Fluid Stewardship During Critical Illness: A Call to Action

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Abstract
Intravenous fluids (IVFs) are the most common drugs administered in the intensive care unit. Despite the ubiquitous use, IVFs are not benign and carry significant risks associated with under- or overadministration. Hypovolemia is associated with decreased organ perfusion, ischemia, and multi-organ failure. Hypervolemia and volume overload are associated with organ dysfunction, delayed liberation from mechanical ventilation, and increased mortality. Despite appropriate provision of IVF, adverse drug effects such as electrolyte abnormalities and acid–base disturbances may occur. The management of volume status in critically ill patients is both dynamic and tenuous, a process that requires frequent monitoring and high clinical acumen. Because patient-specific considerations for fluid therapy evolve across the continuum of critical illness, a standard approach to the assessment of fluid needs and prescription of IVF therapy is necessary. We propose the principle of “fluid stewardship,” guided by 4 rights of medication safety: right patient, right drug, right route, and right dose. The successful implementation of fluid stewardship will aid pharmacists in making decisions regarding IVF therapy to optimize hemodynamic management and improve patient outcomes. Additionally, we highlight several areas of focus for future research, guided by the 4 rights construct of fluid stewardship.

Keywords
critical care, stewardship, fluid therapy, resuscitation, fluid responsiveness

Introduction
With an annual consumption of 1 billion units of 0.9\% sodium chloride (NaCl), intravenous fluids (IVFs) are the most commonly administered drugs in critically ill adults.\textsuperscript{1,2} Like all medications, fluids are not benign. Despite agreement that IVF is a mainstay of management during critical illness, robust trials on safety and efficacy are severely lacking, and inappropriate use of fluids occurs in approximately 20\% of patients.\textsuperscript{3} The purpose of this article is to provide a pharmacist-oriented review of the “Four Rights Construct of Fluid Stewardship” including the vital role of pharmacists in optimizing patient outcomes, the fundamentals of fluid therapy, guidance on the adoption and practice of fluid stewardship, and opportunities for research.\textsuperscript{2,4}

Fluid Overload Necessitates Stewardship
The 4 rights include the right patient, right drug, right route, and right dose. Malbrain et al previously offered the “4 D’s of fluid therapy” to promote fluid stewardship in septic shock; however, we propose to build on this construct with a medication safety emphasis.\textsuperscript{5}

Clinical investigations have defined fluid overload (FO) as an expansion of extracellular fluid volume with a positive fluid balance that produces a weight gain >10\% from baseline.\textsuperscript{6,7} FO is extremely common in critical illness and is consistently described in more than 25\% of intensive care unit (ICU) patients.\textsuperscript{4,6,8} Currently, no universally accepted definitions of FO exist, so a clear definition may offer consistencies in research and guide management strategies. We propose that a total body weight increase by at least 10\% from baseline
Table 1. Organ Systems and Related Effects of Fluid Overload.5-12

| Organ System     | Adverse Drug Effects                                      |
|------------------|-----------------------------------------------------------|
| Central nervous  | Altered mental status                                     |
|                  | Delirium                                                  |
| Respiratory      | Acute respiratory distress syndrome                        |
|                  | Prolonged time to liberation from mechanical ventilation  |
|                  | Increased incidence of ventilator-associated pneumonia    |
|                  | Increased need for thoracentesis                         |
| Cardiovascular   | Disturbance in cardiac conduction and contractility       |
| Renal            | Acute kidney injury                                       |
|                  | Increased need for renal replacement therapy              |
|                  | Increased need for diuretic therapy                       |
| Hepatic          | Impaired hepatic function                                 |
| Gastrointestinal | Intra-abdominal hypertension                              |
|                  | Abdominal compartment syndrome                             |
|                  | Malabsorption                                             |
| Integumentary    | Impaired wound healing                                    |
|                  | Development of pressure ulcers                            |

Complications of FO

Cumulative fluid balance (CFB) impacts nearly every organ system with significant adverse effects on patient outcomes (Table 1).5-12

Mortality. Multiple studies have demonstrated an association between CFB and mortality that persists across multiple time points and patient populations.5,7,9,12 One study found that in patients with sepsis, every 1 L increase in CFB is associated with a 6% increase in mortality.13 Another study analyzed FO in a matched cohort of 127 948 adult ICU patients and found that FO was associated with a 19% increased risk of hospital mortality.14 In surgical ICU patients, positive fluid balance was associated with a 70% increase in mortality 5 days postoperatively.15 Similarly, FO was associated with a 59% increase in mortality and a longer duration of ICU stay after cardiac surgery.16

