Fluid management based on renal function considerations

Arunee Motes MD, Kenneth Nugent MD, Camilo Pena MD

ABSTRACT

Intravenous fluid administration is one of the most commonly used interventions in acutely ill patients. Almost all hospitalized patients receive intravenous fluids for either volume resuscitation or as diluents for drug administration. However, recent studies suggest that fluid overload is associated with acute kidney injury and that fluid administration beyond the volume needed to correct the fluid deficit is associated *with increased morbidity, longer hospital stays, and mortality. The exact cause and effect underlying this association remains uncertain. Previous studies have reported a correlation between fluid overload and mortality in critically ill patients with acute respiratory distress syndrome, acute lung injury, sepsis, and acute kidney injury. In patients with acute kidney injury, a higher percentage of fluid overload has been associated with higher mortality and shorter ventilator-free days starting during the initial management in the intensive care unit. Similarly, in a large multicenter study, a positive fluid balance was an important factor associated with increased 60-day mortality in patients with acute kidney injury. This review analyzes the use of intravenous fluids and renal function, including types of intravenous fluid, cumulative fluid targets, endpoint hemodynamic indicators, and renal replacement therapy for acute kidney injury.*

Keywords: volume status, intravenous fluids, fluid balance, acute kidney injury, volume excess

BASIC PRINCIPLES

Clinicians use intravenous (IV) fluid in clinical practice for three main reasons: to correct volume deficits, to replace electrolytes lost, and to maintain hemodynamic stability and tissue perfusion. The type of patient generally dictates different targets for fluid management; important factors include hydration status, compartmental distribution, and composition of the solution. Fluid distribution is a dynamic process in the human body. Approximately 57% of the total body water is in the intracellular space (approximately 3.6% in red blood cells, 43% in muscle, 7% in visceral organs, and 3.4% in others), approximately 43% is in the extracellular space (6.7% in plasma, 10% in bone and connective tissue, 3.8% in adipose tissue, and 20% in interstitial fluid), and approximately 2.5% is in transcellular fluid.[1]

Corresponding author: **Arunee Motes**
Contact Information: Arunee.Motes@ttuhsc.edu
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Previous studies have shown that fluid overload can be associated with acute kidney injury (AKI), and fluid administration beyond the correction of hypovolemia is *associated* with increased morbidity, longer hospital stays, and mortality.[2–5] Wang et al. analyzed the outcomes of 2526 patients admitted to 30 intensive care units in China and reported that fluid overload was an independent risk factor for the development of AKI and increased the severity of AKI. A higher cumulative fluid balance was an important factor associated with 28-day mortality following AKI.[6]

To evaluate body fluid status and optimize fluid balance in specific group of patients, such as heart failure patients, and patients in the ICU, the use of bioelectrical impedance analysis (BIA), bioelectrical impedance vector analysis (BIVA), and bioelectrical phase angle (PhA) have been studied. Bioelectrical impedance testing can estimate body composition and detects soft

tissue hydration with a 2–3% measurement error. This noninvasive test transforms electrical properties of tissues into clinical information. Bioelectrical impedance vector analysis measures whole body fluid volume and is based on patterns of the resistance-reactance graph, relating body impedance to body hydration. Clinical information on hydration is obtained through patterns of vector distribution in comparison to patients of the same race, gender, body mass index, and age. Changes in tissue hydration status below 500 ml are detected and ranked.[7] Chung et al. found that the use of BIA for volume status estimation is an easy and safe method for critical ill patients after surgery, and that overhydration with extracellular water ratio >0.390 on day 3 after operation was related to postoperative morbidity and in-hospital mortality occurrence.[8] A systematic review with meta-analysis by Lima et al. revealed that a low bioelectrical phase angle was associated with ICU length of stay (difference of 1.79 days) and mortality (increased risk of 1.89 times) while overhydration measured by BIVA was not associated with risk of death in critically ill patients.[9]

