

Water balance, acute kidney injury and mortality of intensive care unit patients

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ABSTRACT

Acute kidney injury (AKI) has a high hospital incidence and is associated to significant morbidity and mortality. Sepsis, major surgery and low cardiac output are the main cause of AKI worldwide. In the majority of these situations, volume expansion is part of both prevention and therapeutic management, restoring peripheral perfusion and attenuating drug nephrotoxicity. Early and aggressive volume resuscitation in septic patients halts tissue ischemia and is associated with higher survival. However, a liberal fluid infusion strategy after six hours can cause fluid overload. Fluid overload has been associated with morbidity and mortality increase in critically ill patients. Herein, we present a review of the main studies that assessed the effects of net fluid balance/fluid overload on the morbidity and mortality of critically ill patients. We suggest that positive water balance may be used as a potential early biomarker of AKI in these patients.

Keywords: acute kidney injury; intensive care unit; mortality; water balance.

ACUTE KIDNEY INJURY AND VOLUME EXPANSION: IS POSITIVE FLUID BALANCE (FB+) BENEFICIAL?

Acute kidney injury (AKI) happens in approximately 3% to 15% of hospitalized patients and can affect 30% to 50% of patients allocated to intensive care units (ICU).¹⁻⁵ AKI overall

hospital mortality is approximately 20% and may exceed 50% in critically ill patients.¹⁻³ Patients who develop in-hospital AKI have higher risk of developing chronic kidney disease,^{4,5} and have higher late mortality after discharge.⁶⁻¹⁰ AKI prevention involves the identification of its main causes. In the clinical context of ICU patients, AKI is predominantly multifactorial in etiology: ischemic and/or nephrotoxic.¹¹ Sepsis is the cause of over 50% of AKI cases in the ICU worldwide, followed by major surgery and low cardiac output.¹⁻¹⁰ In all these situations, volume expansion is the mainstay of prevention and therapeutic management because it contributes to the restoration of peripheral perfusion and attenuates drug-induced nephrotoxicity.^{3,12-15} In 2001, Rivers *et al.*¹⁴ demonstrated in a randomized controlled study that early aggressive fluid resuscitation - driven by protocol with defined goals - significantly decreased mortality in severe sepsis. Despite numerous criticisms during these last 13 years after its publication,¹⁵ this study markedly influenced the treatment of septic patients, having been adopted as a key recommendation in all publications from the *Surviving Sepsis Campaign*.¹⁶ Currently, there are three randomized, controlled clinical trials in progress, aiming to reproduce Rivers's findings: one in the U.S. (Protocolled Care for

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Early Septic Shock - Process), another in Australia (Australasian Resuscitation in Sepsis Evaluation randomized Controlled Trial - ARISE) and the third in England. Although Rivers *et al.* paper did explore the impact of volume resuscitation in the prevention of AKI, Lin *et al.*¹⁷ showed in a later study, that early fluid resuscitation, similar to that used in the Rivers's protocol, reduced the incidence of AKI (55% to 39%, $p = 0.015$) in patients with septic shock.

Thus, adequate fluid resuscitation within the first six hours of hospital care in septic patients seems to be associated with prevention of tissue ischemia (including renal ischemia) and increased survival. A positive fluid balance (FB+) for a short period of time in patients undergoing resuscitation with these protocols can be the cost to be paid to restore tissue perfusion. However, this liberal strategy of fluid infusion after the first six hours of care can cause a continuously positive FB. Indeed, this approach was not endorsed by Rivers;¹⁴ however the situation is common in current clinical practice,¹⁸ with deleterious consequences to the patient.

It is also possible that the goal-oriented fluid resuscitation benefits are not due only to the administration of larger volumes of fluids to patients who specifically so require, in accordance with pre-established hemodynamic parameters, but the earliness and suitability of this measure. Administration of fluids to the limited optimization of hemodynamic parameters set previously could result in less volume of fluid infusion, minimizing FB+.¹⁹ Tokarik *et al.*²⁰ piloted a study with 21 burn patients and showed that fluid response determination using LiDCO (Lithium Dilution Cardiac Output) during resuscitation enabled the administration of less crystalloid volume. The study randomized two groups of burn patients: Group 1, whose resuscitation was based on systolic pressure variation (SPV) measurements and pulse pressure variation (PPV) with LiDCO; and Group 2, whose resuscitation was

based on commonly used formulas (modified Brooke/Parkland) for volume expansion in burn patients. Group 1 received significantly less crystalloid than Group 2 (5090 ± 680 ml and 7.820 ± 1.050 ml, respectively, $p = 0.04$).²⁰ Thus, goal-oriented fluid resuscitation does not necessarily imply larger infusions of fluid and excessively positive FB.^{19,20}

POSITIVE FLUID BALANCE AND ICU MORTALITY: IS FB+ HARMFUL?

Patients with persistently positive FB are more subject to adverse clinical consequences such as liver congestion, bowel edema with ileus, malabsorption, abdominal compartment syndrome/intraabdominal hypertension, myocardial edema with conduction abnormalities and diastolic dysfunction, pulmonary congestion with worsening compliance and gas exchange, cerebral edema, kidney edema and peripheral tissues edema with poor wound healing and infections (Chart 1).²¹⁻²⁵ Encapsulated organs such as the kidney and liver, have limited capacity to accommodate excess fluid, which can determine increased interstitial pressure with consequent impairment of blood flow and functional deterioration.^{13,22} Increased kidney interstitial pressure in patients with buildup FB+ cause blood hypoperfusion and decreased glomerular filtration. Moreover, the increase in intraabdominal pressure (IAP), central venous pressure (CVP) and kidney venous pressure (KVP) increases, in conditions of fluid overload substantially contributes to the decline in glomerular filtration rate, as suggested by experimental studies. Kidney venous pressure above 30 mmHg for 2 hours in intact porcine kidneys results in a significant decline in kidney plasma flow and glomerular filtration rate.²⁶ KVP elevation limited renal blood flow and urine formation more than arterial blood hypoperfusion.^{26,27} In patients with cardiorenal syndrome, with or without low cardiac output, elevation of CVP, KVP IAP may contribute to progressive kidney dysfunction.²⁷

