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## Fluid Stewardship of Maintenance Intravenous Fluids

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### Abstract

Despite the frequent use of maintenance intravenous fluids (mIVF) in critically ill patients, limited guidance is available. Notably, fluid overload secondary to mIVF mismanagement is associated with significant adverse patient outcomes. The Four Rights (right drug, right dose, right duration, right patient) construct of fluid stewardship has been proposed for the safe evaluation and use of fluids. The purpose of this evidence-based review is to offer practical insights for the clinician regarding mIVF selection, dosing, and duration in line with the Four Rights of Fluid Stewardship.

### Keywords

critical care; stewardship; acute kidney injury; drug induced kidney injury; fluid therapy; maintenance fluid

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## Introduction

Intravenous fluids (IVF) are the most commonly prescribed medications in hospitalized patients.<sup>1,2</sup> Due to ubiquitous use and significant potential for patient harm, fluid stewardship has been proposed as a vital component for optimizing patient outcomes.<sup>3–11</sup> The Four Rights Construct of Fluid Stewardship proposes evaluation of the “right patient, right drug, right route, and right dose.”<sup>3</sup> The F<sub>2</sub>ASTHUGS BID mnemonic highlights fluid management as a necessary component of intensive care unit (ICU) care management: Feeding, *Fluids*, Analgesia, Sedation, Thromboembolic prophylaxis, Head of bed elevation, Ulcer prophylaxis, Glycemic control, Spontaneous breathing trial, Bowel Regimen, Indwelling catheter removal, and De-escalation of antibiotics.<sup>3,12</sup> The purpose of this review is to provide a concise yet informative discussion of the indication-specific use and monitoring of maintenance IVF (mIVF). Although resuscitation fluids represent a closely related area of interest in the realm fluid stewardship, the authors limit the scope of this review to maintenance fluids only, leaving resuscitation fluids to be reviewed in depth elsewhere.<sup>3</sup>

## Maintenance Fluids Overview

No standardized definition for mIVF exists. The National Institute for Health and Care Excellence (NICE) guidelines define mIVF as “IV fluids and electrolytes for patients who cannot meet their needs by oral or enteral routes” for patients who “are otherwise well in terms of fluid and electrolyte balance and handling.” This definition includes euvolemic patients and those without electrolyte abnormalities, ongoing fluid losses, or internal redistribution issues.<sup>13</sup> An algorithm for routine mIVF suggests 25–30 mL/kg/d in the average patient or lower requirements for patients who are obese, older, malnourished, or frail, or who have renal or cardiac impairment.<sup>14</sup> In contrast, a workgroup of the 12th Acute Dialysis Quality Initiative (ADQI) conference includes replacement fluids as a component of mIVF. This group defines mIVF more comprehensively as “fluid administration for the provision of fluids for patients who cannot meet their needs by oral route.” They state that mIVF “should be titrated to patient need and context and should include replacement of ongoing losses,” providing a dose of 1–2 mL/kg/h for patients without ongoing losses requiring replacement.<sup>15</sup> We propose that mIVF include any continuously infused IVF prescribed with the intention to provide enough fluid and electrolytes to meet insensible losses, maintain normal status of body fluid compartments, and enable renal excretion of waste products.<sup>13</sup> Notably, many patients are able to achieve these goals without mIVF. Table 1 reviews commonly used mIVF.<sup>13,16–18</sup> Specifically regarding balanced crystalloids, the authors acknowledge that several such crystalloids exist. While lactated Ringer’s (LR) and PlasmaLyte have been compared to chloride rich fluids, there is no evidence to suggest one balanced crystalloid over another. However, inferences can be made based on the ingredients in each of these balanced fluids. i.e. avoidance of LR in patients with advanced cirrhosis due to lactate accumulation, or avoidance of LR in the setting of hypercalcemia. In general, mIVF should be used for shortest duration possible with frequent monitoring to guide fluid composition, volume, and duration to avoid deleterious effects of fluid overload and acid-base and electrolyte disturbances. Monitoring parameters include hemodynamic

indices of fluid status, daily weight and fluid balance, and measurements of “hidden” fluid intake and are summarized in Table 2.

## Specific Indications for the Use of mIVF

### Burns

Patients with burn injuries often require significant fluid administration for both resuscitation and maintenance fluids. Burn injuries that cover greater than 20% of total body surface area (BSA) require particular attention due to intravascular volume depletion from the extravasation of plasma.<sup>41</sup> Although the fluid administration in these patients fits the definition of mIVF, it should be noted that this is also a prolonged resuscitative effort and thus is not a purely maintenance regimen. The Parkland and Brooke formulas may be used to estimate fluid requirements based on the size of the burn injury, but individual fluid requirements must be considered to adequately achieve euvolemia while also avoiding excessive fluid administration. The International Society of Burn Injuries suggests estimating fluid requirements by calculating 2–4 mL/kg/BSA%, to be administered within the first 24 hours of injury; however, these guidelines suggest this fluid be administered with “alertness to over-resuscitation.”<sup>41</sup> Arlati et al. found fluid administration may be safely reduced below Parkland formula recommendations if hemodynamic monitoring is performed with intrathoracic blood volume and cardiac output measurements. Through this invasive monitoring, the researchers noted patients tended to be unresponsive to fluid during the first 12 hours post-burn and hypothesized reducing initial administration rates might reduce post-burn edema formation. This “permissive hypovolemia” resulted in reduced organ dysfunction as measured by the multiorgan dysfunction scale (MODS).<sup>42</sup> Conversely, one retrospective study concluded restrictive fluid administration (defined as less than 4 mL/kg/%BSA) resulted in an increased risk of acute kidney injury (AKI) when adjusted for burn injury severity.<sup>43</sup> However, AKI was defined as an absolute serum creatinine greater than 1.5 mg/dL at any time during hospitalization, rather than utilizing time sensitive criteria or measuring change in renal function with reference to a baseline value. Notably, the restricted fluid resuscitation group also experienced lower rates of acute respiratory distress syndrome, infection, and shorter hospital length of stay. More study is warranted before strongly advocating such a practice; however, if invasive hemodynamic (e.g., cardiac index) monitoring is available, initiating therapy using the lower end of the range (i.e., 2 mL/kg/%BSA) to maintain a cardiac index of at least 2.2 L/min/m<sup>2</sup> is likely reasonable. In the absence of invasive hemodynamic monitoring, we recommend adherence to the Parkland Formula of 4 mL/kg/%BSA titrated to maintain average urine output (UOP) of 0.3–0.5 mL/kg/hr over the first 24 hours.<sup>41</sup> Given the potential large fluid volumes, we give preference to the use of a balanced crystalloid such as LR over isotonic saline, which is consistent with the recommendations of the original Parkland Formula.<sup>44</sup> Additional maintenance fluids totaling approximately 2 liters/day may be required during the acute duration of burn management and should be given enterally if possible.<sup>45</sup> Although the duration of this maintenance fluid requirement is not well defined, it is reasonable to continue until the patient is able to participate in volitional oral intake.