Type of fluid: crystalloid vs colloid

Fluid administration is a ubiquitous management strategy in medicine. The basic principles of fluid administration and distribution must be taken into consideration every time IV fluid is given to patients. Colloids will more than likely stay in the plasma volume for a longer period of time than crystalloids or dextrose solutions.[10] However, the physiological distribution of IV fluid is altered in diseased patients. Endothelial permeability is poorly understood during disease processes; an injured endothelial glycocalyx likely affects fluid distribution not only by the specific disease process but also by the type of fluid administered. Some of the best characterized examples are septic patients who received intravenous albumin; when followed over time in comparison to healthy subjects, albumin seems to remain in the intravascular space for less time and to extravasate faster.[11,12]

A multicenter, randomized controlled open labeled trial, Therapy in the Colloids Versus Crystalloids for the Resuscitation of the Critically Ill (CRISTAL), recruited 2857 ICU patients from February 2003 to August 2012, published in 2013, found that in ICU patients with hypovolemia, the use of colloids vs crystalloids did not result in a significant difference in 28-day mortality. However, the 90-day mortality was lower in patients receiving colloids.[13] In 2013, in a meta-analysis with 38 clinical trials with more than nine thousand patients, there was an association of the use of hydroxyethyl starch (HES) as the resuscitation IV fluid of choice with an increased risk of AKI (relative risk (RR) = 1.27; 95% confidence interval (CI) 1.09–1.47) and mortality (RR = 0.07; 95% CI 1.00–1.14) in ICU patients.[14]

More recently, the FLASH (Fluid loading in abdominal surgery: saline vs hydroxyethyl starch), a multicenter, double-blind, parallel-group, randomized controlled trial, published in 2020, with 775 surgical adult patients, reported no benefit in mortality outcomes when using the colloid solution and more kidney dysfunction within 14 days after surgery when HES vs. crystalloid IV fluid was used (22% vs 16%, RR = 1.34; 95% CI 1.00–1.80; P = 0.05).[15] Consequently, the use of colloid fluid provides no mortality benefit to patients and possibly increases the risk for acute kidney injury.

Type of crystalloid: lactated Ringer's versus normal saline

The two most commonly used crystalloids to hydrate or resuscitate patients in the clinical setting are normal saline and balanced solutions like lactated Ringer's solution. Even though normal saline has been widely used, there has been concern about whether it may be deleterious and inferior to lactated Ringer's solution since it has been associated with the higher frequency of hyperchloremic acidosis and oliguria in patients with diabetic ketoacidosis (DKA).[16–19] In recent randomized trials, lactated Ringer's was superior to normal saline in resolution of DKA (adjusted hazard ratio [aHR] = 1.68; 95% CI 1.18–2.38; P = 0.004).[16]

Despite promising results in DKA patients, it appears that in other critical care patients without DKA, the superiority of lactated Ringer's to normal saline may be less clear. In a multi-randomized clinical trial in critically ill patients in 75 ICUs in Brazil, which included 10,520 patients, there was no statistically significant difference between lactated Ringer's solution and normal saline and mortality rates (aHR = 0.97; 95% CI 0.90–1.05; P = 0.47).[20] Similarly, there

was no statistically significance in 30-day in-hospital mortality in the balanced crystalloid group in comparison to the saline group during the ICU-only period, but there might be a beneficial effect of balanced crystalloid primarily during management in the Emergency Department and ICU (odds ratio (OR) = 0.68; 95% CI 0.52–0.89; P = 0.07).[21] More recently, the multicenter PLUS Trial (Balanced Multi-electrolyte Solution Versus Saline in Critically Ill Adults) in Australia and New Zealand randomized 5,037 patients to either balanced electrolyte solutions or normal saline and found that at 90 days there was no difference in mortality (OR = 0.99; 95% CI 0.8–1.14) or renal outcomes (OR = 0.98; 95% CI 0.83–1.16).[22]

Several studies showed that the intravenous administration of balanced crystalloids rather than saline had a favorable effect on the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction. In a cluster-randomized, multiple-crossover trial, conducted in five intensive care units at an academic center, 15,802 adults received normal saline or balanced crystalloids (lactated Ringer's solution or Plasma-Lyte A). In the 7942 patients in the balanced crystalloids arm, 1139 (14.3%) had a major adverse kidney event; 1211 of 7860 patients (15.4%) in the saline arm (OR = 0.91; 95% CI 0.84–0.99; P = 0.04). In-hospital mortality at 30 days, the incidence of new renal replacement therapy and the incidence of persistent renal dysfunction were lower but not significantly different in the balanced crystalloid group.[23]