And in patients undergoing elective cardiac surgery, having a high CVP is a strong predictor of postoperative AKI, regardless of low heart output.^{27,28}

Under physiological conditions, IAP ranges from sub atmospheric to 0 mmHg. Prolonged elevated IAP or above 12 mmHg defines intra-abdominal hypertension. Levels of IAP between 10 and 15 mmHg cause a reduction in mesenteric perfusion with ischemia, inflammation, and more swelling, which in turn enhances the intra-abdominal pressure, closing the cycle. When the IAP achieves 20 mmHg, there is an increase in the chances of systemic clinical consequences, such as cardiovascular disorders (increased CVP, decreased venous return and cardiac output), kidney disorders (decreased renal plasma flow, increased KVP, renal microvascular congestion, increased renal vascular resistance, elevated catecholamines, angiotensin II, inflammatory cytokines and renal capsule hypertension), lung (reduced chest wall compliance, increased KVP, increased dead space, hypercapnia and hypoxia) and cerebral (increased intracranial pressure and decreased cerebral perfusion pressure), configuring an abdominal compartment syndrome.^{29,30} Primarily, the abdominal compartment syndrome was described in patients undergoing abdominal surgery or trauma victims; however, currently, it is increasingly diagnosed in patients undergoing massive fluid resuscitation, multiple transfusions, hypothermia or coagulation disorders, i.e., patients with successive FB+. There is evidence that intra-abdominal hypertension present at ICU admission

is associated with increased risk of severe organ dysfunction (including AKI) and the highest mortality.^{29,30}

Another no less important aspect, which may contribute to the adverse outcomes associated with FB+, is the type of solution used for fluid resuscitation. Synthetic colloids are potentially nephrotoxic and are associated with increased mortality, especially HES solutions (hydroxyethyl starch) and possibly gelatins.³¹⁻³³ 4% albumin should be avoided in the fluid resuscitation of patients with head injury, but appears to be safe in AKI septic patients or at risk of developing it.³¹⁻³³ The use of 20% albumin has been associated with lower incidence of AKI and reduced mortality in cirrhotic patients with spontaneous bacterial peritonitis, but its routine use ends up being limited by the higher cost of crystalloid.³⁴ Thus, the Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI in its latest edition, suggests that isotonic crystalloids are preferable, instead of synthetic or non-synthetic colloids for volume expansion in patients at risk of developing AKI or AKI installed in the absence of a hemorrhagic shock.³²

However, crystalloids are not without risk. Clinical and experimental studies suggest that unbalanced crystalloid or with higher chlorine content may worsen metabolic acidosis, cause kidney vasoconstriction and reduce the kidney oxygen consumption.³⁵⁻³⁷ Chowdhury *et al.*³⁶ led a crossover study in healthy volunteers, randomized to receiving alternating 2 liters of isotonic 0.9% saline (containing 150 mmol/l chlorine) and 2 liters

CHART 1 POTENTIAL SIDE EFFECTS OF A POSITIVE FLUID BALANCE (FB+)

Edema site	Consequences
Brain	Cognitive changes, delirium.
Myocardium	Contractility change, diastolic dysfunction, conduction disorders.
Lungs	Gas exchange alterations, compliance reduction, increase in respiratory effort.
Liver	Compromised synthetic function and cholestasis.
Kidneys	Reduction in kidney plasma flow and in glomerular filtration rate, fluid and salt retention.
Bowel	Malabsorption and ileum, peaking with abdominal compartment syndrome.
Peripheral tissues	Compromised lymphatics drainage, changes in microcirculation, impaired wound healing, wall infection and pressure ulcers.

of Plasmalyte (containing 98 mmol/l chloride) IV. Upon receiving isotonic saline 0.9%, individuals took longer to have the first urination (from 90 to 142 min, $p = 0.006$), reduced urine volume of 833 ml to 523 ml ($p = 0.002$) and reduced kidney plasma flow velocity and kidney cortical perfusion assessed by MRI.³⁶ Yunos *et al.*³⁷ conducted a prospective, controlled pilot study in critically ill patients, comparing the liberal strategy of fluid infusion containing chlorine (as gelatin and 0.9% saline) with the use of balanced solutions or with less chlorine content such as Hartmann's solution (containing 109 mmol/l chlorine) and Plasmalyte. Fluid handling with balanced solutions reduced the frequency of hyperchloremia, metabolic acidosis and was associated with significant reduction in the incidence of AKI and need for supportive kidney therapy.³⁷ Therefore, not only the amount of fluid infused in the volume resuscitation, but also its composition, can interfere with unfavorable outcomes associated with FB+.

All these deleterious consequences of FB+ have been associated with increased mortality in critically ill patients.³⁸⁻⁵⁴ Tables 1 and 2 summarize the most important studies that sought to assess the impact of FB+ in the morbidity and mortality of critically ill patients.³⁸⁻⁵⁴

