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CKJ REVIEW

Intravenous fluid therapy in accordance with kidney injury risk: when to prescribe what volume of which solution

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ABSTRACT

Acute kidney injury (AKI) is common in hospitalized patients while common risk factors for the development of AKI include postoperative settings, patients with baseline chronic kidney disease (CKD) or congestive heart failure. Intravenous (IV) fluid therapy is a crucial component of care for prevention and treatment of AKI. In this narrative review, we update the approach to IV fluid therapy in hospitalized patients including the timing of fluid prescription, and the choice of fluid type, amount and infusion rate along with the potential adverse effects of various crystalloid and colloid solutions, addressing specifically their use in patients with acute kidney disease, CKD or heart failure, and their potential impact on the risk of hospital-acquired AKI.

Keywords: acute kidney injury, chronic kidney disease, colloid solution, crystalloid solution, intravenous fluid therapy

INTRODUCTION

Intravenous (IV) fluid therapy is a crucial component of critical care of hospitalized patients. Fluid replacement strategies, including the type and dose of fluid administered, are a crucial part of the hospitalized patient care, requiring a high level of clinical experience and knowledge since poor fluid management strategies may result in various complications including metabolic acidosis, electrolyte imbalances, acute kidney injury (AKI) or progression of chronic kidney disease (CKD), volume overload or dehydration, lung injury, imbalance between pro-inflammatory and anti-inflammatory signals, defects in tissue perfusion and tissue damage, all of which have been linked to significant morbidity and mortality along with longer hospital stay. In this narrative review, our aim is to update the approach to IV fluid therapy in hospitalized patients including the timing of fluid prescription, and the choice of fluid type, amount and infusion rate along with the potential adverse effects of various crystalloid and colloid solutions, addressing specifically their use in patients with AKI, CKD or heart failure, and their potential impact on the risk of hospital-acquired AKI. This narrative review is significant by addressing an important

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Table 1: Composition of the most commonly used IV fluids.

	0.9% saline	Lactated Ringer	Plasma-Lyte	5% Dextrose	Hartmanns's solution
Osmolarity (mOsm/L)	308	278	294	252	279
pH	4.5–7.0	6–7.5	7.4	4.0	
Sodium (mmol/L)	154	130	140		131
Chloride (mmol/L)	154	109	98		111
Glucose (g/L)				50	
Bicarbonate (HCO_3^-)	0	28 (lactate)			29 (lactate)
Potassium (mmol/L)	0	4	5		5
Acetate			28		
Calcium		4			4
Magnesium			3		
Common adverse effects	• Volume overload that may lead to brain edema, lung edema, compartment syndrome, cardiorenal syndrome and dilutional coagulopathy				
Solution-specific adverse effects	• Hyperchloremic metabolic acidosis • Dilutional hypokalemia and hypocalcemia	• Metabolic alkalosis • Metabolic acidosis in patients with poor tissue perfusion or liver failure • Coagulation of blood products when co-administered	• Acetate intoxication especially in dialysis patients	• Hyponatremia • Hyperglycemia	• Metabolic alkalosis • Metabolic acidosis in patients with poor tissue perfusion or liver failure • Coagulation of blood products when co-administered
Contraindications	None	Liver failure Cerebral edema	None	Cerebral edema Hyperglycemic states	Liver failure Cerebral edema

aspect of daily patient care in general wards and intensive care units.

FLUID THERAPY: STAGES AND OPTIONS

IV fluid therapy, using either crystalloid or colloid solution, is the most commonly prescribed therapy in hospitalized patients and, thus, the choice of the appropriate type and amount of fluid administered at an adequate rate are crucial. There are four stages of IV fluid therapy, although not all of them may be needed for all clinical settings [1]: the resuscitation phase, aiming to restore tissue perfusion in patients with hemodynamic instability and/or large total body volume loss; the replacement phase, aiming to restore physiological fluid and electrolyte balance in patients with either deficit or ongoing losses; the routine maintenance phase, aiming to maintain physiological fluid and electrolyte balance in patients unable to use the enteral route for fluid intake; and the redistribution phase, aiming to establish the physiological balance between intravascular and extravascular fluids especially in patients with poor intravascular fluid retention.