## Contrast-associated AKI

Contrast-associated AKI (CA-AKI) is defined as a 50% increase in creatinine from baseline within 7 days, an increase by 0.3 mg/dL within 48 hours, or urine output (UOP) <0.5 mL/kg/hr for at least 6 hours after exposure to contrast media.<sup>46</sup> CA-AKI has been cited as the third leading cause of in-hospital AKI and may or may not be reversible.<sup>47</sup> Studies assessing the efficacy of acetylcysteine and statins in preventing CA-AKI have shown conflicting results, leaving the administration of IVF the treatment of choice; however, a lack of consensus for fluid choice and dose remains.<sup>48-51</sup>

While studies addressing the most appropriate choice of IVF are limited, isotonic saline and NaHCO<sub>3</sub> have been studied most often.<sup>52</sup> Isotonic saline has shown to be better than hypotonic saline at preventing CA-AKI (0.7% vs. 2.0%, p=0.04).<sup>53</sup> However, the proposed benefit of alkalinization of tubular fluid to inhibit free radical formation has not been consistently demonstrated.<sup>49,54</sup> Limitations to many of these studies include the heterogeneous patient groups, definition of 'high risk,' volume of contrast received, and route of contrast administration (arterial vs. venous). Co-morbidities could also play a role in determining volume to administer; dosing based on underlying cardiac dysfunction reduced the rate of AKI in one study (6.7% vs. 16.3%; p=0.005).<sup>55</sup>

Hydration with isotonic crystalloid is preferred for the prevention of CA-AKI, but only in those patients deemed at high risk, so patient selection is key (i.e., those with risk factors including pre-existing kidney disease, high-osmolarity contrast agents, volume of contrast, and intra-arterial administration).<sup>56,57</sup> Use of any isotonic crystalloid is reasonable, but more research is warranted to explore the efficacy and safety of balanced solutions. The most effective and conservative dosing strategy of IVF should be used in all high-risk patients. Pre-exposure hydration with up to 3 mL/kg/hr for one hour followed by intra- and post-exposure hydration with 1 –1.5 mL/kg/hr for four to six hours is a practical starting point. Patients receiving intra-arterial contrast (e.g., coronary angiography) may require a different hydration regimen than those receiving intravenous contrast. Dose reductions for patients at higher risk of fluid overload, including critically ill patients, those receiving mechanical ventilation, or those with reduced cardiac function should be considered. A weight-based dose cap of 125 kg may also provide additional safety benefits.<sup>49</sup> Lastly, the risk of CA-AKI is limited to a relatively short period of time following contrast exposure. It is important to consider that contrast has no proven causation of AKI, only association thus warranting scrutiny of the true benefit to risk profile for prophylactic fluid therapy. CA-AKI epidemiology studies are littered with confounding variables and selection biases. The true incidence of CA-AKI is likely much lower than what is reported, but there is a stronger association and physiologic rationale for AKI after intra-arterial administration.<sup>58</sup> When treatment is warranted, determining finite dosing and including stop dates with IVF orders could help limit overprescribing and unwanted effects of IVF.

## Drug Overdose

Patients presenting with a toxic ingestion can display signs and symptoms that may warrant resuscitation with IVF, such as vomiting and hypotension. Use of mIVF after initial fluid resuscitation in the management of a drug overdose is driven by continued fluid losses

(e.g., gastrointestinal or insensible losses), cases in which specific drug elimination may be enhanced (e.g., aspirin), or reversible complications from a toxic exposure (e.g., tricyclic antidepressants).<sup>59</sup> Few studies support the use of IVF and/or diuretics for volume loading to promote a forced diuresis through achieving a urinary flow rate of 3–6 mL/kg/hr; therefore, we only recommend the use of mIVF to enhance drug elimination through increasing urinary pH or as an antidote for specific poisonings.

**Aspirin:** Renal elimination of salicylates is significantly increased through urinary alkalinization, defined as a urine pH > 7, and is much more dependent on urine pH than flow rate.<sup>60</sup> This alkalinization is typically achieved through administration of 100 mEq of NaHCO<sub>3</sub> in 1 liter of D5 W infused over 3 hours in adults or at a rate of 2 mL/kg/hr in children. The infusion rate should be titrated based on hourly urinary pH results to achieve a target pH of 7.5–8.5. Adjustments to the NaHCO<sub>3</sub> infusion should not be based on blood gas values. Complications of urinary alkalinization include alkalemia, volume overload, hypernatremia, and hypokalemia. Notably, hypokalemia is concerning as it will prevent urine alkalinization and increases risk of alkalemia. The addition of 20–40 mEq of potassium chloride to the mIVF is commonly required to maintain a potassium level of 4–4.5 mEq/L. Acetazolamide should not be used to alkalinize urine as the risk for metabolic acidosis can increase salicylate toxicity.<sup>59</sup> To minimize unnecessary fluid administration, salicylate levels should be assessed every 3 hours until a peak concentration is reached. Treatment should continue until plasma salicylate concentrations decrease back into the therapeutic range and the patient is asymptomatic.<sup>60</sup> If the severity of toxicity necessitates renal replacement therapy (RRT), NaHCO<sub>3</sub> infusion should only be considered as a bridge to initiation of RRT. In patients with metabolic acidosis not requiring RRT (pH < 7/3), a bolus dose of 1 mL/kg of 8.4% NaHCO<sub>3</sub> may be administered with a goal of increasing the pH to 7.4.<sup>60</sup>