In patients undergoing elective orthopedic or colorectal surgery in the SOLAR TRIAL, 8,616 patients were included; 4,187 (49%) were assigned to lactated Ringer's solution, and 4,429 (51%) were assigned to saline. Each group received a median 1.9 liters (L) of fluid. There were no important differences in postoperative complications with lactated Ringer's or saline volume replacement. Therefore, either solution can be used during the intraoperative management of patients.[24] However, in non-critically ill hospitalized patients, lactated Ringer's solution was associated with lower rates of major adverse kidney events (new renal replacement therapy, death from any causes, persistent renal dysfunction) in comparison to normal saline (4.7% vs. 5.6%; adjusted OR = 0.82; 95% CI 0.70–0.95; P = 0.01), but the difference in hospital free-days was not significant (OR = 0.98; 95% CI 0.92–1.04; P = 0.41).[25]

In conclusion, the use of IV balanced crystalloids seems to have a favorable effect on the composite outcome of mortality, new renal-replacement therapy, or persistent renal dysfunction; however, mortality benefit in balanced crystalloids has mostly been seen outside the ICUs. More studies should be done with larger cohorts of critically ill patients to determine if there might be a statistically significant effect that may have an impact in this clinical setting.

Cumulative fluid targets

Targeting lower cumulative fluid balance in an attempt to change outcomes in critically ill patients is not a new idea. Albumin, for example, has been administered concurrently with crystalloid fluid in order to lower cumulative fluid balance. In 2014, Caironi et al. randomized more than 1800 patients with severe sepsis to receive either crystalloid solutions or 20% albumin and crystalloids with the intention of providing adequate intravascular and oncotic volume. Although the daily and mean cumulative fluid balance was lower in the albumin group than in the crystalloid-only group (347 mL vs. 1220 mL, P = 0.004), there was no difference in the rate of AKI (P = 0.11) or the need for renal replacement therapy (P = 0.71).[26] The result showed that adding albumin does not improve kidney outcomes even though the cumulative fluid balance was significantly lower.

Neyra et al. recruited 2,632 adult ICU patients with severe sepsis or septic shock, including 1,211 with chronic kidney disease and found that every 1-L increase in cumulative fluid balance at 72 hours of ICU admission was independently associated with hospital mortality in all patients (adjusted OR = 1.06; 95% CI 1.04–1.08; P < 0.001), and in each AKI/chronic kidney disease (CKD) subgroup. There was a significant interaction between AKI and CKD and cumulative fluid balance (p = 0.005), and different cumulative fluid balance cut-offs with the best prognostic accuracy for hospital mortality were identified, including 5.9 L for AKI patients with underlying CKD; 3.8 L for CKD patients with no AKI; 4.3 L for AKI patients with no underlying CKD; and 1.5 L for patients without AKI or CKD. This

study showed that higher cumulative fluid balances at 72 hours of ICU admission were independently associated with hospital mortality regardless of AKI or CKD status.[27]

The CLASSIC (conservative vs. liberal approach to fluid therapy of septic shock in the intensive care unit) trial focused specifically on the effect of the amount intravenous volume given by allocating 151 septic shock patients undergoing resuscitation to receive either a restricted approach and found significant differences in the amount of fluid given during the resuscitation efforts ($P < 0.001$), but no difference in the total cumulative balance during the ICU stay ($P = 0.6$). They also reported a significant reduction in worsening AKI in the fluid restriction group ($P = 0.03$), but no difference in mortality outcomes ($P = 0.32$).[28] In comparison, in 2023 the CLOVERS Trial (Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis) randomized 1,563 adults with sepsis and hypotension to receive in the first 24 hours of resuscitation either a liberal fluid resuscitation approach or a restricted fluid approach with the addition of early vasopressors to control the blood pressure. At 90-days they found no difference in mortality ($P = 0.61$), days free from ventilator use at day 28 (difference, 0.6; 95% CI-0.4-1.6), or days free from renal replacement therapy (difference, 0.2; 95% CI-0.8-1.2).[29]