Length of stay and disposition. FO has been associated with adverse events at each stage of hospitalization.6,9,12 FO was shown to increase ICU and hospital length of stay after multivariate analysis in one report of over 129 000 patients.17 Several other studies have found FO and CFB contribute to longer stay, but these findings are often confounded by severity of illness. After transfer from the ICU to a lower level of care, CFB is associated with an increased risk of ICU readmission.9 At the time of hospital discharge, patients who experienced ICU FO were more likely to be discharged to an acute care or rehabilitation facility compared to home (odds ratio [OR], 2.34; 95% confidence interval [CI], 1.1-4.98; P = .03) and were less likely to ambulate independently (OR, 2.29; 95% CI, 1.24-4.25; P = .01).6

Acute kidney injury. The clear benefits of early fluid resuscitation in patients with shock and AKI are widely accepted; however, the downstream effects of both AKI and FO can be similar (eg, electrolyte abnormalities, need for renal replacement therapy [RRT], prolonged mechanical ventilation, and multi-organ failure).18 Large volume resuscitation and CFB have been identified as risk factors for development of AKI secondary to abdominal compartment syndrome.11,18 While the potential for FO as a consequence of oliguria may be expected, the association between FO and mortality in patients with AKI is independent of urine output.20 Furthermore, FO and AKI may independently necessitate RRT or other fluid-related interventions including thoracentesis and diuretics.8 Regardless of the cause and effect, FO, AKI, and poor clinical outcomes are clearly associated.

Etiology of FO

FO is multifactorial including aggressive resuscitation fluids, inadequate monitoring of fluid responsiveness, “hidden” fluids not recognized by the medical team, and persistent use of maintenance intravenous fluids (mIVF).

Aggressive resuscitation fluids. During vasodilatory shock, fluid resuscitation with a minimum volume of 30 mL/kg is a core measure evaluated by the Center for Medicare and Medicaid Services as part of the SEP-1 bundle for patients with sepsis and hypotension.21,22 Ubiquitous administration of a minimum of 30 mL/kg fluid resuscitation is unevaluated and may be detrimental. Indeed, a survey of the International Fluid Academy revealed that 61% of respondents do not support this recommendation.23 Furthermore, the weight-based dose of fluids administered in practice varies across BMI groups. In 2882 patients with septic shock, all patients received a similar volume of crystalloid (~2500 mL), but the weight-based dose varied from 21.4 ± 16.8 mL/kg in morbidly obese patients to 55 ± 40 mL/kg in underweight patients.24 Outcomes of dosing per ideal, adjusted, or total body weight have not been evaluated; thus, a recommendation on dosing cannot be made. Instead, we suggest individualized attention to patient weight during fluid resuscitation and that the universal adoption of dosing per total body weight be scrutinized, particularly in obese patients. In practice, precision-based fluid resuscitation using small boluses and dynamic monitoring may be beneficial, and 2 clinical trials addressing conservative initial resuscitative strategies in sepsis should shed light on this.25,26 Conservative volumes are being used as highlighted by the
FENICE study of 2279 patients receiving fluid boluses from 311 ICUs across 46 countries, where the median volume of fluid bolus was 500 mL.27

Inadequate monitoring of fluid responsiveness. Approximately half of patients administered a fluid challenge will be “fluid responsive.”28 Thus, techniques to predict fluid responsiveness are essential to ensure correction of hypovolemia without causing hypervolemia. Despite extensive evidence and guideline recommendations supporting dynamic indices (eg, stroke volume variation [SVV]) to predict fluid responsiveness, static measures (eg, central venous pressure [CVP]) are still commonly used. In the FENICE study, static markers of preload were used to test fluid responsiveness in 35% of cases, dynamic indices were used in just 22% of cases, and no variable was used in the remaining 43% of cases.27 Furthermore, in a survey of the American and European Societies of Anesthesiology, 71% and 64% of American and European respondents, respectively, reported using CVP as an indicator for volume expansion despite numerous studies demonstrating a lack of reliability in predicting preload responsiveness.29,30 While practice could have shifted since the 2016 sepsis guidelines updated the recommendation for use of dynamic indices, it is unlikely that this practice has become universally adopted. While all measures of fluid responsiveness have limitations, the lack of utilization of dynamic indices or any measure of volume responsiveness may contribute to FO.

Role of “hidden fluids”. We define “hidden fluids” as requisite fluids administered as part of routine care, the volumes of which are not specifically prescribed (eg, flushes, diluents for intravenous drugs). An observational study characterized the contribution of “obligatory” fluids (necessary diluents for delivery of drugs) and “discretionary” fluids (mIVF, resuscitation boluses, and nutrition) and observed that patients received a median obligatory fluid volume of 645 mL (IQR: 495-1000 mL) with an additional discretionary fluid volume of 2592 mL (IQR: 2000-3030 mL) during a random 24-hour period of ICU admission.31 Careful attention to the contribution of hidden fluids to daily input has the potential to reduce FO.

