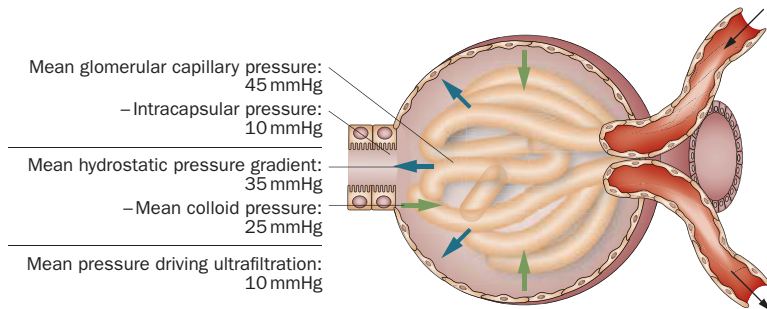
Much of the rationale for fluid therapy in acquired AKI is rooted in the idea of a spectrum that ranges from pre-renal failure to acute tubular necrosis (ATN).<sup>8</sup> According to this conceptual framework, oliguria in critical illness is initially related to reduced glomerular filtration rate (GFR) and increased salt and water retention. Thus,

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**Key points**

- Fluid therapy is common in patients at risk of acute kidney injury (AKI)
- Prolonged fluid resuscitation leads to edema in the kidneys and other organs
- Fluid overload is associated with increased morbidity
- An early transition to a fluid-restrictive strategy might be beneficial in patients with AKI
- Fluid removal in patients with or at risk of AKI should be implemented with appropriate monitoring
- Biomarkers and/or novel fluid assessment methods might contribute to safer fluid management



**Figure 1** | Normal glomerular hemodynamics. Table 1 shows abnormalities that lead to a loss of ultrafiltration pressure in patients with acute kidney injury. Only relatively small pressure changes are required to abolish ultrafiltration.

AKI is believed to be the consequence of reduced cardiac output, systemic hypotension and triggered neuroendocrine reflexes.<sup>9–11</sup> Although initially reversible, persistent renal ischemia and the concentration of filtered nephrotoxins in the renal tubules results in tubular injury—so-called ATN—which causes sustained renal impairment, cell death and delayed renal recovery that requires tissue regeneration.<sup>12–14</sup> Vigorous fluid administration in this setting is therefore aimed at reversing renal ischemia and diluting nephrotoxins, to either avert the onset of ATN or to prevent recurrent injury that might compromise renal recovery. Although this model of the pathogenesis of AKI was developed over 50 years ago<sup>15</sup> and has become dogma, little direct evidence supports the approach in real-world clinical situations. The distinction between prerenal failure and tubular injury is typically based on clinical assessment, supported by the biochemical and microscopic examination of urine. A recent systematic review of urinary biochemistry and microscopy in patients with septic AKI, however, found that the scientific basis for the use of these indices in such patients is weak.<sup>16</sup> Given that sepsis is responsible for >50% of AKI cases in the intensive care unit (ICU), doubt persists about the ability of these tests to diagnose the presence or absence of histological ATN in critically ill patients.

The exact role of ischemia in the initiation and maintenance of AKI also remains unclear.<sup>17</sup> Although it is accepted that the renal corticomedullary region has relatively low oxygen delivery in relation to its large metabolic demands,<sup>18</sup> a decrease in GFR, as occurs in AKI, reduces tubular sodium delivery and decreases metabolic activity. Global renal oxygen saturation therefore

risks, despite a reduction in total renal blood flow.<sup>19,20</sup> Similarly, overt histopathological evidence for tubular injury is conspicuously lacking in critically ill humans dying with renal failure,<sup>21</sup> which raises doubts about the role of persistent renal ischemia and inadequate intravascular volume as causes of sustained renal dysfunction in such patients.