Crystalloid fluids can be classified into non-balanced fluids such as 0.9% normal saline or balanced fluids such as Ringer's lactate or Plasma-Lyte (Table 1). They share potential adverse effects of overdosing, such as hemodilution and, especially those containing sodium, hypervolemia; additionally, they have a fluid-specific safety profile dependent on their composition.

Normal saline (0.9% NaCl; i.e. 154 mmol/L Na and 154 mmol/L Cl, osmolarity 308 mOsm/L) is the most prescribed IV fluid therapy, with more than 200 million liters per year prescribed in the USA alone [2]. However, it is slightly hypertonic compared with plasma and has an acidic pH of 5.6 (4.5–7.0). As a consequence, administration of a large volume of normal saline has been linked to hyperchloremic metabolic acidosis, renal vasoconstriction and increased sensitivity to aldosterone]both of which lead to decline in estimated glomerular filtration rate (eGFR)], secretion of pro-inflammatory cytokines, and disruption of physiological coagulation pathways [3–5]. In healthy subjects, renal artery blood flow velocity and renal cortical tissue perfusion decreased following the administration of 2 L of normal saline but not following balanced crystalloids such as Plasma-Lyte 148, as evidenced by the association between plasma chlorine levels and mean renal artery flow velocity or renal cortical tissue perfusion [6, 7].

Ringer's lactate has been linked to hyperglycemia through the conversion of lactate into glucose via gluconeogenesis, lactic acidosis in patients with chronic liver disease secondary to its inability to convert lactate into bicarbonate, cerebral edema for its hypotonic nature, and chelation of calcium with citrate when administered with blood products and certain antibiotics such as ceftriaxone [2, 3, 8]. Similar chelation considerations should be considered in all solutions containing calcium, including Hartmann's solution [2, 3, 8]. Additionally, acetate-containing solutions have a potential to suppress myocardial contractility and cause hypotension, especially in patients undergoing renal replacement therapy; nevertheless, they undergo extrahepatic conversion and are therefore safe in patients with chronic liver disease [2, 3, 8].

Another important consideration in crystalloid fluid choice is the potassium content, especially in hyperkalemic patients or patients with acute kidney injury (AKI) or chronic kidney disease (CKD). However, studies have demonstrated no benefit of normal saline over balanced crystalloid solutions containing potassium, which may be attributable to the potential acidosis-mediated hyperkalemia observed in the normal saline group [9]. In this

regard, acidosis promotes exit of intracellular potassium to the extracellular space.

Glucose or dextrose (usually 5%–10%) solutions are sodium-free and do not contribute to hypervolemia. They contain a small number of calories (200 to 400 kcal/L for glucose and 170–340 kcal/L for dextrose) and in the presence of a conserved insulin response, will promote potassium entry into cells. However, they facilitate hyponatremia in patients with deficient water excretion mechanisms and may contain 3,4-dideoxyglucosone-3-ene (3,4-DGE), a glucose-degradation product which is cytotoxic to leukocytes and kidney cells [10–14].

Colloid fluids have now been rarely utilized in clinical practice including the care for critically ill patients, while the most commonly utilized colloid solutions include gelatin, dextrane, albumin and hydroxyethyl starch (HES). The use of semisynthetic colloid solutions has been associated with higher risk for AKI, need for renal replacement therapy or mortality among critically ill patients, which may be attributable to endothelial damage induced by colloid solutions which also explains the need for equal or higher amount of required resuscitation fluids compared with crystalloid solutions [15–18]. Another major adverse effect of colloid solutions is the high risk for anaphylaxis as shown by a large-scale multicenter study conducted over approximately 20 000 patients demonstrating anaphylaxis rates of 0.35% for gelatin, 0.10% for albumin and 0.06% for HES [19]. An exception to rare use of colloid solutions in clinical practice is the use of albumin solution in certain patient groups including patients with cirrhosis and hepatorenal syndrome or nephrotic syndrome [20, 21]. Administration of albumin in addition to crystalloid solutions has not been linked to improved survival in patients with sepsis, while the major limitation of its use in clinical practice is the high cost [20].