In contrast, in 2018, the restrictive fluid approach was studied in the RELIF (restrictive versus liberal fluid therapy for major abdominal surgery) trial of 3000 patients undergoing major abdominal surgery. This trial showed that a restricted approach to IV fluid was associated with more AKI events than the liberal IV fluid regimen (8.6% vs. 5.0%, $P < 0.001$).[30]

The differences in these study results have increased the uncertainty about the best IV fluid regimen, and it remains unclear how much IV fluid critically ill patients should receive for optimal outcomes. Nevertheless, IV fluids need to be managed like any other prescription drugs. They are composed of different solvents and solutes and can be dosed in several different ways. When put in perspective, one liter of normal saline contains 154 mmol of sodium, which equals 9 grams of table salt, more than 2–3 times the daily recommended requirements. It has been documented in the literature that critically ill patients in the ICU might gain as much as 12 L of body water during the resuscitation period, requiring up to 3 weeks to excrete the positive fluid balance.[31]

What is the best endpoint?

Several studies have tried to determine the best hemodynamic indicator of AKI in the setting of critically ill patients such as those in septic shock. Most hemodynamic indicators, including mean arterial pressure (MAP), systolic arterial pressure (SAP), and diastolic arterial pressure (DAP), are not associated with higher rates of AKI. Among these studies, a retrospective study done in 137 ICU septic patients in 2006 that evaluated the previously mentioned parameters only demonstrated an association between AKI and higher central venous pressure (CVP) in septic shock patients suggesting renal venous congestion as a mechanism for disease.[32] However, a study done in vasopressor-dependent cardiovascular surgery patients did note a significant association between decreased MAP ($P = 0.027$), mean perfusion pressure (MPP) ($P = 0.023$), DPP ($P = 0.002$) and AKI.[33]

In a recent study in 2023, the prospective observational FINNAKI study that included 423 patients found that patients with progression of AKI had significantly lower time-adjusted MAP, 74.4 mmHg [68.3–80.8], than those without progression, 78.6 mmHg [72.9–85.4], $P < 0.001$. A cut-off value of 73 mmHg for time-adjusted MAP best predicted the progression to AKI. CKD, higher lactate levels, higher doses of furosemide, the use of dobutamine, and time-adjusted MAP below 73 mmHg were independent predictors of progression of AKI.[34]

Volume excess and acute kidney injury

Fluid accumulation in critically ill patients can have significant adverse consequences. A positive fluid balance, volume excess, and peripheral edema translate into internal organ edema (Table 1).[35] Organ perfusion pressure requires adequate blood volume, cardiac output (CO), and venous drainage. Venous congestion impairs venous drainage and leads to organ dysfunction. Perfusion pressure is equivalent to arterial

Table 1. Fluid Overload and Organ System Edema

Organ	Major Findings
Brain edema	Impaired mentation. Delirium.
Heart edema	Diastolic dysfunction. Impaired contractility. Conduction disturbance.
Lung edema	Increased work of breathing. Impaired gas exchange. Reduced compliance.
Liver edema	Cholestasis. Impaired function.
Renal edema	Increased renal venous and interstitial pressure. Reduced renal blood flow. Reduced glomerular filtration rate. Salt and water retention.
Gut edema	Ileus. Malabsorption.
Tissue edema	Impaired wound healing. Pressure ulceration.

pressure minus (compartment pressure plus venous pressure). Abdominal perfusion pressure (APP), which is MAP minus the intra-abdominal pressure, helps us understand how various complications, such as the abdominal compartment syndrome develop. Ongoing research has also shown that targeting an APP of more than 60 mmHg during resuscitation seems to improve organ function. MPP is equivalent to MAP minus CVP, which exemplifies how organ flow factors into venous pressure. Fluid resuscitation or fluid excess will increase CVP, which may be harmful in some patients. Some studies have shown that for each 1 mmHg increase in MPP above 60 mmHg, the risk of progression to acute kidney injury stage III decreases by 4.5%.[36–38]

Multiple studies have shown that excess fluid in ICU patients is an independent risk factor for the incidence of AKI and that cumulative positive fluid balance increases the risk of mortality. By treating excess fluid and restricting the cumulative positive fluid balance, better outcomes and recovery from AKI may occur.[27,39–44]

Acquired AKI: What is the best definition that has clinical consequences?