Although the term ATN is gradually being challenged,<sup>22,23</sup> its conceptual framework continues to promote the use of intravenous fluids in patients with AKI. Within this framework, episodes of oliguria or hypotension prompt intravenous fluid challenges, and maintenance fluids are prescribed to promote diuresis, maintain cardiac output, and keep the patient ‘well filled’.<sup>24</sup> The presumed clinical benefit of this approach is being challenged by increasing evidence that positive fluid balances in the order of 5–10% of body weight are associated with worsening organ dysfunction in the critically ill<sup>6,25</sup> and with worse postoperative outcomes after routine surgery,<sup>26</sup> with no evidence of any beneficial effects on renal function. Given this dichotomy between traditional teaching and evolving evidence, it is unsurprising that wide variations in clinical fluid management continue to exist.<sup>27–29</sup> By examining basic physiological arguments, experimental evidence and current clinical evidence, we suggest that there is a need to develop a more rational and flexible approach to fluid therapy.

**The beneficial role of fluid therapy in AKI**

Adequate fluid resuscitation is essential to the restoration of cardiac output, systemic blood pressure and renal perfusion in patients with shock secondary to low cardiac preload. Prompt treatment can avert or limit subsequent AKI. It is important, however, to consider the physiological rationale of fluid therapy to prevent both undertreatment and excessive volume expansion.

**Cardiovascular optimization**

From a renal standpoint, fluid therapy is used to restore glomerular filtration and thus increase urine output. Glomerular filtration requires an adequate transglomerular pressure gradient, which is mostly determined by total renal blood flow, glomerular arteriolar tone and the colloid osmotic pressure of proteins in the plasma (Figure 1 and Table 1).<sup>30</sup> Fluid therapy is aimed at restoring systemic blood pressure (a major determinant of renal perfusion pressure)<sup>31</sup> and cardiac output (a prerequisite for adequate renal blood flow). Restoration of these parameters might relax the neuroendocrine reflexes responsible for increasing renal vascular resistance and diminishing GFR.<sup>32</sup>

Fluid administration aimed at restoring systemic blood pressure works mechanistically by increasing preload and stroke volume.<sup>33</sup> Fluid responsiveness of cardiac output is dependent on the volume of the central venous reservoirs and venous tone. In hypovolemia, fluid therapy restores right ventricular end-diastolic volume and is an essential first step in resuscitation.<sup>34</sup> Unfortunately, conventional goals of fluid resuscitation and restoration of blood pressure, central venous pressure and/or urine

**Table 1** | Reasons for decreased glomerular ultrafiltration in patients with acute kidney injury

Abnormality	Physiological effect	Consequence
Low systemic blood pressure Afferent arteriole vasoconstriction Efferent arteriole vasodilatation	Low glomerular hydrostatic pressure	Decreased glomerular filtration
Renal interstitial edema Extrinsic compression Tubular obstruction Failure of downstream tubular reabsorption	High intracapsular pressure	Decreased glomerular filtration
Low renal plasma flow	Rapid rise in oncotic pressure	Decreased glomerular filtration

output, are only indirect measures of cardiac output and are much less indicative of the restoration of adequate organ blood flow.<sup>35–37</sup> Similarly, the effects of critical illness, pre-existing chronic disease and pharmacotherapy can unpredictably alter determinants of fluid responsiveness such as myocardial compliance<sup>38</sup> and contractility,<sup>39,40</sup> systemic vascular resistance,<sup>41</sup> regional blood flow distribution,<sup>42,43</sup> venous capacitance and capillary permeability.<sup>44</sup> These effects make the effects of volume resuscitation very variable in extent and duration, and make the assessment of adequacy of volume replacement very challenging. In such situations, fluid therapy is either insufficient to restore hemodynamic stability, or excessive volumes are required. Importantly, fluids do not correct vasodilatation. Invasive monitoring may, therefore, be required to guide treatment, not only to ensure adequate volume expansion, but also to prevent excessive fluid administration.<sup>45</sup> Irrespective of how it is guided, however, indiscriminate use of intravenous fluid and other vasoactive therapies to maximize cardiac output might not be beneficial.<sup>46</sup> Increasing cardiac output from a normal or elevated value might be effective in increasing blood pressure, reducing vasopressor requirement and inducing diuresis, but such responses are unlikely to be sustained and may not improve organ function.<sup>42</sup> In particular, when one considers the short-lived hemodynamic effect of exogenous fluids,<sup>47,48</sup> continuing such an approach beyond the initial few hours of illness would require regular, repeated volume challenges and, inevitably, a markedly positive fluid balance with its associated adverse consequences.