Bouchard *et al.*⁴⁹ evaluated the adult population with AKI in the PICARD study and found that, at the time of AKI diagnosis, the percentage of fluid accumulation in relation to the patient's weight upon ICU admission was lower in survivors than in nonsurvivors ($p = 0.01$). However, this difference was not statistically significant after adjustment for APACHE III ($p = 0.12$) scores. When the rate of fluid accumulation from all patients was greater than 10% - featuring fluid overload, mortality at 30 and 60 days rose from 25 to 37% ($p = 0.02$) and 35 to 48% ($p = 0.01$), respectively. The risk of death associated with fluid overload in dialysis patients was 2.07 (95% CI 1.27 to 3.37), adjusted for severity of illness and dialysis modality. In patients not on dialysis with fluid overload, the risk of death was 3.14 (95% CI 1.18 to 8.33). Patients who kept fluid accumulation during hospitalization had higher mortality, which was proportional to fluid buildup ($p < 0.0001$). Patients in whom dialysis was able to correct fluid overload had lower mortality than those who remained with fluid overload after dialysis (35% *vs.* 56% respectively, $p = 0.002$). The adjusted risk of death associated with fluid overload at the end of dialysis was 2.52 (95% CI 1.55 to 4.08). Patients with fluid overload at the time that creatinine was higher were less likely to recover kidney function (35% *vs.* 52% respectively,

TABLE 1 STUDIES ASSESSING THE IMPACT OF FLUID BALANCE (FB) IN THE MORBIDITY OF INPATIENTS IN AN INTENSIVE CARE UNIT (ICU)

Study	Design	Population and number	n	Less positive FB	More positive FB	AKI criterion	Impact on kidney function of the less positive group	Main outcome of the less positive group
Wiedemann, 2006 ³⁸	CRT multicentric	ARDS	1000	-136 (7 days)	+6992 (7 days)	Kidney Support Therapy	No differences	Duration < MV and ICU
Martin 2005 ³⁹	CRT 1 Center	API	40	-5480 (5 days)	-1490 (5 days)	Increased creatinine	No differences	Improves oxygenation
Mitchel 1992 ⁴⁰	CRT 1 Center	Mixed ICU	102	+142 ml	+2239 ml	Increased creatinine	Mild worsening	Duration < MV and ICU
Adesanya 2008 ⁴³	Observational Retrospective	Surgical ICU	41	+5 kg	+8.3 kg	Increased creatinine	No difference	Duration < MV and ICU
McArdle 2007 ⁴⁴	Observational Retrospective	Surgical ICU	100	+7500 ml	+10000 ml	Increased creatinine	No differences	Postoperative complication
Ariati 2007 ⁴⁵	Prospective	Burn ICU	24	+7500 ml	+12000 ml	Diuresis	No differences	MOSD

AKI: Acute kidney injury; CRT: Controlled randomized trial; ARDS: Acute respiratory distress syndrome; API: Acute pulmonary injury; MV: Mechanical ventilation; MOSD: Multiple organs and systems dysfunction.

TABLE 2 STUDIES ASSESSING THE IMPACT OF POSITIVE FLUID BALANCE IN THE MORTALITY OF IN PATIENTS IN AN INTENSIVE CARE UNIT (ICU)

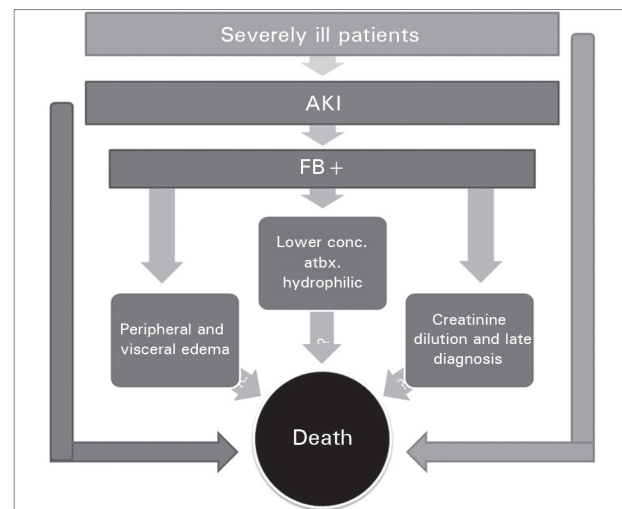
Author and year	Design	Population	n	FO%		FB ml/24 hours		p
				live	dead	live	dead	
Goldstein, 2001 ⁴⁶	Observational Retrospective	Pediatric	21	16	34	-	-	0.03
Goldstein 2005 ⁴⁷	Observational Retrospective	Pediatric	116	14	25	-	-	< 0.03
Foland 2004 ⁴⁸	Observational Retrospective	Pediatric	113	8	15	-	-	0.02
Bouchard 2009 ⁴⁹	Observational Retrospective	AKI	396	9	14	-	-	0.01
Vaara ST 2012 ⁵³	Observational Prospective multicentric	AKI	283	31	59	-	-	0.03
Payen 2008 ⁵¹	Observational Retrospective	AKI	1120	-	-	150*	980*	< 0.001
De Almeida 2012 ⁵²	Observational Prospective	Cancer ICU	122	-	-	887**	1675**	0.017

FO: Fluid overload or gain > 10% of the ICU admission weight; FB ml/24 hours = mean fluid balance in the 24 hours; AKI: Acute kidney injury. * Mean daily FB in the first 3 days of ICU admission; ** Mean daily FB during the entire ICU stay.

$p = 0.007$). This latter finding suggests that, after AKI installing, the administration of excess fluid exerts no protective effect on kidney recovery. However, it is not possible to say that the fluid overload per se was the cause of delayed kidney recovery, or if patients with fluid overload already had a more severe AKI, and therefore also had a later recovery.³⁷

By means of a multicenter prospective observational study with 296 patients from 17 ICUs, Vaara ST *et al.*,⁵³ also reported that fluid overload (defined as fluid accumulation above 10% of the baseline weight) at the time of the Renal Support Therapy (RST) indication, was associated with a higher risk of death at 90 days (OR 2.6), after adjustment for severity of illness, RST onset time, RST modality and sepsis.⁵³ Although the association between FB+ and mortality seems logical and likely, most of the studies that demonstrated it are observational in design, not being able to establish definitive cause and effect relation.^{40,42,43,45-53} None of these studies can clarify whether patients with FB+ have higher mortality for being more severe (and therefore require greater investment on drugs, antibiotics, sedatives, parenteral nutrition etc.) or whether the FB+ has a really independent pathophysiological involvement in the death process. Alternatively, we can speculate that FB+ is an early biomarker of AKI, which is associated with mortality (Figure 1).