Fluid therapy may be monitored by various measures depending on the stage and the purpose of fluid therapy which may include blood pressure, heart rate, urine output, arterial blood gas analysis, serum electrolytes, cardiac output, physical examination findings and signs of ongoing fluid losses [22, 23].

FLUID MANAGEMENT STRATEGIES IN ACUTE KIDNEY INJURY

AKI, defined as an elevation of serum creatinine $\geq$0.3 mg/dL over a 48-h period or over 50% in a week or urine output $<$0.5 mL/kg/hour over a period of 6 h, affects approximately 20% of hospitalized adult patients according to a large-scale systematic review including a total of 49 million patients [24]. Assessment of the volume status of the patient is the key determinant of the fluid replacement strategy. Both the type of fluid and the rate of fluid replacement have consequences for clinical outcomes including the incidence of AKI. Both hypovolemia and increased fluid balance may cause AKI, the latter through increased central venous pressure and kidney congestion [25]. Thus, several randomized clinical trials have explored the optimal rate of fluid replacement. Restrictive fluid replacement mostly refers to restricting daily fluid input to medications and nutritional fluids, either parenteral or enteral, and aiming to achieve a negative fluid balance of $<$300 mL per day even with using diuretic therapy; nonetheless, fluid bolus therapy may be given in cases of clinical necessity. Restrictive versus liberal fluid replacement strategies were similar in terms of AKI incidence according to a randomized clinical trial using crystalloid fluids with interindividual differences on fluid choice with 100 patients with acute lung injury; however, following the correction of serum creatinine levels for fluid balance conservative fluid replacement strategy appears to be protective against AKI [26, 27]. In another randomized controlled trial conducted on 151 patients with septic shock, restrictive fluid therapy following the initial resuscitation period was less likely to cause AKI than standard care [28].

A single-center cross-over trial, conducted on 13 347 patients, assessing the difference between IV crystalloid solutions in patients treated first in emergency departments and subsequently in non-intensive care unit (ICU) hospital setting demonstrated that the use of balanced crystalloid fluids with lactated Ringer's solution or Plasma-Lyte A is associated with fewer major adverse renal events than normal saline, without differences in hospital-free days [29].

CRITICALLY ILL PATIENTS

Fluid replacement therapy is among the cornerstone therapeutic interventions in critically ill patients. Recent pre-clinical and clinical studies indicate that hyperchloremia may be encountered as a result of chloride-liberal fluid replacement strategy (e.g. normal saline), and cause hyperchloremic metabolic acidosis and renal vasoconstriction that may decrease eGFR and urine output in major surgeries, and prolong the time to first micturition [30–33]. However, few large-scale clinical trials have investigated the differences between various fluid replacement strategies in critically ill patients. In a multicenter, double-blind, cluster-randomized, double-crossover trial study conducted on 2278 ICU-admitted patients without baseline AKI requiring renal replacement therapy, no statistically significant difference was observed between balanced crystalloid fluids (Plasma-Lyte) or normal saline in terms of AKI development, need for renal replacement therapy or mortality within 90 days [34]. In contrast, a prospective, open-label, non-randomized study conducted on 1533 patients demonstrated that a chloride-restrictive fluid replacement strategy decreased AKI and the need for renal replacement therapy compared with a chloride-liberal strategy [35]. In another large-scale non-randomized, prospective cohort study on 53 448 patients with sepsis admitted to ICU, administration of balanced crystalloids such as lactated Ringer's solution was associated with lower risk of in-hospital mortality but did not decrease AKI or renal replacement therapy requirement when compared with non-balanced solutions including crystalloid fluids with strong ion difference of zero such as isotonic saline with or without 5% dextrose solution [36]. However, major limitations of the last two studies include removal of gelatin solution, a known risk factor for AKI, from the balanced crystalloid intervention and differences in the use of colloid solutions such as albumin between two intervention groups. Even though no statistically significant difference was observed in critically ill patients receiving either normal saline or balanced solutions in terms of renal adverse events [37], resuscitation with large volumes may result in higher risk of major renal adverse events when using normal saline than when using balanced solutions [38]. Additionally, a recent meta-analysis study on patients with sepsis conducted on 10 489 patients from two randomized controlled trials and five cohort studies concluded that risk for AKI was significantly lower in patients receiving balanced crystalloids (11.3%) compared with normal saline (12.7%) without differences in the need for renal replacement therapy or duration of ICU stay [39]. However, there was a beneficial effect of balanced crystalloids on mortality which may also be attributable to non-renal causes [39].