**Tricyclic Antidepressants:** Because tricyclic antidepressants (TCA) act to block alpha-adrenergic receptors and have antic-holinergic properties, patients presenting with a TCA overdose may exhibit symptomatology for which the use of bolus and/or mIVF are indicated, (e.g., vasodilation, hypotension, dry mouth, and hyperthermia) despite a lack of high quality evidence to support this practice. Management of hemodynamic instability due to TCA overdose should follow general fluid resuscitation principles. Furthermore, patients who experience hypotension or dysrhythmias due to sodium-channel blocking activity of TCAs are at high risk for complications; thus, intervention with isotonic saline or alkalinization with NaHCO<sub>3</sub> is indicated for these patients. Additionally, patients who display QRS prolongation of > 100 msec or R/S ratio > 0.7 in aVR on electrocardiogram (ECG) may also benefit from NaHCO<sub>3</sub> therapy.<sup>61</sup> When indicated, NaHCO<sub>3</sub> therapy is typically administered as an initial dose of 50–100 mL 8.4% NaHCO<sub>3</sub> then as a continuous infusion titrated to achieve a serum pH between 7.45–7.55 and/or a QRS < 100 msec on serial ECG recordings.<sup>62</sup> Treatment should continue until patients are asymptomatic with no significant ECG abnormalities for 6 hours.<sup>61</sup>

## Drug-induced Acute Kidney Injury

Administering IVF for certain medications to help attenuate nephrotoxicity risk is often required.

**Amphotericin:** Nicknamed “amphoterrible” due to its adverse effect profile including nephrotoxicity, amphotericin B remains the antifungal of choice for specific infections such as cryptococcal meningitis. Liposomal amphotericin B is often recommended over traditional dosage forms to decrease overall risk of AKI. The role of fluids with amphotericin administration to decrease nephrotoxicity risk is ambiguous. Hydration with 500–1000 mL isotonic saline pre-infusion is suggested to decrease nephrotoxicity risk, yet overall data are lacking regarding beneficial outcomes.<sup>63</sup> Current manufacturer recommendations from traditional amphotericin products (e.g., amphotericin deoxycholate) state that hydration and sodium repletion “may” reduce nephrotoxicity risk.<sup>64</sup> However, manufacturers of amphotericin B lipid complex and liposomal formulations do not specifically recommend pre-hydration to decrease risk.<sup>65,66</sup> Amphotericin products should not be administered with any saline product due to incompatibilities. Additionally, any line that will be used to administer amphotericin B should be flushed with D5 W instead of saline due to incompatibility risk. A recent national survey of pharmacists demonstrated inconsistency in both amount and frequency of administration of IVF with amphotericin therapy, with 67.7% of respondents using IVF to attempt to mitigate risk of AKI.<sup>67</sup> More data are required to better ascertain nephrotoxicity risk with current fluid recommendations and amphotericin B (both conventional and liposomal). Until definitive data demonstrate a decrease in nephrotoxicity risk, pre-hydration should be limited to traditional formulations of amphotericin B.

**Foscarnet:** Overall data on decreasing nephrotoxicity risk with IVF remain sparse with foscarnet. The manufacturer recommends 750 mL to 1000 mL of D5 W or isotonic saline to be administered prior to initial infusion to promote diuresis.<sup>68</sup> For most patients, isotonic saline should be chosen over D5 W unless the patient is exhibiting hypoglycemia due to concern for capillary leak of D5 W. The same dose of IVF is recommended to be repeated with subsequent infusions of 90–120 mg/kg. If doses are between 40–60 mg/kg, a reduced volume of 500 mL is recommended. The first dose of fluid should be given prior to initiation of foscarnet, and subsequent fluid administration should be given concomitantly with foscarnet. Hydration fluid volume may be decreased if clinically warranted for patients with volume overload, but specific guidance is not provided by the manufacturer.<sup>68</sup>

**Acyclovir:** In critically ill patients, IV acyclovir is used most often for the empiric or definitive treatment of herpes simplex virus encephalitis. The high doses used (10 mg/kg IV q8 h for normal renal function) are a known cause of AKI due to crystal nephropathy.<sup>69</sup> Switching patients to oral valacyclovir to limit the risk of AKI may be possible when intravenous dosage forms are not available, but outcome data are limited.<sup>70</sup> Additionally, due to weight-based dosing, obesity has been demonstrated to be an independent risk factor for nephrotoxicity.<sup>71</sup> Consequently, some experts have recommended dosing of acyclovir on ideal body weight, especially in morbidly obese patients.<sup>72</sup> If IV acyclovir is required for administration, the manufacturer recommends “adequate” hydration, which is not well

defined.<sup>73</sup> In one single center retrospective study, AKI occurred in nearly 20% of patients receiving IV acyclovir.<sup>74</sup> Per the RIFLE criteria, these patients were stratified by severity with 62% Risk, 15.6% Injury, and 21.6% Failure. Total drug dosage, duration of therapy, type of infusion fluid, or hydration amount were not associated with increased risk of AKI. The use of vancomycin and nonsteroidal anti-inflammatory drugs, presence of diabetes, and increased weight were all associated with elevated AKI risk. Patients at this facility received slower acyclovir infusions, hydration per institutional protocol (1 mL/kg/hr with primarily isotonic saline), and dose adjustments in renal dysfunction, which may have contributed to lower rates of AKI than previously reported. External validity may be limited due to single center nature, non-obese population, and lack of urine output data.