Persistent use of maintenance fluids. Despite the volume provided by obligatory fluids in the ICU and limited data supporting their indication, mIVF are common. In a point prevalence study of 49 ICUs, 62% of ICU patients were receiving mIVF on the study day, despite over 80% receiving nutrition. mIVF accounted for one-third of total fluid administration.32 A 12-month pre–post protocol intervention study examining the change from routine mIVF (rate of 125-150 mL/h) to “to keep open” fluids (30 mL/h) in normotensive trauma patients observed a 2 L decrease in cumulative fluid intake and a corresponding decrease in ICU days and ventilator days.33

### Table 2. The 4 Rights Construct of Fluid Stewardship.

| Right | Key Points |
|-------|------------|
| Patient | Resuscitation fluids: |
|        | - Frequent assessment of volume responsiveness is essential to identifying the right patient |
|        | - All measures of volume responsiveness have limitations |
|        | - We suggest passive leg raise as the default measure of volume responsiveness |
| Maintenance fluids: | |
|        | - Routine mIVF therapy is rarely indicated |
|        | - Replacement fluids should be driven by the site and volume of fluid losses |
| Blood products: | |
|        | - pRBCs may be indicated during acute bleeding, large blood loss during procedures, anemia of critical illness, or refractory hypoxemia |
| Drug | |
|        | - The ideal fluid has a chemical composition that mirrors the physiologic composition of blood plasma, has minimal adverse effects, has a long storage life, and is cost-effective |
|        | - Osmotic pressure, oncotic pressure, and acid–base influence fluid composition |
| Hypotonic fluids: | |
|        | - Risk of hyponatremia, neurologic impairment, and increased tissue distribution |
| 0.9% NaCl: | |
|        | - Risk of hyperchloremic metabolic acidosis, gastrointestinal and interstitial edema, renal vasoconstriction, AKI, need for RRT, ileus, intraoperative blood loss, postoperative complications, and mortality |
| Balanced solutions: | |
|        | - Risk of hyperkalemia, lactate accumulation, and calcium citrate binding with blood products |
|        | - Likely no clinical risk in the absence of extreme conditions (eg, hyperkalemia with ECG changes) |
|        | - Recent large studies support their use over normal saline for resuscitation |
|        | - Use as a medication diluent |
| Albumin: | |
|        | - While longer half-life relative to crystalloid, overall short-lived volume expansion |
|        | - Risk of infusion reaction and costly |
|        | - Likely to provide benefit in cases of hypoalbuminemia and when fluid overload is of concern |
|        | - Clinical decision-making and criteria for use should be exercised for albumin prescribing |
| Route | |
|        | - IV to PO conversion is a simple means of reducing obligatory fluid administration |
|        | - Pharmacist-driven protocols for IV to PO conversion are common for antimicrobials, electrolytes, and agents for stress ulcer prophylaxis |
|        | - PO agents may also be used to wean off of IV infusions (eg, midodrine for vasopressors, clonidine for sedatives) |
| Dose | Resuscitation fluids: |
|        | - Standardized dosing of resuscitation fluids (ie, 30 mL/kg) should be abandoned for a more individualized approach based on conservative doses followed by continuous monitoring of volume responsiveness |

(continued)
The Principles of Fluid Stewardship

Fluid stewardship employs the 4 rights of medication administration in order to combat FO and improve patient outcomes (Table 2).

Right Patient

Patient identification is critical to fluid stewardship. While some assert the “ubiquitous need for IVFs in acutely ill patients,” others offer a viable alternative of no or reduced fluids.34,35 General guidelines for the use of IVF have been published by the National Institute for Health and Care Excellence (NICE) and are helpful in patients with clear indications for IVF therapy.36 Here, we offer considerations to help the pharmacist appropriately assess if a given patient has an indication for either resuscitation or maintenance fluid therapy.

The right patient for resuscitation fluid. The ROSE model (Rescue, Optimization, Stabilization, Evacuation) for hemodynamic optimization identifies patients in need of IVF therapy.3 Rescue entails the first critical minutes of lifesaving support. Optimization is guided by dynamic indices to fine-tune fluid therapy and ensure adequate volume repletion. The Rescue and Optimization phases are routinely combined to make up the more general phase, resuscitation. Differentiation of the discrete phases of Rescue and Optimization would better guide fluid therapy but has been difficult to achieve due to the infrequent adoption of fluid responsiveness assessments in clinical practice.27

Assessment of volume responsiveness. Frequent assessments of volume responsiveness using dynamic measures of fluid responsiveness are essential to determining the right patient. Continuous monitoring of cardiac output is needed for assessment of volume responsiveness, but SVV or close monitoring of pulse pressure variation is also acceptable. Limitations with performance of the passive leg raise (PLR) do exist but are less frequently encountered than those seen with monitoring of SVV (ie, inhaled tidal volume >8 mL/kg). Using a fluid challenge may expose patients to unnecessary fluids if they are deemed unresponsive, whereas a PLR offers an assessment strategy without the added exposure.28,30 Based on the advantages and limitations of the various measures of volume responsiveness, we recommend the routine and repeated use of PLR