Moreover, a large-scale randomized, double-blind clinical trial conducted on 10 520 critically ill adults admitted to ICU use of balanced crystalloid fluids has not been linked to improvement in 90-day mortality, whereas another multicenter large-scale crossover clinical trial conducted on 15 802 critically ill adults demonstrated that the use of balanced crystalloid solutions is associated with lower risk of major adverse renal outcome (*P*-value: .04), renal replacement therapy (*P*-value: .08) and in-hospital mortality (*P*-value: .06) without any significant change in persistent renal dysfunction (*P*-value: .60) compared with normal saline in critically ill adults (Table 2) [40, 41].

There is some concern that hyperoncotic solutions may decrease GFR, although preclinical studies were not consistent in this regard [42]. Among 6997 ICU-admitted patients randomized to either 4% albumin solution or normal saline for 28 days, there was no statistically significant difference in terms of AKI, single or multi-organ failure, days on mechanical ventilation, need for renal replacement therapy and mortality [43]. However, in a multicenter prospective, non-randomized clinical trial conducted on 1013 ICU-admitted patients requiring fluid resuscitation for shock, administration of hyperoncotic colloids (odds ratio 2.48; 95% confidence interval 1.24–4.97) and hyperoncotic albumin/20% albumin solution (odds ratio 5.99; 95% confidence interval 2.75–13.08) were associated with higher risk for renal adverse events, including either doubling of serum creatinine or need for dialysis, than crystalloid fluids such as lactated Ringer's solution [44]. Five large-scale randomized controlled trials compared fluid resuscitation with normal saline versus albumin in critically ill patients and no differences were found in terms of renal outcomes [43, 45–48].

Another important aspect of the fluid resuscitation phase in critically ill patients is the target mean arterial blood pressure (MAP). In a multicenter controlled trial conducted on 2463 elderly (>65 years) septic patients admitted to ICU randomized either to permissive hypotension (MAP of 60–65 mmHg) or usual care, permissive hypotension was not linked to different mortality or need for renal replacement therapy [49]. However, milder degrees of AKI were not assessed [49]. Similar results were reported in other multicenter clinical trials; nevertheless, the impact of permissive hypotension may depend on baseline blood pressure, as higher rates of AKI and need for renal replacement therapy were observed in patients with chronic hypertension at baseline randomized to the permissive hypotension group [50, 51].

To conclude, we recommend the preferential use of balanced crystalloids rather than normal saline or colloid solutions for fluid replacement therapy in critically ill patients, with close monitoring of MAP, urine output, acid–base and electrolyte disturbances and signs of hypervolemia to adjust the infusion rate accordingly. The general approach strategy for critically ill patients' fluid management is shown in Fig. 1.