Acute kidney injury is defined as a deterioration of renal function in a period between 6 hours and 7 days. According to KDIGO guidelines, it is defined by at least an increase in 50% of creatinine measurements in 7 days, 0.3 g/dL in 48 hours, or oliguria (<0.5 mL/kg/hour) for at least 4 hours.[45] In a study of 178 children, elevated neutrophil gelatinase–associated lipocalin (NGAL) in comparison to elevated creatinine has been associated with increased risk of AKI at day 3 and an increased risk of AKI by four-fold, in comparison to patients with elevation of creatinine.[46]

Decreases and increases in serial creatinine measurements have been associated with the recovery and development of AKI, respectively. In a study done in 63 patients, a decreased in cystatin was associated with faster recovery of AKI in comparison to decline in creatinine measurements.[47] AKI tends to affect the tubules, while creatinine and urinary output are measurements that predicts glomerular function, which may not be altered until advanced tubular injury has occurred.[47] Also, it tends to underpredict AKI in patients with low muscle mass or receiving IV fluid.[47]

Time frame for de-escalation and the use of renal replacement therapy

The evolving conceptual models of resuscitation include four different phases: rescue, optimization, stabilization, and de-escalation. Early resuscitation and stabilization are key strategies for survival in critically ill patients.[48] The later phase of de-escalation becomes challenging as it is at this point when the patients have developed renal dysfunction and fluid overload. The management will mainly include pharmacological measures vs. extracorporeal measures or renal replacement therapy (RRT). Diuretics, as pharmacological measures, are widely used, non-invasive, less predictable, and have a risk of delay/failure to respond. Renal replacement therapy is invasive, requires specialist expertise, and may have unexpected outcomes, but allows controlled and predictable removal of plasma water and solutes.

Earlier institution of RRT in critically ill patients with AKI may improve survival. Better outcomes in patients treated with RRT were observed when RRT was started early in the course of the ICU stay. In the

Payen study, 3,147 patients were included; 1,120 (36%) had AKI at some point during their ICU stay. Sixty-day mortality rates were 36% in patients with AKI and 16% in patients without AKI ($P < 0.01$). Oliguric patients and patients treated with RRT had higher 60-day mortality rates than patients without oliguria or the need for RRT (41% versus 33% and 52% versus 32%, respectively; $P < 0.01$).[4] Consequently, the development of AKI has important effects on the outcomes in critically ill patients.

In a systematic review and meta-analysis published in 2011, with 15 studies, early compared with late RRT therapy was associated with a significant improvement in 28-day mortality (OR = 0.45; 95% CI 0.28–0.72). A subset of studies reported secondary outcomes; five studies (out of seven) reported greater renal recovery, seven (out of eight) studies reported decreased duration of RRT, and five (out of six) studies reported decreased ICU length of stay in the early, compared with the late RRT group. Early RRT did not significantly affect the odds of dialysis dependence beyond hospitalization (OR = 0.62; 95% CI 0.34–1.13, $I^2 = 69.6\%$).[49]

Conclusion

There is no question that excess IV fluid administration and net positive cumulative fluid balance can be harmful, and evidence suggests a correlation between them and increased renal dysfunction in hospitalized patients and critically ill patients. IV fluid requirements must be addressed continuously with titration and de-escalation based on continuously changing requirements, patient assessment, and homeostasis. Organ perfusion remains the goal of resuscitation when managing patients with failing circulations. Blood pressure determines the blood flow distribution but does not define the state of shock or the adequacy of circulation. There is no gold-standard test to determine organ perfusion and fluid status, and the clinician needs to use the different static (e.g., physical examination, CVP, CO, arterial wave analysis) and/or dynamic (e.g., passive leg raising, IV fluid responses, ventilatory changes) hemodynamic monitors available to assess the adequacy of perfusion. (Table 2). The use of bioelectrical impedance analysis, bioelectrical impedance vector analysis, and bioelectrical phase angle may be useful in the evaluation of body fluid status and help optimize fluid balance in specific groups of patients. The most recent study showed a cut-off value of 73 mmHg for time-adjusted MAP best predicted the progression of AKI, suggesting that her routine blood pressure measurements can provide important information.