Abbreviations: AKI, acute kidney injury; ECG, electrocardiogram; IV, intravenous; IVF, intravenous fluid; mIVF, maintenance intravenous fluid; pRBC, packed red blood cells; PO, oral; RRT, renal replacement therapy.

| Table 2. (continued) |
|---------------------|
| Right Patient       |
| Maintenance fluids:|
| ▪ mIVF doses must be adjusted to account for other sources of fluids, such as enteral and parenteral nutrition, IV medications, flushes, and blood products |
| Blood products:     |
| ▪ In the majority of ICU patients, pRBCs should be dosed to achieve a hemoglobin target of 7 g/dL. |
| ▪ Conservative dosing of blood products decreases cost, volume overload, and transfusion-related adverse events while improving patient outcomes |

| Table 3. Dynamic Assessment of Volume Responsiveness.30,37 |
|----------------------------------------------------------|
| Assessment Measure | Corresponding Value to Validate Responsiveness | Clinical Considerations |
| Passive leg raise | 10% increase in CO | ▪ Must measure cardiac output directly |
| | 10% increase in PPV | ▪ Limited usefulness in severe hypovolemia or in patients with intraabdominal pressures ≥16 mm Hg |
| Fluid challenge | 15% increase in CO | ▪ Must measure cardiac output directly; may induce volume overload |
| Stroke volume variation | Greater than 12% | ▪ Limited use in spontaneous breathing, arrhythmias, increased intraabdominal pressure, and right ventricular failure (false positives) |
| | | ▪ Limited use in patients with low tidal volume/lung compliance, open chest, or high respiratory rate (false negatives) |
| Pulse pressure variation | Greater than 12% | ▪ Limited use in spontaneous breathing, arrhythmias, increased intraabdominal pressure, and right ventricular failure (false positives) |
| | | ▪ Limited use in patients with low tidal volume/lung compliance, open chest, or high respiratory rate (false negatives) |
| IVC collapsibility | 12% change in vessel diameter | ▪ Contraindicated in spontaneous breathing, low tidal volume/lung compliance |

Abbreviations: CO, cardiac output; IVC, inferior vena cava; PPV, pulse pressure variation.
for identifying the right patient for resuscitation fluids. Interpretation of various measures of volume responsiveness is described in Table 3.

The right patient for maintenance fluid. Stabilization is the phase of the ROSE model where patients may require replacement or routine maintenance fluid. Replacement IVF is generally matched both to volume and composition of loss. In the absence of excessive and ongoing fluid losses, routine mIVF is rarely indicated.

The phases of the ROSE model should be applied in an individualized approach, with specific consideration for disease states and comorbidities. Rhabdomyolysis, dysnatremias, excessive fluid loss, burns, tumor lysis syndrome, hyperglycemic crises, and contrast-induced nephropathy are disease states where the careful application of the “right patient” may have significant clinical impact.

Right Drug

Patient-specific factors and the phase of fluid management dictate fluid choice. Optimal qualities for both resuscitation and maintenance fluids include chemical composition that closely approximates the physiologic composition, avoids adverse effects, has a long storage life, and is cost-effective.

The optimal resuscitation fluid will additionally provide an immediate and sustained increase in intravascular volume aimed at improving stroke volume, cardiac output, and blood pressure. Despite general consensus on these qualities, many unknowns remain and a fluid product that meets all of the ideal qualities does not exist. Even so, fluid choice should be undertaken with the same care and caution as with any medication.

Here, we highlight some clinical considerations for a pharmacist to assess the appropriate choice of fluid to be administered.

Principles of Fluid Composition

The principles of fluid composition design include the following key concepts: osmotic pressure, oncotic pressure, and acid–base influence.

Osmotic pressure. Osmolarity (osmotic pressure, tonicity) is the concentration of a solution as described by total solutes per volume. IVF can be classified as being hypertonic, isotonic, or hypotonic based on the concentration of sodium and potassium; in contrast, dextrose has no effect on tonicity due to rapid cellular uptake, except in the setting of insulin resistance.

Hypotonic solutions increase the risk for edema due to the osmotic pull of the tissues compared to the intravascular space, while hypertonic fluid can pull fluid out of the tissues, which may be necessary in clinical scenarios such as increased intracranial pressure. The osmolarity for 0.9% NaCl, lactated Ringer’s (LR), and dextrose 5% in water (D5 W) are 308 mOsm/L, 275 mOsm/L, and 260 mOsm/L, respectively. All are considered isotonic compared to plasma (280-300 mOsm/kg).