### **Subarachnoid Hemorrhage and Traumatic Brain Injury**

mIVF are frequently indicated in patients with brain injury to balance fluid shifts and maintain cerebral perfusion.<sup>75</sup> Isotonic crystalloids are recommended to maintain euvolemia, though a generalizable rate of mIVF is not well described.<sup>76</sup> Unfortunately, euvolemia is not easy to define. To assist with this assessment, guidelines offer direction in the appropriate use of invasive and noninvasive monitoring parameters.<sup>76–78</sup> One author proposed a general weight-based rate of 30–40 mL/kg/hr, suggesting the rate should begin at 40 mL/kg/hr to target a net volume gain of 0–500 mL/day with isotonic saline as the preferential fluid.<sup>75</sup> Initiating mIVFs at this rate in the brain-injured critically ill population is likely an appropriate initial therapy, while assessment of volume status throughout the patient's hospitalization is necessary to prevent adverse events which may occur with hypervolemia or hypovolemia.<sup>76</sup> Hypertonic fluid may be warranted based on patient specific factors (e.g., symptoms serum sodium<sup>79</sup>), but hypotonic fluid should be avoided due to concern for worsening brain edema. Generally, 0.9% NaCl is given preference, as it has the highest osmolarity and sodium content of the widely used isotonic crystalloids. Combining equal quantities of NaCl and sodium acetate to create an isotonic fluid will provide a fluid with sodium content equal to that of 0.9% NaCl and lower chloride content, which minimizes risk of hyperchloremia.<sup>80</sup> Duration of fluid administration is not well-defined but careful monitoring and titration should generally be performed until the acute phase of the bleeding or injury is resolved.

### **High Output Fistula**

For patients with ongoing fluid losses requiring replacement, the site of loss is relevant for determining the appropriate replacement fluid with different sections of the gastrointestinal (GI) tract having different concentrations of sodium, potassium, chloride, bicarbonate, and other electrolytes.<sup>13</sup> As such, sodium, potassium, chloride, and bicarbonate are usually necessary to replace gastrointestinal losses; however, data regarding optimal fluids for high output fistula are lacking.<sup>81</sup> Thus, Clinical decisions regarding fluid choice center around laboratory testing evaluating the specific electrolyte abnormalities present in that patient to dictate fluid composition and generally target a net neutral daily balance.<sup>82,83</sup> Losses from other gastrointestinal sites including severe vomiting and diarrhea warrant similar management (i.e. replacement of lost electrolytes as determined by careful laboratory monitoring).<sup>14</sup> The resulting acid-base disturbances caused by gastrointestinal fluid losses will be corrected by replenishing electrolytes through appropriate fluid selection.<sup>84</sup>

## Hyperglycemic Crises

IVF therapy is a mainstay treatment in both diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar state (HHS) to correct volume deficits, restore tissue perfusion, and reduce insulin resistance.<sup>85,86</sup> Severe hypernatremia may also develop as a byproduct of treatment of hyperglycemia, which requires adequate administration of free water to prevent possible neurologic complications. Adequate administration of mIVF in patients with HHS may be of particular importance as neurologic improvement may be seen with correction of fluid deficits.<sup>85</sup> While the benefits of mIVF administration in DKA and HHS are clear, the choice of fluid remains controversial. Conflicting data exist comparing hypotonic, isotonic, and hypertonic fluid administration in patients with DKA with regards to amount of fluid retained; however, some data suggest hypertonic fluids may be harmful due to worsening hyperosmolarity, hypernatremia, and hyperchloremia.<sup>87</sup> Additionally, hypotonic fluids may induce diuresis that can be harmful in patients presenting with severe dehydration.<sup>86</sup> Further, while crystalloids are preferred, the optimal crystalloid fluid is less clear. Two studies with a small number of patients found beneficial effects using a balanced crystalloid compared with isotonic saline related to prevention or correction of metabolic acidosis, but no difference in clinical outcomes.<sup>88,89</sup> Another small study comparing isotonic saline to a balanced solution found no difference in normalization of acidosis and a longer time to attain target blood glucose in the LR group.<sup>90</sup> Current practice in DKA management is to administer isotonic saline at an initial rate of 15–20 mL/kg/h or 1–1.5 L in the first hour, followed by 0.45% NaCl at 250–500 mL/h in patients with eunatremia or hypernatremia or continue isotonic saline at the same rate in patients with hyponatremia.<sup>85,91</sup> Rate of hydration should be guided by similar principles discussed previously. When plasma glucose levels are below 200 mg/dL or 300 mg/dL for DKA and HHS respectively, the addition of dextrose, as 5% or 10%, should be initiated to prevent hypoglycemia during ongoing insulin administration until ketonemia has resolved.<sup>86</sup>

## Hyponatremia

Potential etiologies of hyponatremia are numerous, and treatment varies according to both severity of the hyponatremia and the volume status of the patient.<sup>92</sup> The use of urine electrolytes and urine osmolarity are useful in the delineating the etiology of hyponatremia. For example, in the absence of diuretics or other medications which induce natriuresis, urine sodium >20–30 mmol/L in the hyponatremic patient often indicates euvolemic hyponatremia. A urine osmolarity >100 mOsm/kg along with elevated urine sodium concentration would support a diagnosis of SIADH.<sup>93–95</sup> In many cases, use of mIVF is not necessary to correct hyponatremia and may even be harmful. In patients with symptomatic hyponatremia, guidelines recommend the use of 3% NaCl given as a bolus dose of 100–150 mL over 10–20 minutes or infused at 0.5–2 mL/kg/hr regardless of acute or chronic onset.<sup>94,96</sup> A bolus strategy is proposed as safe and effective in quickly reducing brain edema and reducing or eliminating symptoms.<sup>97</sup> Following symptom resolution, a continuous infusion of isotonic saline is appropriate in hypovolemic hyponatremia until euvolemia is restored.<sup>94,96</sup> If a continuous infusion is utilized, the rate may be determined by the Adrogue-Madias equation:<sup>92</sup>



$$\text{Change in serum } Na^+ = \frac{\text{Infusate } Na^+ - \text{serum } Na^+}{\text{Liters of total body water} + 1}$$