Table 2. Common Invasive and Non-invasive Hemodynamic Monitor Systems

Invasive	Non-invasive
Central venous pressure	Physical examination
Continuous central venous oxygen saturation	Capillary refill
Pulmonary arterial catheters	Passive leg raising
Continuous cardiac output monitoring	Telemetry/Blood pressure monitoring
Transesophageal echocardiography	Bioreactance
Pulse pressure variation/Stroke volume variation	Near-infrared spectroscopy
Capillary microvasculature microscope	Plethysmography variability index

It is challenging to determine the optimal timing to begin de-escalation of IV fluid. Clinical and hemodynamic support stability might be the starting point, and mobilization of fluids with diuretics or mechanical therapies, such as renal replacement therapy to optimize the cumulative fluid balance needs to be considered, but restricting the fluid balance may provide better outcomes.

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References

1. Bhave G, Neilson EG. Body fluid dynamics: back to the future. J Am Soc Nephrol Dec 2011;22(12):2166–81. DOI: 10.1681/ASN.2011080865.
2. Hayashi Y, Shimazui T, Tomita K, et al. Associations between fluid overload and outcomes in critically ill patients with acute kidney injury: a retrospective observational study. Sci Rep 13, 17410 (2023). DOI: 10.1038/s41598-023-44778-0.
3. Alobaidi R, Morgan C, Basu RK, et al. Association between fluid balance and outcomes in critically ill children: A systematic review and meta-analysis. JAMA Pediatr 2018;172(3): 257–268. DOI: 10.1001/jamapediatrics.2017.4540.
4. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. Crit Care 2008;12(3):R74. DOI: 10.1186/cc6916.
5. Ostermann M, Straaten HM, Forni LG. Fluid overload and acute kidney injury: cause or consequence? Crit Care 2015 Dec 27;19:443. doi: 10.1186/s13054-015-1163-7.
6. Wang N, Jiang L, Zhu B, et al. The Beijing Acute Kidney Injury Trial (BAKIT) workgroup Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study. Crit Care 2015; 19:371. doi: 10.1186/s13054-015-1085-4.
7. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. BMC Nephrol 17, 109 (2016). https://doi.org/10.1186/s12882-016-0323-6.
8. Chung YJ, Kim EY. Usefulness of bioelectrical impedance analysis and ECW ratio as a guidance for fluid management in critically ill patients after operation. Sci Rep 11, 12168 (2021). https://doi.org/10.1038/s41598-021-91819-7.
9. Lima J, Eckert I, Gonzalez MC, et al. Prognostic value of phase angle and bioelectrical impedance vector in critically ill patients: A systematic review and meta-analysis of observational studies. Clinical Nutrition 2022;41(12):2801–16. https://doi.org/10.1016/j.clnu.2022.10.010.
10. Lobo DN. Fluid, electrolytes, and nutrition: physiological and clinical aspects. Proc Nutr Soc Aug 2004;63(3):453–66. doi:10.1079/pns2004376.
11. Myburgh JA, Mythen MG. Resuscitation fluids. N Engl J Med 2013;369(25):2462–3. doi:10.1056/NEJMc1313345.
12. Margarson MP, Soni NC. Changes in serum albumin concentration and volume expanding effects following a bolus of albumin 20% in septic patients. Br J Anaesth Jun 2004; 92(6):821–6. doi:10.1093/bja/aeh111.
13. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: The CRISTAL randomized trial. JAMA 2013;310(17):1809–1817. doi:10.1001/jama.2013.280502.
14. Zarychanski R, Abou-Setta AM, Turgeon AF, et al. Association of hydroxyethyl starch administration with mortality and acute kidney injury in critically ill patients requiring volume resuscitation: a systematic review and meta-analysis JAMA. Feb 2013;309(7):678–88. doi:10.1001/jama.2013.430.
15. Futier E, Garot M, Godet T, et al. effect of hydroxyethyl starch vs saline for volume replacement therapy on death or postoperative complications among high-risk patients undergoing major abdominal surgery: The FLASH randomized clinical trial. JAMA 01 2020;323(3):225–236. doi:10.1001/jama.2019.20833.
16. Self WH, Evans CS, Jenkins CA, et al. Pragmatic critical care research group. Clinical effects of balanced crystalloids vs saline in adults with diabetic ketoacidosis: A subgroup analysis of cluster randomized clinical trials. JAMA Netw Open 2020 Nov 2;3(11):e2024596. doi: 10.1001/jamanetworkopen.2020.24596.
17. Oh MS, Carroll HJ, Uribarri J. Mechanism of normochloremic and hyperchloremic acidosis in diabetic ketoacidosis. Nephron 1990;54:1–6.
18. Taylor D, Durward A, Tibby SM, et al. The influence of hyperchloraemia on acid base interpretation in diabetic ketoacidosis. Intensive Care Med 2006;32:295–301.
19. Chua HR, Venkatesh B, Stachowski E, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. J Crit Care 2012 Apr;27(2):138–45. doi: 10.1016/j.jcrc.2012.01.007.
20. Zampieri FG, Machado FR, Biondi RS, et al; BaSICS investigators and the BRICNet members. Effect of intravenous fluid treatment with a balanced solution vs 0.9% saline solution on mortality in critically ill patients: The BaSICS randomized clinical trial. JAMA. 2021 Aug 10;326(9):1–12. doi: 10.1001/jama.2021.11684.
21. Jackson KE, Wang L, Casey JD, et al. SMART Investigators and the Pragmatic Critical Care Research Group. Effect of early balanced crystalloids before ICU admission on sepsis outcomes. Chest 2021 Feb;159(2):585–595. doi: 10.1016/j.chest.2020.08.2068.
22. Finfer S, Micallef S, Hammond, N et al. Balanced multielectrolyte solution versus saline in critically ill adults. N Engl J Med 2022; 386:815–826. DOI: 10.1056/NEJMoa2114464.
23. Semler MW, Self WH, Rice TW. balanced crystalloids versus saline in critically ill adults. N Engl J Med 2018 May 17;378(20):1951. doi: 10.1056/NEJMc1804294.
24. Maheshwari K, Turan A, Makarova N, et al. Saline versus lactated ringer's solution: the saline or lactated ringer's (SOLAR) trial. Anesthesiology 2020 Apr;132(4):614–624. doi: 10.1097/ALN.0000000000003130.
25. Self WH, Semler MW, Wanderer JP, et al. SALT-ED Investigators. balanced crystalloids versus saline in noncritically