Oncotic pressure. Oncotic pressure (colloid osmotic pressure, oncoticity) is a form of osmotic pressure exerted by proteins in the intravascular space. Oncotic pressure shifts volume from the extravascular space, or tissues, into the intravascular space. Thus, depleted oncotic pressure increases the risk of interstitial edema. A higher oncotic pressure of a fluid prolongs the intravascular half-life and consequently results in sustained effects on blood pressure and perfusion. The volume of plasma expansion varies by rate of administration and fluid type. For 1 L of fluid, D5 W increases intravascular volume by 100 mL, 0.9% NaCl by 275 mL, 5% albumin by 700 mL, and 7.5% NaCl by 2140 mL.

The intravascular half-life is inversely proportional to the infusion time and is the supporting theory behind rapid administration rates recommended for fluid resuscitation.

Acid–base influence. Stewart’s approach to acid–base equilibrium is helpful for predicting the effects of IVF on physiologic pH and understanding the types of “balanced/buffered” crystalloid solutions currently available.

Stewart identified 3 variables that can independently influence the pH of biologic fluids: the partial pressure of carbon dioxide, the concentration of nonvolatile weak acids, and the strong ion difference (SID). The SID is the difference between the sum of strong cations and the sum of strong anions (abbreviated SID = [Na⁺ + K⁺] − Cl⁻). A general rule is that when the SID of the infusion fluid (SIDinf) is greater than the baseline concentration of HCO₃⁻, the pH will tend toward alkalosis (and vice versa). When the SIDinf is equal to the baseline concentration of plasma HCO₃⁻, the pH will be unchanged.

The normal plasma HCO₃⁻ is approximately 24 mEq/L. To obtain this desired SIDinf, IVFs frequently have supraphysiologic levels of chloride. Alternatively, physiologic chloride levels increase the SIDinf, resulting in an alkalinizing effect. In this way, no truly balanced crystalloid solution exists. Because the terms “balanced” or “buffered” are used to refer to a variety of different characteristics of the IVF, the pharmacist must identify which characteristic has been balanced to thus predict the other ramifications of fluids administered based on composition. Although calculations of SID are not recommended as a routine component of pharmacy practice, the concept is important to understand the clinical implications of fluid choice.

Resuscitation Fluids

Resuscitation fluids are a core component of both treatment and supportive care of critically ill patients. The role of colloids, hydroxyethyl starches, and crystalloids has been extensively reviewed in other forums.

NaCl, particularly as 0.9% NaCl, is the most commonly utilized resuscitation fluid but has been associated with unintended negative effects including hyperchloremic metabolic acidosis, gastrointestinal (GI) and intestinal edema, renal vasoconstriction, AKI, need for RRT, ileus, intraoperative blood loss, postoperative complications, and mortality.

Despite general consensus on the deleterious effects of NaCl, an adequate alternative is not well defined. Isotonic,
chloride-restricted solutions have been proposed as a "pragmatic initial resuscitation fluid for the majority of acutely ill patients" and as a "reasonable default choice." However, these solutions are not ideal in all clinical scenarios, and patient-specific criteria should be used. Recent large studies have investigated resuscitation fluid composition and are summarized below.

The 2015 SPLIT trial compared 0.9% NaCl with a buffered crystalloid solution (PlasmaLyte 148) in 2278 ICU patients. Each group received a median of 2000 mL of study fluid, and no difference in the incidence of AKI, RRT, or mortality was observed. However, the study was limited by a largely post-operative population with low severity of illness, exclusion of patients with chronic kidney disease, and lack of delineation between resuscitation and maintenance fluids.

The 2017 SALT trial was a cluster-randomized, multiple crossover trial of 974 ICU patients comparing 0.9% NaCl with balanced solutions. The groups received similar median volumes of fluid by 30 days, 1424 and 1617 mL, respectively. The saline group developed higher chloride levels, but no difference was observed in the incidence of RRT, AKI, or mortality. MAKE30 (major adverse kidney events at 30 days) was defined as a composite of death, receipt of new RRT, or final creatinine levels >200% of baseline and was similar between groups overall. MAKE30 was more common in patients who received large cumulative volumes of 0.9% NaCl to day 30 when compared to balanced solutions (P = .026).

In 2018, 2 single-center seminal trials comparing 0.9% NaCl and balanced fluids were published: the SALT-ED and SMART trials. SALT-ED evaluated 13 347 noncritically ill adults in the emergency department setting who received at least 500 mL of isotonic crystalloid with the primary outcome of hospital-free days. Although hospital-free days did not differ between groups, balanced crystalloids resulted in a lower incidence of MAKE30 (adjusted OR: 0.82; 95% CI: 0.70-0.95). Interestingly, the average fluid volume was about 1000 mL (IQR: 1000-2000 mL), highlighting that even 1 L of 0.9% NaCl can be harmful.