Colloid solutions are frequently used for resuscitation despite limited evidence to justify their use.<sup>49</sup> Gelatins and commercial medium molecular weight (70–80 kDa) starch solutions are lost from the circulation within hours.<sup>50</sup> Similarly, 60% of total body albumin is normally present in extravascular compartments,<sup>51</sup> even before the large increases in transcapillary albumin leakage that occur during systemic inflammation.<sup>44</sup> Most fluids administered as iso-oncotic albumin solutions are also likely to leak into the extravascular compartment, have a limited theoretical advantage over crystalloids in preventing tissue edema and lead to only a small decrease in the total quantity of fluid administered.<sup>52</sup> Higher molecular weight (>200 kDa), hyperoncotic starches might be more efficacious as fluid-sparing volume expanders,

but as they are associated with an increased risk of AKI,<sup>53–55</sup> they have limited application in patients with or at risk of AKI.

### Maintenance of urine output

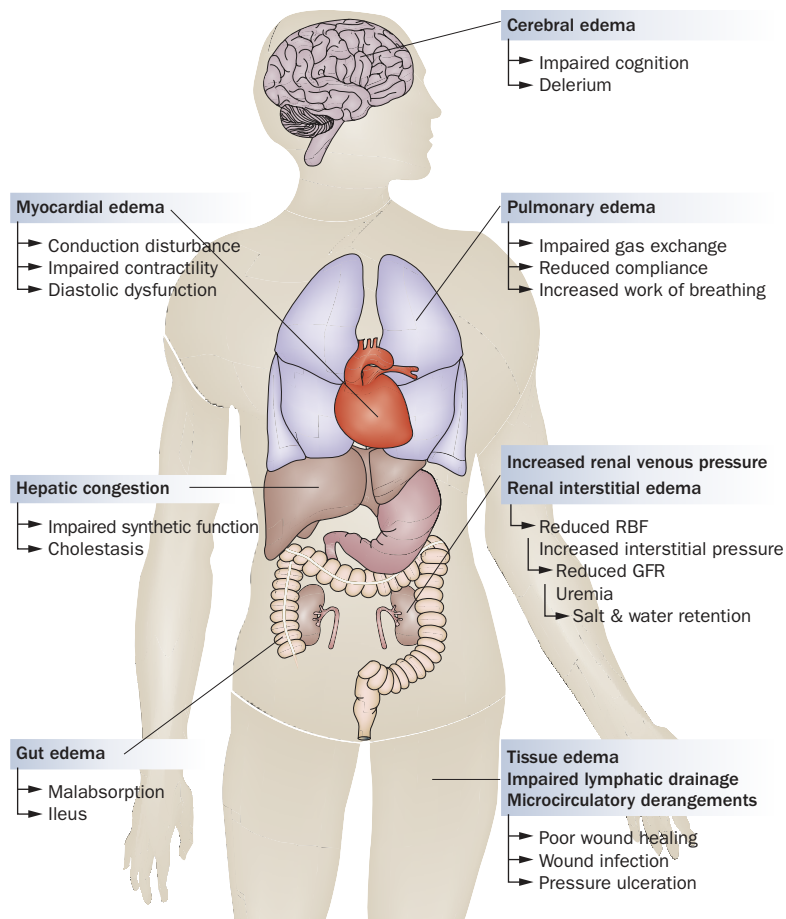
Another rationale for fluid prescription is to promote diuresis, dilute tubular toxins and attenuate tubular obstruction from casts.<sup>56</sup> Such effects may be particularly important in the prophylaxis of intravenous radiocontrast nephropathy<sup>57</sup> and the treatment of rhabdomyolysis.<sup>58</sup> Evolutionarily, the kidney is better adapted to conserving sodium and water than to excreting an excess of either.<sup>59</sup> During acute illness, factors such as hypotension, pain and tissue injury will cause activation of the sympathetic nervous system, responses in the renin–angiotensin system and increased secretion of antidiuretic hormone, which override normal homeostatic mechanisms and trigger sodium and water retention.<sup>32</sup> Therefore, even before renal impairment has occurred, the relationship between fluid input and natriuresis is weak, and the administration of intravenous fluid to maintain urine output would lead to salt and water accumulation.<sup>48,60</sup>