Figure 1. Possible associations between acute kidney injury (AKI), positive fluid balance (FB+) and mortality. The FB+ may be associated with increased mortality for several pathophysiological pathways (blue arrows): to cause visceral and peripheral edema, making the organic functioning difficult; by dilution of hydrophilic antibiotics, reducing their effectiveness, or even by hemodilution of serum creatinine, delaying diagnosis of acute kidney injury (AKI). However, the FB+ is more often found in patients with higher clinical severity (orange arrow) and in patients with AKF (red arrow), both situations already independently associated with increased mortality.



There are only a few randomized clinical trials that studied the association between mortality and FB+. Wiedemann *et al.*³⁸ randomized 1,000 patients with acute respiratory distress syndrome (ARDS) into two fluid management strategies, one conservative and the other liberal. This is the

largest prospective, controlled study evaluating the impact of fluid overload on the duration of mechanical ventilation and mortality in ARDS. The conservative strategy of fluid infusion reduced the duration of mechanical ventilation, without worsening kidney function; however, mortality was similar in both grupos.³⁸

The largest randomized controlled trial designed to evaluate the impact of strategies for fluid resuscitation on mortality was developed in six clinical centers in Africa.⁵⁴ The authors studied septic children (< 12 years of age) with signs of peripheral hypoperfusion who were randomized to resuscitation with a bolus of saline (20 ml/kg IV at 1 hour), albumin bolus (20 ml/kg IV at 1 hour) or no bolus (control). The three groups equally received 2.5 to 4 ml/kg/h as maintenance fluids, blood transfusions if hemoglobin was below 5 g/dL and appropriate antibiotics. Children with gastroenteritis, severe malnutrition and shock of noninfectious causes were excluded. Children with severe hypotension were randomized to saline bolus or albumin, with no control group. The 48-hour mortality was higher in the groups receiving intravenous bolus of 0.9% saline or albumin compared to the group who received bolus (11% both groups *versus* 7% bolus, RR 1.45, $p = 0.003$).⁵⁴ No FB data from each group was shown. Furthermore, the study was conducted in the pediatric population and health centers without advanced life support, making it difficult to generalize these results for adult patients admitted to intensive care units.

The morbid effects of fluid overload in the various organs may be responsible for the association between mortality and FB+. However, another aspect that could also contribute to higher mortality in patients with fluid overload is reduced plasma concentrations of hydrophilic antibiotics by increasing the volume of their distribution.⁵⁵ As will be discussed below in the topic, it is known that inflamed/septic patients develop endothelial damage with increased capillary permeability predisposing to fluid shifts from the intravascular compartment to the interstitium. Hydrophilic antibiotics such as aminoglycosides, beta-lactam and glycopeptides

may follow this fluid diversion, resulting in subtherapeutic plasma concentrations.⁵⁵ Thus, the complex association between FB+ and mortality has not been clearly elucidated. FB+ would be a severity marker of cardio/kidney/microvascular severity or is it an independent factor for higher mortality in critically ill patients? (Figure 1).

POSITIVE FLUID BALANCE AND AKI DIAGNOSIS: DOES FB+ INTERFERE WITH THE AKI DIAGNOSIS?

Currently, AKI diagnosis is based on the RIFLE criteria (Risk, Injury, Failure, Loss, End stage Kidney Disease), AKIN (Acute Kidney Injury Network) and KDIGO (Kidney Disease Improving Global Outcomes), which are based on serum creatinine increase and reductions in urinary volume.^{56,57} These criteria were constructed from the observation that small increases in serum creatinine⁵⁷ and diuresis reductions⁵⁸ imply a worse prognosis for patients. The three classification systems are divided into severity stages and there is growing evidence of a correlation between the AKI stage by RIFLE and AKIN criteria and mortality.⁵⁹ Fluid balance was not included in the diagnosis of AKI by any of these currently adopted criteria, a fact which leads us to reflect on renal physiology.

It is known that a patient with normal renal function and usual diet (generating 800 mOsm of excreta per day) is able to eliminate up to 16 liters of maximally dilute urine (50 mOsm/L), for physiological suppression of antidiuretic hormone (ADH).⁶⁰ In turn, when a critically ill patient develops AKI diagnosed by standard criteria and receives large fluid infusions (antibiotics, sedation, vasoactive drugs etc.), it is easy to understand why he develops FB+, since there is obvious impairment in their ability to excrete the sodium overload received. However, critically ill patients without a diagnosis of AKF by the RIFLE, AKIN or KDIGO criteria also evolve with positive FB. Why they could not adequately increase the excretion of free salt and water, in response to sodium overload?

There are medical conditions in the ICU that may predispose FB+, even in patients without AKI. Hypotension, low cardiac output, vasodilation of sepsis (albeit without hypotension),

hypoalbuminemia, mechanical ventilation (MV) are able to activate the neuroendocrine system (antidiuretic hormone, sympathetic nervous system, renin-angiotensin-aldosterone system), with tubular retention of free water and sodium.^{12,13} Because these patients usually receive large infusions of water and salt, the result is positive FB and edema. MV with positive pressure can also reduce lymphatic drainage, contributing to edema formation.^{12-14,25}