The SMART trial evaluated 15 802 adult patients in 5 ICUs who received either 0.9% NaCl or balanced crystalloid. The incidence of MAKE30 was decreased in the balanced crystalloid group (marginal OR: 0.91; 95% CI: 0.82-0.99). Death was nonsignificantly decreased (adjusted OR: 0.9, 95% CI: 0.80-1.01).

The SALT-ED and SMART studies demonstrated that even relatively small volumes of 0.9% NaCl have the ability to harm patients and emphasize that the most profound effects of balanced fluids are observed with larger volumes and in more acutely ill patients. Given the pervasive use of fluids, these results likely have large implications at the population level, as hemorrhagic or hypovolemic shock, although no complications were seen in trauma resuscitation. Due to the physiologic implications of hypertonic fluid resuscitation strategies, more research is needed to assess safety and efficacy, notably in distributive shock states.

**Maintenance Fluids**

Mortiz and Ayus reviewed mIVF with broad conclusion statements: (1) mIVF are a core component of supportive care; (2) most recommendations regarding fluid choice and dosing are opinion based; (3) hypotonic solutions are associated with hyponatremia and significant adverse events; and (4) an evidence base on which to build consensus guidelines, including the role of balanced fluids, are lacking. Since that time, several studies have attempted to address the question of appropriate choice of mIVF.

The MIHMoSA study was a crossover study that evaluated 12 healthy adults treated with 48 hours of isotonic (0.9% NaCl with 5% dextrose and 40 mEq KCl; tonicity 373 mOsm/L) versus hypotonic (Glucion 5%; tonicity 169 mOsm/L) mIVF. The patients received a total of 3462 mL of each fluid per study period. After 48 hours, the isotonic group voided less urine, had lower aldosterone levels, and had higher sodium and chloride concentrations. This trial highlights that even in a relatively short period of time and in a healthy population, 0.9% NaCl solutions may cause adverse effects. External validity is highly limited by the healthy nature of its subjects and the use of 0.9% NaCl instead of a more balanced isotonic solution.

The TOPMAST trial was estimated to conclude in December 2017 and will build upon the MIHMoSA study. This trial compared isotonic (0.9% NaCl with 5% dextrose and 40 mEq KCl) with hypotonic (Glucion 5%) mIVF during the intra- and postoperative settings in patients undergoing major thoracic surgery.

**Hypotonic mIVF.** Hypotonic solutions have been recommended against due to risks of hyponatremia, neurologic impairment, and death observed in the real-world setting. Additionally, compared to isotonic fluids, a greater volume of hypotonic fluids administered will distribute to the tissues due to...
decreased osmolarity. The effect of long-term use of hypotonic fluids on fluid balance has not been evaluated.

**Balanced mIVF.** Arguments against the use of balanced solutions for mIVF include the potassium content, potential for lactate accumulation in advanced liver cirrhosis, and calcium content when given with citrate-containing products, notably blood products. Because the potassium content is only 4 to 5 mEq/L, even if infused at 100 mL/h, the amount of potassium administered would only total 10 to 12 mEq/24 hours. By conventional wisdom, this would result in an increase in serum potassium concentration by 0.1 mEq/L, which is likely negligible. Even in patients undergoing renal transplantation, the dangers of hyperkalemia have not been realized. Given this, the risk from potassium in balanced solutions is often inconsequential, although it may be reasonable to avoid in the setting of hyperkalemia with active electrocardiographic changes. Limited data exist to support the accumulation of lactate from LR, although it may be reasonable to avoid in decompensated liver cirrhosis when large volumes of fluid are necessary. Finally, although calcium may bind with citrate in blood products, an increased infusion time or clot formation has not been observed.

Much of the literature is suggestive that the routine use of 0.9% NaCl should be dismissed and the term “normal saline” be abandoned, given the evidence contradicting its normalcy. Based on the outcomes associated with balanced crystalloids and 0.9% NaCl, we suggest balanced crystalloids be utilized as the predominant resuscitation strategy. Although balanced crystalloids refer to multiple products, no specific advantage has been observed of one product over another, and further research comparing balanced crystalloids head to head is warranted. Notably, LR is less costly than PlasmaLyte. Saline may be preferred in patients who present with a hypochloremic metabolic alkalosis, but this recommendation also needs to be evaluated. For mIVF therapy, the very limited data would suggest a hypotonic fluid be used, but there are significant limitations given the subgroup of patients evaluated, and findings cannot be extrapolated to a more heterogeneous critically ill population. Recommendations for further research are summarized in Table 4.