ill adults. N Engl J Med 2018 Mar 1;378(9):819-828. doi: 10.1056/NEJMoa1711586.

26. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. N Engl J Med Apr 2014;370(15):1412-21. doi:10.1056/NEJMoa1305727.

27. Neyra JA, Li X, Canepa-Escaro F, et al. acute kidney injury in critical illness study group. cumulative fluid balance and mortality in septic patients with or without acute kidney injury and chronic kidney disease. Crit Care Med 2016 Oct;44(10): 1891–900. doi: 10.1097/CCM.0000000000001835.

28. Hjortrup PB, Haase N, Bundgaard H, et al. Restricting volumes of resuscitation fluid in adults with septic shock after initial management: the CLASSIC randomized, parallel-group, multicentre feasibility trial. Intensive Care Med Nov 2016; 42(11):1695–1705. doi:10.1007/s00134-016-4500-7.

29. National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network, Shapiro NI, Douglas IS, et al. Early restrictive or liberal fluid management for sepsis-induced hypotension. N Engl J Med 2023;388(6):499-510. doi:10.1056/NEJMoa2212663.

30. Myles PS, Bellomo R, Corcoran T, et al. Restrictive versus liberal fluid therapy for major abdominal surgery. N Engl J Med Jun 2018;378(24):2263–2274. doi:10.1056/NEJMoa1801601.

31. Plank LD, Connolly AB, Hill GL. Sequential changes in the metabolic response in severely septic patients during the first 23 days after the onset of peritonitis. Ann Surg Aug 1998; 228(2):146–58. doi:10.1097/00000658-199808000-00002.

32. Wong BT, Chan MJ, Glassford NJ, et al. Mean arterial pressure and mean perfusion pressure deficit in septic acute kidney injury. J Crit Care 2015 Oct;30(5):975–81. doi: 10.1016/j.jcrc.2015.05.003.