CONTRAST-INDUCED NEPHROPATHY

Contrast-induced nephropathy (CIN) may develop in patients with CKD that receive IV or intra-arterial iodinated contrast agents for imaging or therapeutic interventions. CIN may be prevented by administering 1 mL/kg/h hydration normal saline for 6–12 h both pre- and post-procedure unless the patient is already hypervolemic or receiving renal replacement therapy [52, 53]. For urgent procedures, a higher dose (3 mL/kg/h) may be infused 1 h prior to and 6 h post-procedure. Additional preventive measures include the use of low or iso-osmolality contrast material at the lowest possible dose and withdrawal of certain medications including metformin that may trigger adverse events (e.g. lactic acidosis) if accumulated because of AKI development. A large-scale meta-analysis study demonstrated no clinically significant beneficial effects of N-acetyl cysteine or sodium bicarbonate therapy compared with isotonic saline [54]. However, in CKD patients, short (1 h), low volume (250 mL) 1.4% sodium bicarbonate hydration before contrast-enhanced computed tomography was non-inferior to peri-procedural saline hydration with respect to renal safety and may result in healthcare savings [55].

INTRAOPERATIVE MANAGEMENT OF CKD PATIENTS

CKD is among the most common causes of death globally and affects approximately 15% of the adult population in the USA and an estimated 13.4% of the global population [56]. CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m^2 for 3 months or more, irrespective of cause [57]. Patients with CKD are prone to fluid and electrolyte imbalances and need to be monitored closely. Since fluid overload is common in patients with CKD, they are often prescribed diuretics rather than IV fluid infusions. However, they may require IV fluids for prophylaxis for contrast nephropathy, as described above, intraoperatively and during hypovolemic septic shock. CKD is associated with increased risk for AKI also during or following surgery [58]. Intraoperatively, usage of diuretics is discouraged due to their association with AKI development unless fluid overload is severe [59]. By contrast, fluid restriction during abdominal surgery was not associated with AKI development in a meta-analysis [60]. Type of fluid is at least as important as the amount of fluid. Hyperchloremia is associated with worsened eGFR at baseline [61]. A meta-analysis of 21 studies with 6253 patients confirmed that perioperative fluids containing high chloride concentrations increased the risk of hyperchloremia, metabolic acidosis and AKI [62]. The colloid HES has been associated with AKI, and the Critical Care Nephrology Working Group of the European Society of Intensive Care Medicine recommended avoiding high-molecular-weight HES preparations and the US Food and Drug Administration added a black box warning to the prescribing information recommending avoiding HES solutions in critically ill adult patients, including those with sepsis and in patients with pre-existing renal dysfunction, and discontinuing HES at the first sign of renal injury [18, 63, 64].

SEPTIC SHOCK IN PATIENTS WITH CKD

Patients with on hemodialysis are 100- to 300-fold more likely to have bacterial infections and septic shock and the risk is also increased in other patients with CKD [65]. The most recent Surviving Sepsis Guidelines recommends early, aggressive fluid resuscitation with 30 mL/kg crystalloid for hypotension within the first 3 h of suspected sepsis. They also suggest using balanced crystalloids rather than normal saline due to potential adverse effects that include hyperchloremic metabolic acidosis, renal vasoconstriction, increased cytokine secretion and concern about AKI [66]. These guidelines are not always applied to septic patients with end-stage renal disease (ESRD) due to fear of volume overload. In a retrospective study, resuscitation in ESRD patients with $\geq$30 mL/kg crystalloid was not associated with higher risk of volume overload than $<$30 mL/kg

Table 2: The basic characteristics of the major clinical trials comparing normal saline with other major balanced crystalloid solutions.