### Potential adverse effects of liberal fluid therapy

The administration of exogenous crystalloid solution expands the extracellular compartment, and, over time, will leave the circulation and distribute in the extracellular volume,<sup>61</sup> particularly in critically ill patients with increased capillary leakiness. Renal excretion of exogenous sodium is slow even in healthy individuals and is further impaired in acute illness.<sup>60</sup> Fluid overload might, therefore, impede its own resolution. Although studies of fluid overload have been only observational in nature, and confounded by the fact that sicker patients are likely to have received more intravenous fluids, several lines of evidence have emerged about the potential adverse effects of fluid therapy.

### Development of interstitial edema

Kidneys, or indeed renal replacement therapy (RRT) devices, can only access intravascular fluid. Net fluid removal requires a refilling of the circulation along a colloid osmotic gradient. As plasma colloid osmotic pressure is impaired by the increased capillary permeability that occurs during acute illness, slow vascular refilling may contribute to diuretic resistance or hemodynamic



**Figure 2** | Pathological sequelae of fluid overload in organ systems. Abbreviations: GFR, glomerular filtration rate; RBF, renal blood flow.

instability during fluid removal in patients on conventional intermittent hemodialysis.<sup>62</sup>

In the ICU, 0.9% saline is still widely used as an intravenous crystalloid; in addition, many colloids and drugs that are administered in the ICU are suspended in saline. Saline contains 154 mmol/l chloride and its administration in a large volume will result in relative or absolute hyperchloremia.<sup>63,64</sup> Hyperchloremia has been shown to reduce renal blood flow<sup>65</sup> and to impair sodium excretion in humans.<sup>63,66</sup>

Gross fluid overload and resultant visceral edema is a risk factor for intra-abdominal hypertension (IAH).<sup>67</sup> Raised intra-abdominal pressure increases renal venous pressure, reduces blood flow and increases the pressure in the Bowman's space.<sup>68,69</sup> In an ICU population, positive fluid balances have been associated with an increased risk of IAH,<sup>70–72</sup> which in turn is strongly associated with the development of AKI.<sup>71,72</sup>

In the absence of overt IAH, renal interstitial edema alone might impair renal function. As an encapsulated organ, the kidney is affected by fluid congestion and raised venous pressures with a disproportionate elevation in intracapsular pressure, which leads to a decrease in renal blood flow and GFR.<sup>73</sup> An observational study in critically ill patients found an association between a positive fluid balance and an increased risk of AKI;<sup>6</sup> another

study found an association between a positive fluid balance and nonrecovery of renal function in AKI.<sup>25</sup> In both of these studies, a positive fluid balance was associated with increased mortality in patients who developed AKI. Similarly, high venous pressures have been associated with the deterioration of renal function in patients with advanced chronic cardiac failure.<sup>74</sup> Indeed, in such patients, a high central venous pressure (but not low mean arterial pressure or low cardiac output) is an independent predictor of AKI. Historically, renal decapsulation was shown to be protective against AKI in patients with hemorrhagic shock requiring massive resuscitation.<sup>75</sup> Elevated tubular pressure may have a role in the continued loss of renal function during the maintenance phase of AKI,<sup>76</sup> providing physiological evidence for yet another mechanism by which persistent fluid overload might increase the duration and severity of AKI.

**Interstitial edema and organ dysfunction**

Physiologically, fluid overload results in tissue edema. Impaired oxygen and metabolite diffusion, distorted tissue architecture, obstruction of capillary blood flow and lymphatic drainage, and disturbed cell–cell interactions may then contribute to progressive organ dysfunction (Figure 2). These effects are pronounced in encapsulated organs—such as the liver and kidneys—which lack the capacity to accommodate additional volume without an increase in interstitial pressure and compromised organ blood flow. Through these mechanisms, tissue edema may directly participate in the progression of AKI. Myocardial edema in the heart can worsen ventricular function, oxygen delivery and synchronized intraventricular conduction.<sup>39,77–79</sup> Liver function can be similarly compromised by interstitial edema.<sup>73</sup> Recovery of gastrointestinal function, wound healing, and coagulation are also adversely affected by interstitial edema.<sup>5,26,28,80,81</sup> (Figure 2).