33. Saito S, Uchino S, Takinami M, et al. Postoperative blood pressure deficit and acute kidney injury progression in vasopressor-dependent cardiovascular surgery patients. Crit Care 2016 Mar 24;20:74. doi: 10.1186/s13054-016-1253-1.

34. Poukkanen M, Wilkman E, Vaara ST, et al. FINNAKI Study Group. Hemodynamic variables and progression of acute kidney injury in critically ill patients with severe sepsis: data from the prospective observational FINNAKI study. Crit Care 2013 Dec 13;17(6): R295. doi: 10.1186/cc13161.

35. Prowle JR, Echeverri JE, Ligabo EV, et al. Fluid balance and acute kidney injury. Nat Rev Nephrol Feb 2010;6(2): 107–15. doi:10.1038/nrneph.2009.213.

36. Mohmand H, Goldfarb S. Renal dysfunction associated with intra-abdominal hypertension and the abdominal compartment syndrome. J Am Soc Nephrol Apr 2011;22(4):615–21. doi:10.1681/ASN.2010121222

37. Ostermann M, Hall A, Crichton S. Low mean perfusion pressure is a risk factor for progression of acute kidney injury in critically ill patients – A retrospective analysis. BMC Nephrol May 2017;18(1):151. doi:10.1186/s12882-017-0568-8.

38. Panwar R, Lanyon N, Davies AR, et al. Mean perfusion pressure deficit during the initial management of shock–an observational cohort study. J Crit Care Oct 2013;28(5):816–24. doi: 10.1016/j.jcrc.2013.05.009.

39. Wang N, Jiang L, Zhu B, et al. Workgroup BAKITB. Fluid balance and mortality in critically ill patients with acute kidney injury: a multicenter prospective epidemiological study. Crit Care Oct 2015;19:371. doi:10.1186/s13054-015-1085-4

40. Vaara ST, Ostermann M, Bitker L, et al. Restrictive fluid management versus usual care in acute kidney injury (REVERSE-AKI): a pilot randomized controlled feasibility trial. Intensive Care Med May 2021; doi:10.1007/s00134-021-06401-6.

41. Douglas IS, Alapat PM, Corl KA, et al. fluid response evaluation in sepsis hypotension and shock: a randomized clinical trial. Chest 10 2020;158(4):1431–1445. doi:10.1016/j.chest.2020.04.025.

42. Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. Br J Anaesth Nov 2014;113(5):740-7. doi:10.1093/bja/aeu300.

43. Finfer S, Myburgh J, Bellomo R. Intravenous fluid therapy in critically ill adults. Nat Rev Nephrol 09 2018;14(9): 541–557. doi:10.1038/s41581-018-0044-0.

44. Teixeira C, Garzotto F, Piccinni P, et al. NEFROlogia e Cura INTensiva (NEFROINT) investigators. Fluid balance and urine volume are independent predictors of mortality in acute kidney injury. Crit Care 2013 Jan 24;17(1):R14. doi: 10.1186/cc12484.

45. Levey AS. Defining AKD: The spectrum of AKI, AKD, and CKD. Nephron 2022;146(3):302–305. doi: 10.1159/000516647.

46. Stanski N, Menon S, Goldstein SL, et al. Integration of urinary neutrophil gelatinase-associated lipocalin with serum creatinine delineates acute kidney injury phenotypes in critically ill children. J Crit Care 2019 Oct;53:1–7. doi: 10.1016/j.jcrc.2019.05.017.

47. Wen Y, Parikh CR. Current concepts and advances in biomarkers of acute kidney injury. Crit Rev Clin Lab Sci 2021 Aug;58(5):354–368. doi: 10.1080/10408363.2021.1879000.

48. Ward MA, Kuttab HI, Tuck N, et al. The effect of fluid initiation timing on sepsis mortality: a meta-analysis. J Intensive Care Med 2022 Nov;37(11):1504–1511. doi: 10.1177/08850666221118513.

49. Karvellas CJ, Farhat MR, Sajjad I, et al. A comparison of early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury: a systematic review and meta-analysis. Crit Care 2011;15(1):R72. doi: 10.1186/cc10061.