Study	Design	Participant characteristics	Fluids	Major outcome
Semler *et al.* (2018) [40]	Multicenter randomized multiple cross-over clinical trial	Balanced crystalloid group: N = 7942 (57.2% male) Median age: 58 years Baseline creatinine: 0.89 mg/dL Need for mechanical ventilation: 65.7% Need for vasopressor: 73.6% Normal saline group: N = 7860 (58.0% male) Median age: 58 years Baseline creatinine: 0.89 mg/dL Need for mechanical ventilation: 65.3% Need for vasopressors: 73.8%	Normal saline (median volume: 1020 mL) versus lactated Ringer's solution or Plasma-Lyte A (median volume: 1000 mL)	Use of balanced crystalloid solutions is associated with lower risk of major adverse renal outcome (*P*-value: .04), renal replacement therapy (*P*-value: .08) and in-hospital mortality (*P*-value: .06) without any significant change in persistent renal dysfunction (*P*-value: .60) compared with normal saline in critically ill adults
Self *et al.* (2018) [29]	Single-center multiple crossover clinical trial	Balanced crystalloid group: N = 6708 (47.7% male) Median age: 54 years Baseline creatinine: 0.84 mg/dL Normal saline group: N = 6639 (49.1% male) Median age: 53 years Baseline creatinine: 0.85 mg/dL	Normal saline versus lactated Ringer's solution or Plasma-Lyte A (median volume: 1079 mL)	Use of balanced crystalloid solutions is associated with lower risk of major adverse renal events within 30 days (*P*-value: .01) without any significant change in hospital-free days (*P*-value: .41) among non-critically ill adults
Zampieri *et al.* (2021) [41]	Randomized double-blind clinical trial	Balanced crystalloid group: N = 5230 (55.6% male) Mean age: 60.9 years Baseline creatinine: 1.2 mg/dL Normal saline group: N = 5290 (55.9% male) Mean age: 61.2 years Baseline creatinine: 1.2 mg/dL	Normal saline (mean volume: 4100 mL; mean volume at Day 1: 1500 mL) versus lactated Ringer's solution or Plasma-Lyte A (mean volume over 3 days: 2900 mL; mean volume at Day 1: 1500 mL)	Use of balanced crystalloid solutions has not been associated with better 90-day survival outcome (*P*-value: .47) compared with normal saline among critically ill adults
Finfer *et al.* (2022) [37]	Randomized double-blind controlled clinical trial	Balanced crystalloid group: N = 2515 (67.2% male) Mean age: 61.7 years Baseline creatinine: 1.44 mg/dL Normal saline group: N = 2522 (59.9% male) Mean age: 62.1 years Baseline creatinine: 1.42 mg/dL	Normal saline (median volume: 3900 mL) versus lactated Ringer's solution or Plasma-Lyte A (median volume: 3700 mL)	Use of balanced crystalloid solutions is not associated with lower risk of AKI, need for renal replacement therapy or 90-day mortality (*P*-value: .90) compared with normal saline group among critically ill adults
Raghunathan *et al.* (2014) [36]	Retrospective cohort study	Not applicable	Normal saline (median volume: 7000 mL) versus lactated Ringer's solution or Plasma-Lyte A (median volume: 5000 mL)	Use of balanced crystalloid solutions is associated with lower risk of in-hospital mortality compared with normal saline among critically ill adults with sepsis
Young *et al.* (2015) [34]	Randomized double-blind double-crossover clinical trial	Balanced crystalloid group: N = 1152 (64% male) Mean age: 60.1 years Baseline creatinine: 0.98 mg/dL Normal saline group: N = 1110 (67% male) Mean age: 60.95 years Baseline creatinine: 0.99 mg/dL	Normal saline (median volume: 2000 mL) versus lactated Ringer's solution or Plasma-Lyte A (median volume: 2000 mL)	Use of balanced crystalloid solutions is not associated with lower risk for AKI (*P*-value: .77), need for renal replacement therapy (*P*-value: .91) or in-hospital mortality (*P*-value: .40) compared with normal saline among ICU patients