The adverse effects of fluid overload are perhaps most evident in the lungs, where overzealous fluid resuscitation can lead to acute pulmonary edema or ‘pseudo acute respiratory distress syndrome’ (ARDS).<sup>82</sup> In patients with established acute lung injury (ALI), retrospective analyses<sup>45,83,84</sup> and prospective, multicenter, randomized, controlled trials<sup>85–88</sup> have provided evidence associating more-positive fluid balances with poorer pulmonary outcomes.

To more formally assess the evidence associating fluid overload with adverse outcome in the ICU we systematically interrogated the PubMed electronic reference database using specific search terms to identify clinical studies examining fluid balance or therapy in critically ill adults (see Supplementary Information online for our strategy). Studies comparing two or more groups of adults in ICUs with significantly different fluid balances were identified and evaluated (Table 2).

Importantly, no studies examining restrictive fluid strategies in the ICU demonstrated clinically significant worsening of renal function with fluid restriction (Table 2). Indeed, the Fluid and Catheter Treatment Trial (FACTT),<sup>88</sup> by far the largest multicenter, randomized,



**Table 2** | Publications describing two groups of critically ill patients with differing fluid balances where a renal outcome was reported\*

Reference	Study type	Population	n	Average fluid balance in less-positive group	Average fluid balance in more-positive group	Renal function measure	Renal outcome with more-restrictive fluid balance strategy	Principal outcome with more-restrictive fluid balance strategy
ARDS Clinical Trials Network (2006) <sup>88</sup>	Multicenter RCT	ARDS	1,000	-136 ml on day 7	+6,992 ml on day 7	Need for RRT; change in creatinine	No difference	Shorter duration of ventilation and ICU stay
Martin <i>et al.</i> (2005) <sup>86</sup>	Single-center RCT	Mixed ALI	40	-5,480 ml on day 5	-1,490 ml on day 5	Change in creatinine	No difference	Improved oxygenation
Martin <i>et al.</i> (2002) <sup>85</sup>	Single-center RCT	ALI after trauma	37	-3,300 ml on day 5	+500 ml on day 5	Change in creatinine	No difference	Improved oxygenation
Mitchell <i>et al.</i> (1992) <sup>127</sup>	Single-center RCT	Mixed ICU needing PAC	102	+142 ml	+2,239 ml	Change in creatinine	Small rise in creatinine	Shorter duration of ventilation and ICU stay
Bouchard <i>et al.</i> (2009) <sup>25</sup>	Retrospective observational	Mixed ICU with AKI	542	<10% rise	>10% rise	Dialysis independence	Improved	Decrease in mortality
Payen <i>et al.</i> (2008) <sup>6</sup>	Retrospective observational	Mixed ICU with or without AKI	3,147	-1,000 ml	+3,000 ml	Renal SOFA score	Improved	Decrease in mortality in patients with AKI
Vidal <i>et al.</i> (2008) <sup>72</sup>	Prospective observational	Mixed ICU with elevated or normal IAP	83	+5,000 ml	+9,000 ml	Renal SOFA score	Improved	Normal IAP associated with less organ failure and shorter ICU stay
Adesanya <i>et al.</i> (2008) <sup>128</sup>	Retrospective observational	Surgical ICU	41	+5 kg	+8.3 kg	Change in creatinine	No difference	Shorter duration of ventilation and ICU stay
McArdle <i>et al.</i> (2007) <sup>87</sup>	Retrospective observational	Surgical ICU	100	+7,500 ml	+10,000 ml	Change in creatinine	No difference	Decrease in postoperative complications
Arlati <i>et al.</i> (2007) <sup>99</sup>	Prospective observational	Burns ICU	24	+7,500 ml	+12,000 ml	Urine output	No difference	Decrease in organ dysfunction score