Other pathophysiological mechanisms that mediated the development of FB+ in critically ill patients without a diagnosis of AKI by current criteria, possibly involve two molecular systems: the angiotensin/Tie (Ang/Tie)^{61,62} system and the endothelial glycocalyx.^{63,64} The angiotensin/Tie (Ang/Tie) system participates in major endothelial functions: angiogenesis, fluid homeostasis maintenance, electrolytes and protein transport by endothelial cells and inflammation/coagulation triggered by endothelial injury. These three endothelial functions are altered in multiple organ dysfunction syndrome (MODS): blood flow regulation is changed, vascular permeability becomes higher with fluid and cell extravasation into the surrounding tissues and the mechanisms of inflammation and coagulation are activated. Experimental and clinical studies suggest that the Ang/Tie system participates in the vascular barrier dysfunction observed in critically ill patients.^{61,62} Angiotensin 1 (Ang-1), a glycoprotein produced by pericytes causes vascular stability by binding to the transmembrane Tie-2 receptor of endothelial cells. Rather, angiotensin 2 (Ang-2) released by the Weibel-Palade corpuscles of endothelial cell cytoplasm by inflammatory stimuli, antagonizes the stabilizing effect of Ang-1 by binding competitively to the same receptor Tie-2, weakening the intercellular junctions, predisposing to fluid leakage, inflammation and coagulation. Patients with septic shock have high plasma levels of Ang-2, that correlate with FB+, pulmonary dysfunction and mortality.⁶²

It is also possible that the endothelial glycocalyx is reduced in situations of ischemia and/or inflammation, such as sepsis or systemic inflammatory response syndrome (SIRS).⁶³ Glycocalyx is a structure composed of glycosaminoglycans and

proteoglycans, which covers the endothelial surface facing the capillary lumen, forming a barrier against the passage of macromolecules and limiting the adhesion of inflammatory cells. The reduction of its thickness, in situations of ischemia/inflammation, causes an increase in vascular permeability and leukocyte adhesion, contributing to leakage of fluid and macromolecules to the interstitium.^{63,64} Therefore, ischemic and inflammatory attacks, so frequent in critically ill patients cause endothelial dysfunction mediated by changes in the angiotensin 2/Tie-2 system and endothelial glycocalyx stripping, contributing to the diversion of fluid and macromolecules from the intravascular compartment to the interstitium and, again, activating the neuroendocrine system to retain fluids.^{63,64}

On the other hand, critically ill patients may develop early and subtle AKI alone or together with events described above, manifested by the inability to properly control the fluid and sodium balance. The ability to concentrate and dilute urine depends on the functional integrity of the renal medullary microcirculation and may be impaired in the very early stages of kidney disease. While the cortical microcirculation is able to make its self-regulation through changes in tone of afferent and efferent arterioles up to certain limits for mean arterial pressure (MAP), the medullary microcirculation seems to be more dependent on MAP and renal perfusion pressure, more susceptible to ischemia and endothelial dysfunction in circulatory shock.⁶⁵ Thus, positive FB can potentially be an AKI biomarker, preceding the elevation of creatinine or decreased urine output. Moreover, fluid overload can cause hemodilution and underestimate the level of serum creatinine, delaying AKI diagnosis by the usual criteria.¹⁸ By analyzing data from the PICARD study, Macedo *et al.*, proposed using the following formula to adjust serum creatinine for FB+:

$$\text{Adjusted creatinine} = \text{dosed creatinine} \times \text{correction factor}^*$$

* correction factor = ((weight upon admission × 0,6) + ∑ daily built up FB)/(weight upon admission × 0,6).

The use of creatinine adjusted for this “correction factor” enabled the anticipation of the AKI diagnosis, in at least one day.¹⁸

This set of facts suggests that it is necessary to consider the possible inclusion of FB+ as an AKI criterion besides creatinine and urinary volume. Three observational studies, a retrospective with 90 patients,⁶⁶ another prospective with 100 patient⁶⁷ and the last: a secondary analysis of a prospective study involving 98 children suggested that FB+ is an early marker of renal dysfunction. All studies evaluated patients undergoing cardiovascular surgery^{65,66} Dass *et al.*⁶⁶ conducted a post-hoc analysis of the Nesiritide Study, a randomized placebo-controlled clinical trial, from a single center, a study designed to assess the impact of prophylactic use of nesiritide in patients requiring renal support therapy and/or in the mortality of patients undergoing cardiovascular surgery. These authors investigated the hypothesis that FB+ in the first 24 hours after cardiac surgery could be an indicator of postoperative AKI. In this study, the incidence of AKI in patients with a median FB greater than +849 ml/24 hours was 80%, *versus* 25% in those patients with a median FB -1221 ml/24 hours ($p = 0.001$).

In a prospective observational study, Kambhampati *et al.*⁶⁷ divided the groups into FB quartiles, from the intraoperative up to 48 hours postoperatively. AKI incidence in the 4th quartile (FB+ median of 5000 ml/24 hours) was 52%, compared with a 16% incidence of AKI in the 1st quartile (FB+ median of 500 ml/24 h), $p = 0.016$. Multivariate analysis adjusted for confounding variables such as age, diabetes, hypertension, cardiopulmonary bypass time greater than 200 min, type of surgery and rate of basal glomerular filtration revealed that the higher FB+ quartile (4th quartile) was associated with a significantly higher risk of AKI (OR 4.89; 95% CI; 1.38 to 24.1, $p = 0.046$).⁶⁷

The third and most recent study evaluated whether fluid overload in the early postoperative period of cardiac surgery in 98 children would be associated with higher morbidity, including increased incidence of AKI.⁶⁸ Early postoperative fluid overload was defined as FB+ greater than 5% of baseline weight, from the immediate postoperative period in the ICU until the first postoperative day. Fifty percent of children with fluid overload upon ICU admission developed AKI in the first postoperative day, whereas only 14.4% of those who did not have early fluid overload developed

AKI ($p = 0.023$). Fluid overload preceded the onset of AKI, which occurred in any postoperative day. 8% fluid overload (equivalent to 80 ml/kg) showed a specificity of 90% for the subsequent development of AKI RIFLE I or F. Fluid overload was also associated with a longer hospital stay (3.5 days more), two more days under inotropes, and higher prevalence of prolonged MV.⁶⁸ To date, there is no available evidence testing the hypothesis that FB+ is an early marker of AKI, also in non-surgical patients.