**Replacement Fluids**

In the case of excessive fluid losses, consideration of the site of loss should guide choice of the “Right Drug.” The NICE guidelines for fluid replacement include a helpful diagram that explains the composition of fluids lost from various sites. Generally, loss from lower GI sources (eg, diarrhea, colostomy, ileal, or jejunal loss) and pancreatic or biliary drainage will require replacement with 0.9% NaCl, with the addition of potassium and bicarbonate while adjusting the concentration of NaCl to ensure appropriate tonicity. Vomiting or nasogastric tube loss should focus on chloride replacement, as chloride loss generally drives the acid–base disorders that occur from upper GI losses. Insensible water loss (eg, sweating, fever, loss from ventilation) is often considered to be “pure” water loss with minimal loss of solutes. Thus, hypotonic fluid administration, such as 0.45% NaCl, may be acceptable in these patients, although

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**Table 4. Direction for Stewardship Research Guided by the 4 Rights.**

| Right | Research Questions |
|-------|--------------------|
| Patient | Are mIVF routinely necessary?  
| | Is patient reported thirst an effective means of determining IVF requirements in medically ill patients? |
| Drug | Development of an algorithm that accounts for serum electrolyte concentration, comorbidities, and phase of fluid administration to aid in IVF selection and dosing  
| | How does the osmolarity of resuscitation or mIVF affect patient-centered outcomes?  
| | What is the role of albumin in each phase of fluid administration?  
| | What is the comparative safety and efficacy of lactated Ringer’s and PlasmaLyte?  
| | Evaluation of medication stability in balanced IVF diluents |
| Route | What is the comparative safety and efficacy of maintenance fluid administered by IV or enteral route?  
| | Is oral fluid resuscitation safe and effective?  
| | What is the impact of IV to PO conversion protocols on daily fluid balance? |
| Dose | What is the comparative safety and efficacy of fluid resuscitation based on actual, ideal, and adjusted body weights?  
| | What qualitative or quantitative measures may be used to guide weight-based dosing of empiric large volume resuscitation?  
| | What is the appropriate dosing for mIVF?  
| | Feasibility of protocolized daily adjustment of mIVF dose based on discrete fluid input  
| | Feasibility of daily patient weight assessment to guide dosing of mIVF therapy  
| | Do patient-specific factors such as fever or mechanical ventilation alter mIVF requirements in a predictable and quantifiable manner? |
| Other | What is the optimal monitoring strategy for mIVF?  
| | What signs may be used for early identification of the evacuation phase?  
| | What is the optimal timing for initiating interventions for fluid mobilization such as diuretics or renal replacement therapy?  
| | How do IV medication concentrations and electrolyte contents affect daily fluid balance?  
| | What is the comparative incidence of hypervolemia in daily versus twice-daily fluid balance assessment?  
| | What degree of hypervolemia is associated with clinically relevant fluid overload?  
| | Does fluid overload increase the incidence of ICU delirium? |

**Abbreviations:** ICU, intensive care unit; IV, intravenous; IVF, intravenous fluid; mIVF, maintenance intravenous fluid; PO, oral.
sodium should be monitored carefully. Notably, “hidden fluids” and/or enteral fluids can provide sufficient or even excess volume to replace insensible losses. Due to variations in fluid loss, requirements should be assessed daily by consistent monitoring of electrolytes, acid–base status, and hemodynamic status.

**Utilization of Colloids**

**Albumin.** Albumin has fallen out of favor based on cost and multiple studies, including SAFE, CRISTAL, and ALBIOS, which failed to show a mortality difference in critically ill patients with and without sepsis. Post hoc analyses have indicated potential benefits in specific subgroups (eg, improved mortality at 90, but not 28 days in septic shock) and have been the basis for ongoing debate regarding albumin in sepsis.

Despite the lack of evidence demonstrating a clear benefit for albumin, several points should be considered: (1) endogenous albumin is the main determinant of plasma oncotic pressure, thus playing a key role in regulating microvascular fluid dynamics; (2) a higher degree of hypoalbuminemia is associated with increased mortality in patients with severe sepsis and septic shock; and (3) in randomized trials, patients receiving albumin routinely had a decreased net fluid balance compared to those receiving crystalloid. While albumin is not the right drug for all patients, clinical decision-making and criteria for use can be exercised to prescribe albumin in select patients likely to benefit, particularly when FO in the presence of hypoalbuminemia is of concern.

**Packed red blood cells.** Patients suffering acute exsanguination or with large estimated blood loss during procedures are obvious candidates for packed red blood cells (pRBCs) during the Rescue and Optimization phases. Other hemostatic agents could be used in conjunction with transfusions to help reduce transfusion requirements and inadvertent fluid administration. Transfusion of pRBC could play a role in the Stabilization phase as well, due to gradual losses from anemia of critical illness and frequent blood sampling. Refractory hypoxemia is another consideration for pRBC, which could be encountered in the Rescue, Optimization, or Stabilization phases.