This method may underestimate the actual rate of correction and should be used cautiously with appropriate monitoring of serum sodium and urine output.<sup>92,98</sup> In patients with asymptomatic hyponatremia, the urgency is lower, and 3% NaCl is generally unnecessary. In patients with hypovolemic hyponatremia, a continuous infusion of 0.9% NaCl may be used with doses guided by the Adrogue-Madias equation or at a rate of 0.5–1 mL/kg/hr.<sup>94,96</sup> Alternatively, patients with euvolemic or hypervolemic hyponatremia should not be treated with mIVF and instead should be treated with fluid restriction, loop diuretics, oral NaCl tablets, or vasopressin receptor antagonists based on underlying cause. In all cases of hyponatremia, etiology should be determined following urgent symptom management, and treatment should be directed accordingly. Monitoring for all patients should include frequent assessment of serum sodium concentration with a goal increase of approximately 8 mEq/L in 24 hours. Although the maximum increase generally recognized to be safe is 10–12 mEq/L per 24 hours, we suggest the goal should be below this maximum to reduce the risk of overcorrection.<sup>92</sup> We recommend the use of continuous IVF infusion for hyponatremia only as a means of restoring euvoolemia while simultaneously correcting sodium at an appropriate rate. Fluid administration should be discontinued when euvoolemia and eunatremia are restored.

### Hypernatremia

Hypernatremia is generally caused by hypovolemia, although hospitalized patients may develop iatrogenic hypernatremia due to excessive sodium administration.<sup>93</sup> Hypovolemic hypernatremia warrants treatment with mIVF. As in hyponatremia, cautious correction is necessary in most cases to prevent brain edema.<sup>99</sup> Adrogue and Madias suggested two equations which may be helpful for the treatment of hypernatremia: the previously mentioned equation to predict rate of correction by one liter of fluid and an equation to determine total body deficit:<sup>93</sup>

$$\text{water deficit} = \text{Liters of total body water} \times \left(1 - \frac{140}{\text{serum sodium concentration}}\right)$$

These equations may be used to guide duration and rate of fluid administration. Fluid replacement in hypovolemic hypernatremia with 0.45% NaCl or D5 W is recommended, unless the patient is hemodynamically unstable, in which case 0.9% NaCl should be used until hemodynamic stability has been restored.<sup>100,101</sup> To prevent overcorrection of sodium, 0.45% NaCl may be preferable over D5 W. Treatment of hypervolemic hypernatremia should include the use of loop diuretics; however, this strategy alone may cause greater relative aquaresis over natriuresis. Therefore, D5 W may be co-administered with a loop diuretic to restore volume without supplying additional sodium.<sup>100</sup> Use of D5 W alone is inadvisable, as this will exacerbate hypervolemia. The underlying cause of hypernatremia should always be identified and addressed while eunatremia is being achieved. Strategies

for euvolemic hypernatremia involve treatment modalities other than IVF therapy which are targeted at the underlying cause and are beyond the scope of the article.

### Methotrexate Use

Treatment with high-dose methotrexate (HD-MTX; doses > 500–1000 mg/m<sup>2</sup>) can directly cause nephrotoxicity from crystal nephropathy, precipitation of MTX and its metabolites within the tubular lumens, and direct tubular toxicity from oxygen free radicals, all of which reduce clearance and increase toxicities.<sup>102,103</sup> Risk factors for nephrotoxicity include low urine flow, acidic urine pH, and pre-existing renal impairment which may be overcome with appropriate hydration.<sup>104,105</sup>

High urinary flow to protect the kidneys from HD-MTX is achieved with hyperhydration; however, no specific fluid type or rate is universally recommended. Several protocols are available which vary in timing of initiation of hydration before HD-MTX, rate of fluid, type of fluid, and duration of hydration. Pre-hydration with 150–200 mL/hour of NaHCO<sub>3</sub> containing IVF to a total of 2 L before HD-MTX and maintaining urine flow of at least 2.5 L/m<sup>2</sup>/d have been recommended.<sup>103,104</sup>

Few studies have evaluated specific hydration measures, presenting a major gap in current literature. Conflicting evidence surrounds amount of fluid required and timing of pre-hydration before MTX. Despite these varying outcomes from existing comparisons, initiating hydration pre-MTX with 2 L/m<sup>2</sup> starting at least 1–4 hours before and to only initiate the chemotherapy once urine pH is above 7 and diuresis is established is recommended. Specifics about these regimens may be found in Table 3.

Alkalinization is imperative, as the association between low urine pH and high-risk MTX concentrations is well established.<sup>105</sup> Indeed, some studies have suggested alkalinization is more effective than hyperhydration.<sup>116,117</sup> Mir et al. evaluated daily IV NaHCO<sub>3</sub> without hyperhydration (e.g., only oral hydration of 2 L/day recommended) before HD-MTX (8–12 gm/m<sup>2</sup>) where they found no cases of severe nephrotoxicity or significant worsening of creatinine clearance.<sup>108</sup> Various methods of alkalinization have been reported, primarily IV NaHCO<sub>3</sub> or acetate in continuous fluids or as a bolus<sup>104,105,106,108,109</sup> starting one to four hours before MTX as detailed above. However, IV route is not required as oral alkalinization and/or acetazolamide regimens have been reportedly efficacious.<sup>104,118,119</sup> A single-center retrospective study found no difference in time to alkalinization, time to MTX clearance, or incidence of MTX toxicities for patients receiving oral NaHCO<sub>3</sub> tablets and sodium citrate/citric acid solution versus IV NaHCO<sub>3</sub>.<sup>115</sup> Further, providing oral NaHCO<sub>3</sub> before admission for HD-MTX has been shown to improve the number of patients able to initiate chemotherapy on admission date and reduce hospitalization time.<sup>109</sup> Employing oral strategies for urinary alkalinization could significantly mitigate the risk of iatrogenic fluid overload. Regardless of alkalinization strategy employed, urine pH should be > 7 before initiation of HD-MTX therapy with ongoing monitoring of urine pH and MTX concentrations with NaHCO<sub>3</sub> supplementation until MTX clearance is achieved.

## Rhabdomyolysis

While the prognosis of rhabdomyolysis is generally good, mortality is increased by almost 40% in critically ill patients when AKI occurs.<sup>120</sup> Early and aggressive administration of IVF remains the mainstay of treatment for rhabdomyolysis, as dilution of toxins and increased renal tubule flow decrease the incidence and severity of AKI; however, no definitive guidelines for fluid choice or dosing schemes are available.