ABSTRACT

Early volume expansion guided by the optimization parameters of microcirculatory perfusion remains a recommendation to reduce the incidence of AKI and minimizes mortality in septic patients. Volume expansion is also a preventive measure for nephrotoxic AKI, as in the iodine contrast-induced AKI, to aminoglycosides, amphotericin B, rhabdomyolysis and tumor lysis syndrome, among other situations. In turn, the maintenance of ad libitum fluid infusion in critically ill patients with or without acute kidney failure, can lead to accumulated FB+ and increase morbidity and mortality. FB+ can also delay AKI diagnosis, by serum creatinine hemodilution.

FB+ could be a manifestation of the inability to adequately control fluid and salt balance in critically ill and inflamed patients by changes in the kidney medullary microcirculation function integrity.

In conclusion, FB+ may be an early AKI biomarker and an independent risk factor for mortality in ICU patients. Randomized clinical trials are needed to evaluate the complex interrelationship between FB+, AKI and death.

REFERENCES

1. Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, Tan I, et al. Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. *Intensive Care Med* 2007;33:1563-70.
2. Fang Y, Ding X, Zhong Y, Zou J, Teng J, Tang Y, et al. Acute kidney injury in a Chinese hospitalized population. *Blood Purif* 2010;30:120-6. DOI: <http://dx.doi.org/10.1159/000319972>
3. Singbartl K, Kellum JA. AKI in the ICU: definition, epidemiology, risk stratification, and outcomes. *Kidney Int* 2012;81:819-25. PMID: 21975865 DOI: <http://dx.doi.org/10.1038/ki.2011.339>
4. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012;81:442-8. PMID: 22113526 DOI: <http://dx.doi.org/10.1038/ki.2011.379>

5. Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012;81:477-85. PMID: 22157656 DOI: <http://dx.doi.org/10.1038/ki.2011.405>
6. Lafrance JP, Miller DR. Acute kidney injury associates with increased long-term mortality. *J Am Soc Nephrol* 2010;21:345-52. DOI: <http://dx.doi.org/10.1681/ASN.2009060636>
7. Gammelager H, Christiansen CF, Johansen MB, Tønnesen E, Jespersen B, Sørensen HT. One-year mortality among Danish intensive care patients with acute kidney injury: a cohort study. *Crit Care* 2012;16:R124. DOI: <http://dx.doi.org/10.1186/cc11420>
8. Ponce D, Zorzenon Cde P, dos Santos NY, Balbi AL. Early nephrology consultation can have an impact on outcome of acute kidney injury patients. *Nephrol Dial Transplant* 2011;26:3202-6. DOI: <http://dx.doi.org/10.1093/ndt/gfr359>
9. Macedo E, Castro I, Yu L, Abdulkader RR, Vieira JM Jr. Impact of mild acute kidney injury (AKI) on outcome after open repair of aortic aneurysms. *Ren Fail* 2008;30:287-96. DOI: <http://dx.doi.org/10.1080/08860220701857522>
10. United States Renal Data System USRDS 2012 Annual Data Report: Atlas of CKD and ESRD in the United States. *Am J Kidney Dis* 2013;61:e1-e480.
11. Santos WJ, Zanetta DM, Pires AC, Lobo SM, Lima EQ, Burdman EA. Patients with ischaemic, mixed and nephrotoxic acute tubular necrosis in the intensive care unit-a homogeneous population? *Crit Care* 2006;10:R68. DOI: <http://dx.doi.org/10.1186/cc4904>
12. Schrier R. Fluid administration in critically ill patients with acute kidney injury. *Clin J Am Soc Nephrol* 2010;5:733-9. DOI: <http://dx.doi.org/10.2215/CJN.00060110>
13. Townsend DR, Bagshaw SM. New insights on intravenous fluids, diuretics and acute kidney injury. *Nephron Clin Pract* 2008;109:c206-16. PMID: 18802369 DOI: <http://dx.doi.org/10.1159/000142930>
14. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368-77. DOI: <http://dx.doi.org/10.1056/NEJMoa010307>
15. Venkataraman R, Kellum JA. Sepsis: update in the management. *Adv Chronic Kidney Dis* 2013;20:6-13. DOI: <http://dx.doi.org/10.1053/j.ackd.2012.10.013>
16. Bion J, Jaeschke R, Thompson BT, Levy M, Dellinger RP. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Intensive Care Med*. 2008;34:1163-4. DOI: <http://dx.doi.org/10.1007/s00134-008-1090-z>
17. Lin SM, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. *Shock* 2006;26:551-7. PMID: 17117128 DOI: <http://dx.doi.org/10.1097/01.shk.0000232271.09440.8f>
18. Macedo E, Bouchard J, Soroko SH, Chertow GM, Himmelfarb J, Ikin TA, et al. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care* 2010;14:R82. DOI: <http://dx.doi.org/10.1186/cc9004>
19. Prowle JR, Chua HR, Bagshaw SM, Bellomo R. Clinical review: Volume of fluid resuscitation and the incidence of acute kidney injury - a systematic review. *Crit Care* 2012;16:230. DOI: <http://dx.doi.org/10.1186/cc11345>
20. Tokarik M, Sjöberg F, Balik M, Pafcuga I, Broz L. Fluid therapy LiDCO controlled trial-optimization of volume resuscitation of extensively burned patients through noninvasive continuous real-time hemodynamic monitoring LiDCO. *J Burn Care Res* 2013;34:537-42. DOI: <http://dx.doi.org/10.1097/BCR.0b013e318278197e>
21. Yohannes S, Chawla LS. Evolving practices in the management of acute kidney injury in the ICU (Intensive Care Unit). *Clin Nephrol* 2009;71:602-7. DOI: <http://dx.doi.org/10.5414/CNP71602>
22. Grams ME, Estrella MM, Coresh J, Brower RG, Liu KD; National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Network. Fluid balance, diuretic use, and mortality in acute kidney injury. *Clin J Am Soc Nephrol* 2011;6:966-73. DOI: <http://dx.doi.org/10.2215/CJN.08781010>
23. Prowle JR, Echeverri JE, Ligabo EV, Ronco C, Bellomo R. Fluid balance and acute kidney injury. *Nat Rev Nephrol* 2010;6:107-15. DOI: <http://dx.doi.org/10.1038/nrneph.2009.213>
24. Bagshaw SM, Brophy PD, Cruz D, Ronco C. Fluid balance as a biomarker: impact of fluid overload on outcome in critically ill patients with acute kidney injury. *Crit Care* 2008;12:169. DOI: <http://dx.doi.org/10.1186/cc6948>
25. Bouchard J, Mehta RL. Fluid accumulation and acute kidney injury: consequence or cause. *Curr Opin Crit Care* 2009;15:509-13. DOI: <http://dx.doi.org/10.1097/MCC.0b013e328332f653>
26. Doty JM, Saggi BH, Sugerman HJ, Blocher CR, Pin R, Fakhry I, et al. Effect of increased renal venous pressure on renal function *J Trauma* 1999;47:1000-3. PMID: 10608524 DOI: <http://dx.doi.org/10.1097/00005373-199901000-00057>
27. Lazzeri C, Valente S, Tarquini R, Gensini GF. Cardiorenal syndrome caused by heart failure with preserved ejection fraction *Int J Nephrol* 2011;2011:634903. PMID: 21331316 DOI: <http://dx.doi.org/10.4061/2011/634903>
28. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, et al. Cardiorenal interactions: insights from the ESCAPE trial. *J Am Coll Cardiol* 2008;51:1268-74. DOI: <http://dx.doi.org/10.1016/j.jacc.2007.08.072>
29. Dalfino L, Siculo A, Paparella D, Mongelli M, Rubino G, Brienza N. Intra-abdominal hypertension in cardiac surgery. *Interact Cardiovasc Thorac Surg* 2013;17:644-51. DOI: <http://dx.doi.org/10.1093/icvts/ivt272>
30. Cheatham ML, Malbrain ML, Kirkpatrick A, Sugrue M, Parr M, De Waele J, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. II. Recommendations. *Intensive Care Med* 2007;33:951-62.
31. Prowle JR, Bellomo R. Fluid administration and the kidney. *Curr Opin Crit Care* 2013;19:308-14. DOI: <http://dx.doi.org/10.1097/MCC.0b013e3283632e29>
32. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl*. 2012;2:S1-138.
33. Severs D, Hoorn EJ, Rookmaaker MB. A critical appraisal of intravenous fluids: from the physiological basis to clinical evidence. *Nephrol Dial Transplant* 2014 Jan 23. [Epub ahead of print] DOI: <http://dx.doi.org/10.1093/ndt/gfu005>
34. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med* 1999;341:403-9. PMID: 10432325 DOI: <http://dx.doi.org/10.1056/NEJM199908053410603>
35. Aksu U, Bezemer R, Yavuz B, Kandil A, Demirci C, Ince C. Balanced vs unbalanced crystalloid resuscitation in a near-fatal model of hemorrhagic shock and the effects on renal oxygenation, oxidative stress, and inflammation. *Resuscitation* 2012;83:767-73. DOI: <http://dx.doi.org/10.1016/j.resuscitation.2011.11.022>
36. 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. *Ann Surg* 2012;256:18-24. PMID: 22580944 DOI: <http://dx.doi.org/10.1097/SLA.0b013e318256be72>
37. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012;308:1566-72. PMID: 23073953 DOI: <http://dx.doi.org/10.1001/jama.2012.13356>
38. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network; Wiedemann HP, Wheeler AP, Bernard GR, Thompson BT, Hayden D, deBoisblanc B, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006;354:2564-75. PMID: 16714767 DOI: <http://dx.doi.org/10.1056/NEJMoa062200>

39. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med* 2005;33:1681-7. PMID: 16096441 DOI: <http://dx.doi.org/10.1097/01.CCM.0000171539.47006.02>
40. Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis* 1992;145:990-8. PMID: 1586077 DOI: <http://dx.doi.org/10.1164/ajrccm/145.5.990>
41. Brandstrup B, Tønnesen H, Beier-Holgersen R, Hjortso E, Ørding H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003;238:641-8. PMID: 14578723 DOI: <http://dx.doi.org/10.1097/01.sla.0000094387.50865.23>
42. Vidal MG, Ruiz Weissner J, Gonzalez F, Toro MA, Loudet C, Balasini C, et al. Incidence and clinical effects of intra-abdominal hypertension in critically ill patients. *Crit Care Med* 2008;36:1823-31. DOI: <http://dx.doi.org/10.1097/CCM.0b013e31817c7a4d>
43. Adesanya A, Rosero E, Timaran C, Clagett P, Johnston WE. Intraoperative fluid restriction predicts improved outcomes in major vascular surgery. *Vasc Endovascular Surg* 2008;42:531-6. PMID: 18583299 DOI: <http://dx.doi.org/10.1177/1538574408318474>
44. McArdle GT, McAuley DF, McKinley A, Blair P, Hoper M, Harkin DW. Preliminary results of a prospective randomized trial of restrictive versus standard fluid regime in elective open abdominal aortic aneurysm repair. *Ann Surg* 2009;250:28-34. PMID: 19561485 DOI: <http://dx.doi.org/10.1097/SLA.0b013e3181ad61c8>
45. Arlati S, Storti E, Pradella V, Bucci L, Vitolo A, Pulici M. Decreased fluid volume to reduce organ damage: a new approach to burn shock resuscitation? A preliminary study. *Resuscitation* 2007;72:371-8. PMID: 17137702 DOI: <http://dx.doi.org/10.1016/j.resuscitation.2006.07.010>
46. Goldstein SL, Currier H, Graf Cd, Cosio CC, Brewer ED, Sachdeva R. Outcome in children receiving continuous venovenous hemofiltration. *Pediatrics* 2001;107:1309-12. DOI: <http://dx.doi.org/10.1542/peds.107.6.1309>
47. Goldstein SL, Somers MJ, Baum MA, Symons JM, Brophy PD, Blowey D, et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. *Kidney Int* 2005;67:653-8. PMID: 15673313 DOI: <http://dx.doi.org/10.1111/j.1523-1755.2005.67121.x>
48. Foland JA, Fortenberry JD, Warshaw BL, Pettignano R, Merritt RK, Heard ML, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. *Crit Care Med* 2004;32:1771-6. DOI: <http://dx.doi.org/10.1097/01.CCM.0000132897.52737.49>
49. Bouchard J, Soroko SB, Chertow GM, Himmelfarb J, Ikizler TA, Paganini EP, et al.; Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009;76:422-7.
50. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al.; Sepsis Occurrence in Acutely Ill Patients Investigators. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med* 2006;34:344-53. DOI: <http://dx.doi.org/10.1097/01.CCM.0000194725.48928.3A>
51. Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008;12:R74. DOI: <http://dx.doi.org/10.1186/cc6916>
52. de Almeida JP, Palomba H, Galas FR, Fukushima JT, Duarte FA, Nagaoka D, et al. Positive fluid balance is associated with reduced survival in critically ill patients with cancer. *Acta Anaesthesiol Scand* 2012;56:712-7. DOI: <http://dx.doi.org/10.1111/j.1399-6576.2012.02717.x>
53. Vaara ST, Korhonen AM, Kaukonen KM, Nisula S, Inkinen O, Hoppu S, et al.; The FINNAKI study group. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. *Crit Care* 2012;16:R197. DOI: <http://dx.doi.org/10.1186/cc11682>
54. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al.; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011;364:2483-95. PMID: 21615299 DOI: <http://dx.doi.org/10.1056/NEJMoa1101549>
55. Eyley RF, Mueller BA; Medscape. Antibiotic dosing in critically ill patients with acute kidney injury. *Nat Rev Nephrol* 2011;7:226-35. DOI: <http://dx.doi.org/10.1038/nrneph.2011.12>
56. 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. *Crit Care* 2004;8:R204-12.
57. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? *Crit Care Med* 2008;36:1129-37. DOI: <http://dx.doi.org/10.1097/CCM.0b013e318169181a>
58. Avila MO, Zanetta DM, Abdulkader RC, Yu L, Burdmann EA. Urine volume in acute kidney injury: how much is enough? *Ren Fail* 2009;31:884-90.
59. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: A systematic review. *Kidney Int* 2008;73:538-46. DOI: <http://dx.doi.org/10.1038/sj.ki.5002743>
60. Bichet DG. Urine Output in Diabetes Insipidus. In: Sterns RH, Forman JP, eds. *Up to Date*; 2013 [Accessed May 18 2014]. Available from: http://www.uptodate.com/contents/urine-output-in-diabetes-insipidus?source=search_result&search=Urine+Output+in+Diabetes+Insipidus.&selectedTitle=1%7E150
61. van Meurs M, Kumpers P, Ligtenberg JJ, Meertens JH, Molema G, Zijlstra JG. Bench-to-bedside review: Angiotensin signalling in critical illness - a future target? *Crit Care* 2009;13:207. DOI: <http://dx.doi.org/10.1186/cc7153>
62. van der Heijden M, Pickkers P, van Nieuw Amerongen GP, van Hinderberg VW, Bouw MP, van der Hoeven JG, et al. Circulating angiotensin-2 levels in the course of septic shock: relation with fluid balance, pulmonary dysfunction and mortality. *Intensive Care Med* 2009;35:1567-74. DOI: <http://dx.doi.org/10.1007/s00134-009-1560-y>
63. De Backer D, Donadello K, Taccone FS, Ospina-Tascon G, Salgado D, Vincent JL. Microcirculatory alterations: potential mechanisms and implications for therapy. *Ann Intensive Care* 2011;1:27. DOI: <http://dx.doi.org/10.1186/2110-5820-1-27>
64. Mulivor AW, Lipowsky HH. Inflammation- and ischemia-induced shedding of venular glycocalyx. *Am J Physiol Heart Circ Physiol* 2004;286:H1672-80. PMID: 14704229 DOI: <http://dx.doi.org/10.1152/ajpheart.00832.2003>
65. Chappell D, Jacob M, Hofmann-Kiefer K, Conzen P, Rehm M. A rational approach to perioperative fluid management. *Anesthesiology* 2008;109:723-40. PMID: 18813052 DOI: <http://dx.doi.org/10.1097/ALN.0b013e3181863117>
66. Dass B, Shimada M, Kambhampati G, Ejaz NI, Arif AA, Ejaz AA. Fluid balance as an early indicator of acute kidney injury in CV surgery. *Clin Nephrol* 2012;77:438-44. PMID: 22595385 DOI: <http://dx.doi.org/10.5414/CN107278>
67. Kambhampati G, Ross EA, Alsabbagh MM, Asmar A, Pakkivenkata U, Ejaz NI, et al. Perioperative fluid balance and acute kidney injury. *Clin Exp Nephrol* 2012;16:730-8. DOI: <http://dx.doi.org/10.1007/s10157-012-0623-5>
68. Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. *Pediatr Crit Care Med* 2014;15:131-8. DOI: <http://dx.doi.org/10.1097/PCC.0000000000000043>