**Right Route**

The provision of resuscitation fluid via the enteral route has been limited to animal models. Although urine output increased with an oral rehydration strategy in porcine burn models, this route is likely not ideal given the shunting of blood flow during symptomatic hypovolemia, which translates into delayed gastric emptying, delayed intestinal absorption, and a harmful delay in increasing circulating blood volume. In addition, enteral water will preferentially fill the interstitial compartment before the intravascular compartment. These concerns are diminished during the Stabilization phase, where mIVF are commonly prescribed. mIVF are administered in 88% of patients during shock and in 82% after shock resolution, accounting for 25% to 30% of daily fluid input. Transitioning patients in need of mIVF to enteral administration to mitigate the harm associated with mIVF is likely reasonable.

Accounting for “hidden fluids” and adjusting IVF accordingly is vital as fluids associated with medication administration can contribute unnoticeably to fluid intake and adverse effects. A simple, yet impactful component of fluid stewardship is to minimize the number of medications given IV to reduce the burden of “hidden fluids.” Several avenues to decrease medication-related IVF intake exist. Conversion of IV dosage forms to enterally administered alternatives (“IV to by mouth conversion”) is a simple means of reducing obligatory fluid administration. Antimicrobials, electrolytes, and agents for stress ulcer prophylaxis are commonly targeted for this intervention and may often be converted directly to enteral dosage forms by pharmacist-driven protocols. Enteral alternatives can also be used to transition from IV agents (eg, midodrine for the recovery phase of shock to hasten liberation from continuously infused catecholamines, thereby reducing obligatory fluid intake). Likewise, clonidine may be useful as an enteral sedative agent to transition from dexametomidine. Future research should investigate the clinical impact of hidden fluid, the impact of enteral fluid administration, and patient thirst to guide fluid administration.

**Right Dose**

The development of protocolized assessment and management of fluid requirements are essential for fluid stewardship. To mitigate harm associated with inappropriate fluid dosing, pharmacists should be aware of the importance of conservative dosing strategies and the need for recurrent bedside assessment.

**Resuscitation fluid.** A standardized approach to rescue therapy for specific disease states does not promote precision-guided resuscitation therapy and should be abandoned for a more individualized approach. Time to completion of initial resuscitation did not impact in-hospital, risk-adjusted mortality, contrary to time to initiation of antibiotics and time to completion of a 3-hour bundle in early sepsis management. This brings to question the true need for such aggressive early fluid resuscitation. Weight-based dosing by total body weight should be reevaluated as assessments of volume responsiveness identify patients in need of IVF but do not dictate an appropriate dose. We recommend conservative dosing strategies (ie, 250-500 mL bolus) followed by frequent and even continuous monitoring.

**Maintenance fluid.** Published formulas and online calculators are at risk of providing surplus fluid to the majority of patients, as they do not account for “hidden fluids.” The administration of mIVF is further plagued by a “set it and forget it” mentality. Due to the labile status of critically ill patients, the dose of mIVF should be assessed daily, at minimum. Furthermore, the use of stop dates on mIVF, accurate assessment of fluid losses,
and a keen eye for early signs of overload are necessary to guide the appropriate dosing of mIVF.

**Judicious use of blood products.** Blood transfusion has been identified as one of the top 5 most overused therapies in the United States. Blood products also contribute significant volume, comprising 8.1% of total volume administered in the first day of ICU admission for medical patients in a single-center study. Thus, when the right patient has been identified to receive blood products, the right dose is essential to maximize benefit and reduce adverse effects. For the majority of ICU patients, pRBC should be administered to target a hemoglobin level of 7 g/dL, with each unit of pRBC expected to produce a hemoglobin increase of approximately 1 g/dL in patients who are not actively bleeding. A higher hemoglobin target may be utilized in patients with active coronary disease (8 g/dL) or in those with refractory hypoxemia. The volume of blood products should be considered with total daily fluid intake and should be dosed conservatively to decrease cost, volume overload, and transfusion-related adverse events, while improving patient outcomes.

**Fluid Stewardship at the Bedside**

Fluid stewardship is a comprehensive, multidimensional concept. The Four Rights (patient, drug, route, and dose) should be assessed routinely. To provide a pragmatic approach to clinical implementation, we propose an update to the FASTHUGS BID (feeding, analgesia, sedation, thromboembolic prophylaxis, head of bed elevation, ulcer prophylaxis, glycemic control, spontaneous breathing trial, bowel regimen, indwelling catheter removal, de-escalation of antibiotics) mnemonic to include “fluids.” F₂ASTHUGS BID incorporates fluids as the second “F” and may be a useful way to incorporate fluid stewardship as a daily component of ICU care.

**Conclusion**

Fluid stewardship is a novel concept that has great potential to improve patient outcomes. Through the adoption of the 4 rights of medication administration on prescription and monitoring of IVF, pharmacists may play a key role in optimizing patient outcomes.

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