A common goal for mIVF is to maintain a UOP of 200 to 300 mL/h.<sup>121,122</sup> Patients with rhabdomyolysis secondary to trauma are at higher risk of AKI; therefore, more aggressive fluid administration (i.e., >10 L in the first 24 hours) is recommended.<sup>123</sup> Rhabdomyolysis from non-traumatic causes and patients with creatinine kinase levels <5000 units/L are at lower risk of AKI and may tolerate more conservative fluid administration strategies.<sup>124–126</sup>

Isotonic saline is most commonly used due to availability and because it does not contain potassium.<sup>121,127</sup> Concerns do exist with the use of isotonic saline in this population, given the incidence of metabolic acidosis and associated clinical ramifications.<sup>128</sup> As urine acidifies, myoglobin dissociates into the directly nephrotoxic ferrihemate, and precipitation of the Tamm-Horsfall protein-myoglobin complex is increased.<sup>120</sup> NaHCO<sub>3</sub> and mannitol have been evaluated as alkalizing agents and to induce diuresis, respectively, but this combination added to isotonic saline increased the incidence of AKI, with an adjusted OR of 2.1 (95% CI 1.3–3.2).<sup>125</sup>

Although LR is often avoided in rhabdomyolysis due to the risk of rhabdomyolysis-associated hyperkalemia and lactic acidosis, studies do support its use. When compared to isotonic saline at 400 mL/hr, LR produced a higher urine pH (7.25 vs 5.5,  $p<0.001$ ), normalized CK quicker (96 h vs. 120 h,  $p=0.06$ ), and did not impact serum potassium (3.7 vs. 3.95 mEq/L,  $p=0.125$ ).<sup>129</sup>

Use of mIVF is only warranted for the prevention of AKI in patients with rhabdomyolysis that have a CK value above 5000 u/L. Serial monitoring of CK should be done in all patients with rhabdomyolysis to assess the treatment threshold, with more frequent monitoring if trauma-induced. Whether the most important factor is the degree of hydration or the promotion of diuresis is unclear. If fluids are warranted, LR or other isotonic crystalloids are reasonable options. With non-trauma induced rhabdomyolysis, a more conservative dosing regimen (i.e., 125 mL/hr and titrated to UOP of at least 200 mL/hr or until CK is trending back to normal) is preferred. If trauma-induced, a more aggressive initial regimen is warranted (i.e., 400–500 mL/hr). If combination therapy with loop diuretics or mannitol is used, fluid administration may be reduced. Mannitol should be avoided in patients who are anuric or hypovolemic.

## Targeted Temperature Management (TTM)

Chilled IVF are a common cooling technique for induction of TTM.<sup>130</sup> Although useful in achieving target temperatures, chilled saline was not shown to be as effective in maintaining target temperatures compared to other modalities (e.g., surface cooling).<sup>131–133</sup> Primary advantages of cold IVF are ease of administration and low cost; however, adverse effects have been observed from pre-hospital administration. Timing of IVF has been evaluated

and results summarized in the 2015 Post-Cardiac Arrest Care guidelines with the notable conclusion that pre-hospital induction of TTM with large volumes of chilled crystalloids did not improve neurologic outcome (RR, 1.00; 95% CI, 0.95–1.06) or mortality (RR, 0.98; 95% CI, 0.92–1.04) and therefore should not be used.<sup>134</sup> The studies evaluated large volumes of chilled 0.9% NaCl (2 L or 20–30 mL/kg). Analysis of four trials observed increased rates of rearrest among patients who received prehospital induced hypothermia (RR, 1.22; 95% CI, 1.01–1.46).<sup>130</sup> Patients in the pre-hospital cooling group had higher observed rates of pulmonary edema (RR, 1.34; 95% CI, 1.15–1.57).<sup>135</sup> In a one-year follow up of survivors from the same study, no differences in neurologic outcomes were observed.<sup>136</sup> If surface cooling techniques are used, mIVF are only indicated for replacement of losses secondary to hypothermia-induced diuresis.<sup>137</sup> Specific advantages for the purpose of TTM of 0.9% NaCl vs. balanced crystalloids have not been evaluated; however, the usual concerns with large volumes of 0.9% NaCl (e.g., hyperchloremia, acidosis, etc.) should be considered with fluid choice. When surface cooling is not an option, the most conservative volume of chilled IVF for target temperature achievement is necessary to minimize fluid overload.

### Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an oncologic emergency caused by the breakdown of malignant cells leading to laboratory abnormalities and potentially fatal complications.<sup>138–140</sup> TLS-induced AKI is associated with increased mortality; therefore, prevention of AKI or its progression is critical to long term survival.<sup>141,142</sup> Prevention of TLS includes fluid therapy to enhance excretion of intracellular components via increased intravascular volume and improved renal perfusion enhancing glomerular filtration;<sup>140</sup> however, no trials have evaluated different fluid types or specific hydration rates. Current guidelines recommend hydration with 2.5–3 L/m<sup>2</sup>/day for patients at intermediate to high risk of TLS.<sup>138,139</sup> Other recommendations include fluid intake to be maintained with 1–2 times typical maintenance requirements with a goal UOP of 80–100 mL/m<sup>2</sup>/hr.<sup>140</sup> Fluid choice is generally isotonic saline or a dextrose containing product. The use of potassium containing fluids has been discouraged;<sup>138</sup> while LR should be avoided if possible, it may be considered in some patient (e.g. in patients without existing hyperkalemia or those at low risk of TLS) due to its relatively low K content. The use of 0.9% NaCl may promote acidosis, which can exacerbate hyperkalemia by promoting extracellular shifting of potassium; however, the impact on this patient population has not been well evaluated. For these reasons, fluids such as 5% dextrose combined with 0.45% NaCl or an isotonic mixture of equal parts NaCl and NaHCO<sub>3</sub> may be preferable on a theoretical basis. Individual anticancer regimens may require specific hydration due to drug specific TLS risk, and expert consultation is recommended.<sup>143</sup>