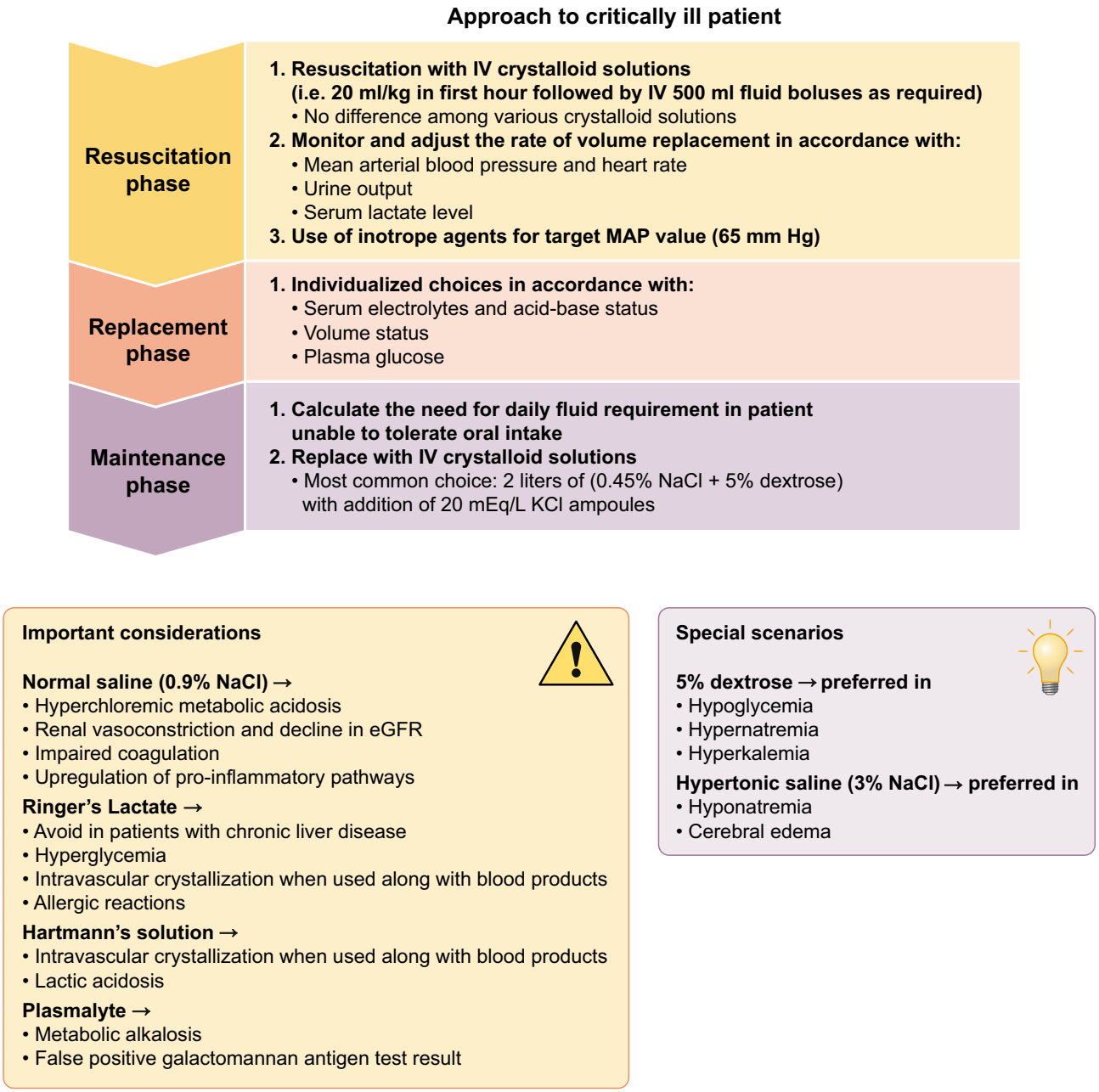

Figure 1: The approach for fluid replacement therapy in critically ill adults and important considerations in various solutions.

crystalloid. However, confounding by indication cannot be excluded, i.e. that lower volumes were administered to patients at higher risk of volume overload [67]. In another retrospective study of 104 ESRD patients with septic shock, fluid resuscitation with normal saline infusion or Ringer lactate was also safe [68]. However, so far chloride-liberal and chloride-restrictive IV fluids have not been compared in ERSD patients with septic shock. In any case, the available literature supports the safety of fluid resuscitation among ESRD patients with septic shock, and following the 2021 Surviving Sepsis guideline, balanced crystalloid fluids (≥30 mL/kg) are recommended in the first place alongside with the suggestion of invasive monitoring of arterial pressure over non-invasive monitoring for a higher accuracy.