\* See Supplementary Information online for systematic search strategy. Abbreviations: AKI, acute kidney injury; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; IAP, intra-abdominal pressure; ICU, intensive care unit; PAC, pulmonary artery catheter; RCT, randomized, controlled trial; RRT, renal replacement therapy; SOFA, sequential organ failure assessment.

controlled trial examining fluid balance in patients with ALI, reported an almost statistically significant decrease in the requirement for RRT in the conservative fluid management group (10% versus 14% in the liberal fluid management group;  $P=0.06$ ). This finding is crucial because it occurred in patients with ALI who were on mechanical ventilation at high levels of positive end-expiratory pressure. In these conditions, patients would be expected to be at particular risk of AKI secondary to hypoperfusion. If, despite this high risk, aggressive fluid restriction resulted in a near significant decrease in the need for RRT, it seems unlikely that similar fluid restriction in less-severe acute illness would contribute to AKI. It is important to note, however, that fluid removal was pursued in the FACTT study only when hemodynamically appropriate, as the protocol specified that no fluid removal should take place in either group during periods of hemodynamic instability (mean arterial pressure <60 mmHg or the need for vasopressor infusion).

### Recommendations

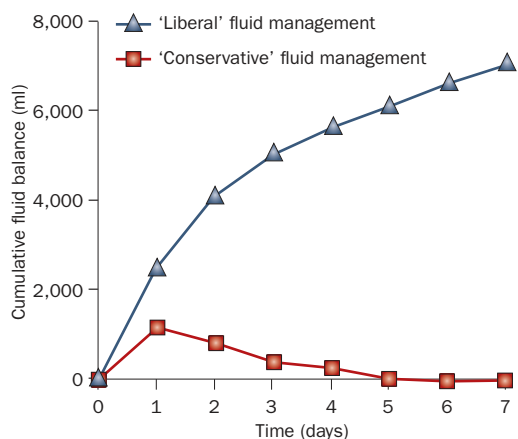
Excessive intravenous fluid therapy leading to positive fluid balances and interstitial edema is associated with organ dysfunction and adverse outcomes in acute illness. Once established, fluid overload is difficult to resolve and may result in inappropriate attempts to normalize fluid balance too quickly, which can lead to further complications. Contrary to received opinion, maintaining a positive fluid balance may worsen renal function and impede

recovery from AKI. How then, should we adjust fluid management in patients with acute illness and acquired AKI in the light of these observations?

### Guided fluid resuscitation

Acute low cardiac output that arises from external fluid losses, fluid redistribution or venodilation demands prompt and targeted correction of the volume deficit. Timely fluid resuscitation may actually reduce later volume requirements.<sup>89</sup>

Although correction of the relative volume deficit is crucial, restoration of preload can fail to normalize blood pressure or cardiac output in many situations, including sepsis and postoperative vasodilatory states. Invasive cardiovascular monitoring may be required to recognize such situations and to allow the timely institution of vasopressor and/or inotropic support. Numerous methods for preload assessment are available,<sup>90</sup> but any measurement is only as useful as its clinical interpretation. Rather than focusing on fluid responsiveness and the maximization of cardiac output to combat hypotension (which is a path towards a relentlessly positive fluid balance), it might be better to merely ensure that preload is sufficient to generate an adequate cardiac output, so that the appropriate point to stop fluid resuscitation can be determined. Such an approach may require earlier or greater use of vasopressor therapy. Historically, vasopressor use was limited by concerns over renal vasoconstriction and consequent ischemia;<sup>91,92</sup> the available evidence suggests, however,



**Figure 3** | Cumulative fluid balances achieved in the FACTT trial<sup>88</sup> of liberal (more-conventional) versus conservative (more-restrictive) fluid management strategies in critically ill patients with acute lung injury. No significant differences in renal outcome were found between groups but respiratory parameters were better in patients treated using the conservative approach.

that use of vasopressors to restore blood pressure in systemic vasodilation is in fact associated with increased renal blood flow and restoration of urine output.<sup>93–98</sup>

### Maintaining fluid balance

Despite guided fluid resuscitation and early vasopressor support, initial resuscitation of acute severe illness almost always results in a positive fluid balance and tissue edema. Thus, in the subsequent plateau phase of acute severe illness, which usually occurs after the first day, the treatment focus should shift towards the prevention of further fluid overload and the removal of accumulated excess salt and water.