While hydration is the preferred method to increase UOP, loop diuretics can be administered if baseline cardiorenal disease with fluid overload is present or to target UOP of >2 mL/kg/hour.<sup>140,144,145</sup> Diuretics should be avoided in cases of hypovolemia or obstruction.<sup>140</sup>

Urine alkalization with addition of NaHCO<sub>3</sub> to fluid therapy or use of acetazolamide is no longer recommended unless severe metabolic acidosis is present.<sup>138,140</sup> Alkaline urine

enhances urate crystal excretion but does not enhance hypoxanthine or xanthine removal and has not been shown to improve outcomes particularly in the era of rasburicase.<sup>138,140,145</sup>

Specific evidence-based monitoring recommendations are scant but some recommend evaluation of UOP hourly and fluid balance four times a day.<sup>138</sup> Criteria for discontinuation of mIVF started for prevention or management of TLS are nonexistent. Consideration of comorbidities (e.g., cardiac disease and renal impairment) along with strict evaluation of fluid balance is prudent. Discontinuing TLS prophylaxis is reasonable once laboratory abnormalities are normalized on two consecutive measurements with ongoing monitoring for at least 24 hours.<sup>144,145</sup>

## Conclusion

mIVF are a commonly encountered medication therapy in hospitalized patients, but specific indications are generally limited to those reviewed here. Deliberate evaluation of the four rights construct of fluid stewardship may improve patient outcomes.

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Table 1.

## Considerations for Specific Types of Maintenance IV Fluid13.

Type of mIVF	Example(s)	Considerations
Isotonic saline	0.9% NaCl	<ul style="list-style-type: none"> <li>Distributed throughout extracellular fluid compartment</li> <li>High Na<sup>+</sup> content may promote Na<sup>+</sup> and water retention</li> <li>Supraphysiologic Cl<sup>-</sup> content may promote hyperchloremia and development of hyperchloremic metabolic acidosis and renal dysfunction<sup>19-23</sup></li> <li>Not effective to alkalinize urine or plasma</li> </ul>
Hypotonic salines	0.45% NaCl, 0.225% NaCl	<ul style="list-style-type: none"> <li>Greater distribution to tissues compared to isotonic crystalloids</li> <li>Risk of hyponatremia</li> </ul>
Hypertonic salines	3% NaCl	<ul style="list-style-type: none"> <li>Less distribution to tissues compared with isotonic crystalloids</li> <li>Risk of hypernatremia</li> <li>Generally used in low volumes for sodium replacement or effects on tonicity, not fluid replacement</li> </ul>
Dextrose solutions	D5W, D10W	<ul style="list-style-type: none"> <li>Fluid distributed throughout total body water</li> <li>Glucose content prevents starvation ketosis</li> <li>Risk of hyponatremia</li> <li>Risk of hyperglycemia</li> </ul>
Dextrose-containing crystalloids	D5NS, D5LR, D5½NS	<ul style="list-style-type: none"> <li>Glucose content prevents starvation ketosis</li> <li>Risk of hyperglycemia</li> <li>Lower risk of hyponatremia compared to pure dextrose solutions</li> </ul>
Balanced crystalloids	LR, PlasmaLyte	<ul style="list-style-type: none"> <li>Distributed throughout extracellular fluid compartment</li> <li>Less risk of hyperchloremia compared to 0.9% NaCl</li> <li>Contains other electrolytes that may meet overall maintenance needs</li> <li>Contains 4–5 mEq/L of potassium</li> <li>Risk of lactate accumulation in advanced liver cirrhosis</li> </ul>
NaHCO <sup>3</sup>	50–100 mEq in 1/2NS; 150 mEq in sterile water or D5W	<ul style="list-style-type: none"> <li>Effective plasma and urine alkalinization</li> <li>Risk of metabolic alkalosis</li> <li>Consider patient specific factors when choosing diluent</li> <li>In patients at higher risk or currently hypervolemic, consider no diluent and adjust administration rate.</li> </ul>

Type of mIVF	Example(s)	Considerations
	May be helpful in AKI with pH<7.20 <sup>24</sup> or sepsis with pH<7.15 <sup>25</sup>	<ul style="list-style-type: none"> <li>• When used in acidemia, overcorrection of pH may worsen end-organ perfusion<sup>2,6,27</sup></li> </ul>

Abbreviations: mIVF, maintenance intravenous fluid; NaCl, sodium chloride; D5W, 5% dextrose in water; D10W, 10% dextrose in water; D5NS, 5% dextrose in 0.9% NaCl; D5LR, 5% dextrose in lactated Ringer's; D5½NS, 5% dextrose in 0.45% NaCl; LR, Lactated Ringer's; D5LR, 5% dextrose in lactated Ringer's.

**Table 2.**

Monitoring of Maintenance IV Fluids.

Monitoring parameter	Specific tests	Considerations	Recommendation for use
Static Hemodynamic Parameters	• CVP	• Not recommended for assessing volume responsiveness (i.e., for guiding resuscitation fluids)	• Use as safety parameter; decrease/discontinue mIVF if elevated
	• PCWP	• Good indicators of preload	
	• EDV	• “Normal” values higher in mechanically ventilated patients	
Dynamic Hemodynamic Parameters <sup>28,25,29,30</sup>	• SVV	• Good indicators of volume responsiveness	• Use for monitoring resuscitation fluids; do not use for monitoring mIVF
	• PPV	• Use limited to specific populations (e.g., must be mechanically ventilated for SVV)	•
	• IVC collapsibility	• Risk of volume overload with fluid challenge	
	• Fluid challenge		
	• Passive leg raise		
Fluid Balance <sup>4,7,10,31–34</sup>	• Daily fluid balance over 24 hours	• Assumes baseline status was intravascularly replete	• Recommend to monitor daily and report during interdisciplinary rounds
	• Cumulative fluid balance over ICU stay	• Excludes interventions made in pre-ICU setting • Does not account for fluid shifts • Does not account for output from insensible losses • Must have accurate and complete charting, including measured urinary voids • Should include enteral intake	
Weight <sup>34–36</sup>	• Change in weight from baseline	• Assumes baseline weight represents intravascularly replete status • Must have reliable measurement and charting • Limited by gaps in frequency of measurement	• Recommend to monitor daily and report during interdisciplinary rounds
	• “Hidden” Fluid Intake <sup>37–10</sup>	• Must have reliable and up-to-date charting • Must be aware of institutional policies and procedures for IV flushes	• Recommend to monitor daily and report during interdisciplinary rounds

Abbreviations: CVP, central venous pressure; PCWP, pulmonary capillary wedge pressure; EDV, end diastolic volume; mIVF, maintenance intravenous fluids; SVV, stroke volume variation; PPV, pulse pressure variation; IVC, inferior vena cava; IV, intravenous.