HEART FAILURE PATIENTS

Heart failure is most commonly a chronic debilitating condition associated with high short and long term mortality and affects approximately 1.5% of the adult population in developed countries [69]. Optimal fluid management in patients with heart failure is key to preventing volume overload or depletion and to prevent and correct electrolyte disturbances. The American Heart Association recommends fluid restriction with 1.5–2 L per day especially in Stage D patients while the European Society of Cardiology recommends restriction of fluid intake of 30–35 mL/kg body weight in patients weighing >85 kg, and to administer this fluid preferably through the enteral route [70]. Despite such

general recommendations globally, the scientific evidence for fluid restriction in patients with heart failure is relatively weak. No difference in terms of readmission rates, duration of IV diuretic therapy, mortality rate, perceived thirst or serum sodium levels were detected in a large-scale meta-analysis of six randomized clinical trials totaling 751 patients with heart failure that were either on liberal or restrictive fluid management. Nonetheless, serum B-type natriuretic peptide (BNP) and creatinine levels along with AKI incidence were significantly higher in the liberal fluid group [71]. Similar findings were reported in another meta-analysis of six randomized controlled trials totaling 816 subjects [72]. Few randomized controlled trials report beneficial effects of fluid restriction of 1–1.5 L/day on renal function, though these studies have considerable limitations including low number of subjects, lack of actual fluid and salt intake data, which generates uncertainty regarding the adherence to therapy, multiple interventions simultaneously and which hampers the interpretation of results and inclusion of subjects from different heart failure classes [73–76].

FUTURE PERSPECTIVES

Even though the prescription of various types of IV crystalloid fluids is widespread in hospitalized patients for different purposes, none of them is without significant adverse effects. The search for better IV fluid replacement strategy and choice is far from concluded and multiple ongoing clinical trials are attempting to generate data that allows to define a definitive algorithm. These trials are enrolling participants with sepsis/septic shock (NCT03155126, NCT03277677), trauma (NCT03630224) or surgery (NCT02020538). Additionally, new IV fluid types are under development for specific purposes such as Oxsealife which has been assessed as a potential non-blood product resuscitation in hemorrhagic shock in pigs with comparable efficiency with blood products in terms of tissue oxygenation, metabolic parameters and perfusion [77]. Future large-scale randomized controlled trials are required in various patient populations for determining the best IV fluid therapeutic option in hospitalized patients for the different stages of IV fluid therapy and for the different contexts of use.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

AUTHORS' CONTRIBUTIONS

Contributed substantially to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work: S.C., B.M. and M.K. Drafted the work or revised it critically for important intellectual content: M.J.S., A.O. and M.K.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

CONFLICT OF INTEREST STATEMENT

A.O. has received grants from Sanofi and consultancy or speaker fees or travel support from Advicciene, Astellas, AstraZeneca, Amicus, Amgen, Fresenius Medical Care, GSK, Bayer, Sanofi-Genzyme, Menarini, Mundipharma, Kyowa Kirin, Alexion, Freeline, Idorsia, Chiesi, Otsuka, Novo-Nordisk, Sysmex and Vifor Fresenius Medical Care Renal Pharma, and is Director of the Catedra Mundipharma-UAM of diabetic kidney disease and the Catedra Astrazeneca-UAM of chronic kidney disease and electrolytes. A.O. is the former Editor-in-Chief of CKJ. M.K. is member of the CKJ Editorial Board. M.J.S. reports honorarium for conferences, consulting fees, and advisory boards from AstraZeneca, Novo Nordsik, Esteve, Vifor, Bayer, Mundipharma, Ingelheim Lilly, Jansen, Fresenius, ICU Medical, Travere Therapeutics, and Boehringer. M.J.S. also has received grants from Boehringer-Ingelheim. M.J.S. is Editor-in-Chief of CKJ.

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