As acutely ill patients generally have high mandatory water and sodium intake in drugs and nutrition, 'maintenance' intravenous fluids are rarely required. Most insensible losses are low in sodium and free water replacement should be titrated to maintain normal plasma sodium levels. The volume and expected electrolyte composition of gastrointestinal and wound losses should be assessed and replaced as appropriate. Even in the context of burns, evidence exists to suggest that traditional volumes of fluid replacement are associated with more adverse outcomes.<sup>99</sup> Fluid challenges for hypotension or oliguria should be performed judiciously in the context of an overall cardiovascular assessment. In conclusion, it is much easier not to give fluid than to remove edema once accumulated. Furthermore, as soon as it can be hemodynamically tolerated, sodium and water balance should be neutral, or even negative, as was achieved in the FACTT trial (Figure 3).

Achieving a neutral or negative fluid balance spontaneously during acute illness can be difficult. Loop diuretics are frequently employed in this context,<sup>100,101</sup> but their use can be complicated by electrolyte abnormalities, worsening of renal function and progressive diuretic resistance. Resistance can be overcome by the administration of diuretics that target the distal tubule and collecting ducts.

Even with such treatment, however, sufficient and sustained natriuresis can be difficult to achieve.<sup>102</sup> Hyperoncotic colloids can be used to encourage vascular refilling<sup>103</sup> but, as already noted, may themselves be nephrotoxic, particularly high molecular weight starches.<sup>53–55</sup>

The prevention of edema is particularly difficult in patients with AKI as diuretic therapy may worsen renal function, induce hypernatremia and/or be unable to induce sufficient diuresis. Indeed, diuretics have not been shown to beneficially affect the clinical course of AKI<sup>104</sup> or to speed up recovery after RRT.<sup>105</sup> Initiation of RRT may be required to successfully maintain neutral fluid balance. However, intermittent ultrafiltration during conventional hemodialysis might be associated with intradialytic hypotension<sup>106</sup> and an increased risk of recurrent renal injury.<sup>62,107,108</sup> Continuous renal replacement therapy (CRRT) has many theoretical advantages in this setting<sup>109</sup> because a constant slow rate of ultrafiltration allows time for vascular refilling and effective control of fluid balance while maintaining hemodynamic stability. In the treatment of AKI in the ICU, use of intermittent hemodialysis (IHD) was found to be correlated with progressively positive fluid balances whereas CRRT enabled net fluid removal,<sup>25</sup> despite the fact that CRRT was preferred for sicker, more hemodynamically unstable patients. Similarly, use of CRRT for initial treatment has been associated with higher rates of renal recovery than immediate use of IHD in critically ill individuals.<sup>110–113</sup> These observations have been strengthened recently by the findings of a large, randomized, controlled trial that investigated use of CRRT for the treatment of AKI in the ICU.<sup>114</sup> In our opinion, consideration should be given to the early initiation of CRRT—in advance of classic indications—if fluid balance cannot be adequately controlled with diuretic therapy. This approach anticipates and limits the extent of fluid overload rather than treating its consequences. In addition, it permits adequate nutritional support without worsening fluid balance. Therefore, in a large proportion—perhaps the majority—of critically ill AKI patients, we believe that CRRT should be initiated within the first 24 h of ICU admission. Such earlier intervention with CRRT is now commonly practiced worldwide<sup>115</sup> and has been associated with improved survival.<sup>115</sup> However, this practice does remain controversial, particularly as no prospective, randomized, controlled trials have confirmed a clinical benefit or justified the additional costs involved.

### Fluid removal

Despite measures to limit fluid excess, resolution of accumulated interstitial edema often requires active fluid removal. A physiological assessment of fluid status is as important during fluid removal as it is in the initial resuscitation. If fluid removal is excessive or out of pace with vascular refilling, hypovolemia-induced falls in cardiac output can increase the risk of recurrent renal injury. Assessment of the appropriate quantity and rate of fluid removal is challenging, but a number of newer techniques are being developed that might help guide this process.