Table 3.

## HD-MTX Hydration Strategies.

Reference	Demographics	Hydration and alkalization measures
Studies reporting hydration/alkalinization strategies:		
Relling et al. 1994 <sup>105</sup>	N = 134 patients with 481 HD-MTX cycles MTX dose: 1.5 gm/m <sup>2</sup> or adjusted per individual clearance	Pre-hydration 2 hr before HD-MTX with D5W with 40 mEq/m <sup>2</sup> /L NaHCO <sub>3</sub> at 100 mL/m <sup>2</sup> /hr to continue at least 42 hours from start of MTX
Hempel et al. 2003 <sup>106</sup>	N = 58 Adult and pediatric patients Diseases: ALL, NHL, osteosarcoma, brain tumor MTX dose: 1, 5, or 12 gm/m <sup>2</sup>	Pre-hydration 4 hr before HD-MTX with 2 mEq/kg NaHCO <sub>3</sub> 8.4% followed by 250 mL NaCl 0.9% plus D5W with 40 mEq NaHCO <sub>3</sub> 8.4% With HD-MTX infusion given 3 L/m <sup>2</sup> /d of NaCl 0.9% plus glucose 5% (1:1) and NaHCO <sub>3</sub> 8.4% 180 mEq/m <sup>2</sup> /d for at least 3 days
Zelcer et al. 2008, <sup>107</sup>	N = 708 MTX courses Pediatric patients MTX dose: 12 gm/m <sup>2</sup>	MTX mixed in 1L D5W with 50 mEq/L of NaHCO <sub>3</sub> IV NaHCO <sub>3</sub> bolus of 1 mEq/kg (max 100 mEq, may repeat); oral NaHCO <sub>3</sub> 3 tablets q6h, plus 3 additional tablets if urine pH < 7, plus IV hydration with D5W with 50 mEq/L NaHCO <sub>3</sub> to maintain urine output 3–4 L/m <sup>2</sup>
Mir et al. 2010 <sup>108</sup>	N = 26 for 344 courses Ages: 18 years (15–25) Disease: osteosarcoma MTX dose: 8–12 gm/m <sup>2</sup>	NaHCO <sub>3</sub> 8.4% 500 mL / 500 mEq given 1 hour pre-MTX on day 1 then daily for three days Oral hydration of 2 L/d recommended
Kintzel et al. 2011 <sup>109</sup>	N = 10 for 79 courses Adults	D5W with NaHCO <sub>3</sub> at 100-150 mEq/L to attain urine pH > 7 or 7.5 and UOP above 100 mL/hr versus Oral NaHCO <sub>3</sub> 1300 mg every 4 hours beginning the morning of chemotherapy admission
Studies comparing hydration/alkalinization strategies:		
Christensen et al. 1988, <sup>110</sup>	N = 100 pediatric patients Disease: acute lymphocytic leukemia MTX dose: 2 gm/m <sup>2</sup>	75–165 mL/m <sup>2</sup> for 5 hours with 2.5 gm/m <sup>2</sup> NaHCO <sub>3</sub> starting 2 hours before HD-MTX versus 200 mL/m <sup>2</sup> /h with 5.4 gm/m <sup>2</sup> NaHCO <sub>3</sub> starting 8 hours before HD-MTX More alkaline regimen associated with lower MTX levels and fewer severe toxicities
Ferrari et al. 1992, <sup>111</sup>	Disease: osteosarcoma MTX dose: 8 gm/m <sup>2</sup>	2 L/m <sup>2</sup> versus 1.5 L/m <sup>2</sup> hydration No difference in MTX toxicities
Yanagimachi et al. 2013, <sup>112</sup>	N = 51 patients for 127 courses Disease: acute lymphoblastic leukemia MTX dose: 3 gm/m <sup>2</sup>	2.5–3 L/m <sup>2</sup> /d of alkalized hydration given 4 hours versus 12 hours pre-MTX Shorter time was associated with prolonged high MTX concentrations and incidence of renal toxicity
Karremann et al. 2014, <sup>113</sup>	N = 17 pediatric patients with 66 cycles Diseases: acute lymphocytic leukemia or lymphoblastic lymphoma MTX dose: 5 gm/m <sup>2</sup>	1 hour pre-MTX NaHCO <sub>3</sub> 2 mM/kg followed by 1.5 L/m <sup>2</sup> /d hydration (70 mM NaCl, 2.5% glucose, 20 mM potassium chloride, and 60 mM NaHCO <sub>3</sub> ) versus 16–20 hour pre-hydration of the same fluid and rate No difference in MTX clearance or toxicities
Mikkelsen et al. 2014, <sup>114</sup>	Pediatric patients Diseases: acute lymphoblastic leukemia, non-Hodgkin lymphoma MTX dose: 5 or 8 gm/m <sup>2</sup>	4 versus 12 hours of 5% glucose with 40 mM NaHCO <sub>3</sub> and 20 mM potassium chloride at 125–150 mL/m <sup>2</sup> /h No impact on MTX clearance or renal toxicity
Rouch et al. 2017, <sup>115</sup>	N = 118 adult and pediatric patients MTX dose: median ~ 6 gm/m <sup>2</sup>	Oral NaHCO <sub>3</sub> tablets plus sodium citrate/citric acid solution versus IV NaHCO <sub>3</sub> (mEq/rate unspecified) No difference in time to alkalization, time to MTX clearance, or incidence of MTX toxicities