Changes in serum creatinine level poorly reflect underlying renal function in acute illness,<sup>116</sup> even before being

confounded by the use of RRT. Novel biomarkers of renal injury have shown promise in the early identification of patients with incipient AKI.<sup>117</sup> Monitoring of such biomarkers could potentially be extended to the detection of recurrent renal injury during recovery from AKI, enabling early intervention to maximize likelihood of renal recovery.

Extracellular and intracellular volume expansion can be quantified using a variety of bioimpedance techniques.<sup>118–120</sup> Titration of fluid removal to such measurements might ensure avoidance of excessive fluid removal. For ultrafiltration during IHD, blood volume monitoring (a continuous hematocrit measurement) enables the early detection of inadequate intravascular refilling, which might enable fluid removal rates to be adjusted so that intradialytic hypotension and recurrent renal injury might be prevented.<sup>121–123</sup> Finally, brain natriuretic peptide (BNP) and related molecules, which are biomarkers of congestive cardiac failure, have been correlated with echocardiographic and bioimpedance measures of fluid overload in patients on RRT.<sup>124,125</sup> Measurement of BNP could aid assessment of the degree of fluid overload, particularly in the presence of coexisting cardiac failure; although its interpretation would require a dissection of the relative contributions of baseline cardiac disease and superimposed fluid overload to the elevated BNP level.

## Conclusions

Intravenous fluids are drugs that have widespread systemic effects. The correct application of these fluids requires detailed clinical assessment and a sound understanding of renal and cardiovascular physiology. As with other drugs, intravenous fluids should be used only when specifically indicated. In patient groups where evidence to justify such use is lacking, intravenous fluid use should be rigorously evaluated in large, suitably powered, randomized, controlled trials. The correct 'dose' of these fluids should be similarly tested in such trials. Sadly, the opposite is continuing to occur. Fluids remain one of the mostly widely used and abused medical therapies and their management is too often delegated to the most junior members of the medical team. No randomized, controlled study exists to show that a positive fluid balance is either beneficial or necessary in acquired AKI or during acute illness in general. Large studies in critically ill patients found no

differential renal effect when 4% albumin in saline was compared with saline alone for fluid resuscitation,<sup>52</sup> and a trend towards decreased use of RRT was seen in ALI with a fluid-conservative (versus a fluid-liberal) approach.<sup>88</sup> A 7,000-patient study comparing a novel starch preparation in saline with saline alone is scheduled to begin in Australia and New Zealand in 2010.<sup>126</sup> This study will provide further high-quality data to help clinicians practice safely. Until then, the approach to fluid therapy must be based on a rational assessment of what is known so far.

We advocate a two-stage approach of directed resuscitation in acute illness, with an early transition to neutral and then negative fluid balances, to best limit the adverse consequences of fluid overload. This philosophy is in harmony with recent consensus guidelines for the management of perioperative patients.<sup>60</sup> Further clinical trials are clearly warranted to examine optimal fluid balances and to better document renal outcomes; yet, the evidence available so far favors more-restrictive fluid management strategies than have been employed historically. These strategies should be implemented with appropriate monitoring to avoid iatrogenic hypovolemia and further functional renal impairment, particularly during active fluid removal. Medical education, practice patterns and clinical guidelines should increasingly reflect these new paradigms.

## Review criteria

The PubMed database was searched in July 2009 to identify clinical studies examining fluid balance or therapy in adult critically ill patients. Three searches were performed by combining Medical Subject Headings (MeSH) using the Boolean operator "OR". The first search used the terms: "fluid therapy", "water-electrolyte balance" and "hydrostatic pressure". The second search used the terms: "intensive care", "intensive care units", "critical illness", "critical care", "renal insufficiency, acute", "sepsis", "respiratory distress syndrome, adult" and "diuretics/therapeutic use". The third search used the terms: "intensive care units, pediatric" and "models, animal" and the following publication types: "review", "case report", "editorial", "letter" and "practice guideline". We combined the first two searches with the Boolean operator "AND" and the third one with the Boolean operator "NOT". The search was further limited to articles published in the English language.

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#### Supplementary information

Supplementary information is linked to the online version of the paper at [www.nature.com/nrneph](http://www.nature.com/nrneph)