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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.[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.[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.[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.[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.[6,7] FO is extremely common in critical illness and is consistently described in more than 25% of intensive care unit (ICU) patients.[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

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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

secondary to fluid administration be used to define "class I FO." We further suggest that research should be conducted to determine the degree of hypervolemia associated with a second tier, class II FO and its relative impact on patient outcomes.

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.[4,7-9,13] 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.[11,19] 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 ($\sim$2500 mL), but the weight-based dose varied from 21.4 $\pm$ 16.8 mL/kg in morbidly obese patients to 55 $\pm$ 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)

Table 2. (continued)

Right	Key Points
	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

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.

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

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 10% increase in PPV	▪ Must measure cardiac output directly ▪ Limited usefulness in severe hypovolemia or in patients with intra-abdominal pressures $\geq$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.[34] 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.[2] 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.[38] 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.[39]

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.[39] 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.[40] The intravascular half-life is inversely proportional to the infusion time and is the supporting theory behind rapid administration rates recommended for fluid resuscitation.[21,41]

Acid–base influence. Stewart's approach to acid–base equilibrium is helpful for predicting the effects of IVF on physiological pH and understanding the types of "balanced/buffered" crystalloid solutions currently available.[42] 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 (SID_{inf}) is greater than the baseline concentration of HCO_3^-, the pH will tend toward alkalosis (and vice versa). When the SID_{inf} is equal to the baseline concentration of plasma HCO_3^-, the pH will be unchanged.[43] The normal plasma HCO_3^- is approximately 24 mEq/L. To obtain this desired SID_{inf}, IVFs frequently have supraphysiologic levels of chloride. Alternatively, physiologic chloride levels increase the SID_{inf}, resulting in an alkalizing 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.[38] The role of colloids, hydroxyethyl starches, and crystalloids has been extensively reviewed in other forums.[38,44] 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 interstitial edema, renal vasoconstriction, AKI, need for RRT, ileus, intraoperative blood loss, postoperative complications, and mortality.[38,45,46]

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."[38,44,45] 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.[47] 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 postoperative 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.[48] 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.[49]

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).[50]

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.[49,50] Given the pervasive use of fluids, these results likely have large implications at the population level, as the number needed to treat to prevent 1 MAKE30 event was 111 in SALT-ED and 91 in SMART.

Much of the recent literature has aimed to compare various isotonic crystalloids. Hypotonic fluid is not evaluated for resuscitation strategies due to its predominant shift to the extravascular compartment and poor ability to increase circulating blood volume. There is, however, merit in the use of hypertonic solution. This was a popular resuscitation strategy for some time but has recently fallen out of practice. Its use is well-documented and recommended in neurologic injury, where the hypertonic effects help to evacuate fluid from the intracranial extravascular compartment to alleviate elevated intracranial pressure.[51] In other shock states, namely distributive shock, a hypertonic solution may be a preferred resuscitation strategy. It allows smaller total volumes to be infused and to mobilize edema while also increasing circulating blood volume. Alterations to electrolytes and serum osmolarity are short lived.[52] The use of a hypertonic solution would cause a less predictable increase in circulating blood volume, which could be detrimental to patients with tenuous cardiac or renal function. Hypertonic solution would not be an optimal resuscitation strategy in shock states where patients' total body fluid were down, such as hemorrhagic or hypovolemic shock, although no complications were seen in trauma resuscitation.[53] 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.[34] 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.[54] 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.[55] 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.[56,57] 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.[58] 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.[59]

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.

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.

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.[36] 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, hypo-osmolar fluid administration, such as 0.45% NaCl, may be acceptable in these patients, although

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.[60-62] 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[63]; (2) a higher degree of hypoalbuminemia is associated with increased mortality in patients with severe sepsis and septic shock[64]; and (3) in randomized trials, patients receiving albumin routinely had a decreased net fluid balance compared to those receiving crystalloid.[60,62] 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.[65,66] 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.[67]

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.[68] 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.[6,32,69] Transitioning patients in need of mIVF to enteral administration to mitigate the harm associated with mIVF is likely reasonable.[69]

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.[70] A simple, yet impactful component of fluid stewardship is to minimize the number of medications given IV to reduce the burden of "hidden fluids."[70] 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.[71] 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).[72] Likewise, clonidine may be useful as an enteral sedative agent to transition from dexmedetomidine.[73] 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.[74] 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.[75] 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.[69] 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.[76] A higher hemoglobin target may be utilized in patients with active coronary disease (8 g/dL) or in those with refractory hypoxemia.[77] 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."[78] F_2ASTHUGS 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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References

1. Finfer S, Liu B, Taylor C, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care*. 2010;14(5):R185.
2. Glassford NJ, Bellomo R. The complexities of intravenous fluid research: questions of scale, volume, and accumulation. *J Crit Care Med*. 2016;31(4):276-299.
3. Hoste EA, Maitland K, Brudney CS, et al. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth*.2014; 113(5):740-747.
4. Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med*. 2011;39(2):259-265.
5. Malbrain M, Van Regenmortel N, Saugel B, et al. Principles of fluid management and stewardship in septic shock: it is time to consider the four D's and the four phases of fluid therapy. *Ann Intensive Care*. 2018;8(1):66.
6. Mitchell KH, Carlbom D, Caldwell E, et al. Volume overload: prevalence, risk factors, and functional outcome in survivors of septic shock. *Ann Am Thorac Soc*. 2015;12(12):1837-1844.
7. Vaara ST, Korhonen AM, Kaukonen KM, et al. Fluid overload is associated with an increased risk for 90-day mortality in critically ill patients with renal replacement therapy: data from the prospective FINNAKI study. *Crit Care*. 2012;16(5):R197.
8. Kelm DJ, Perrin JT, Cartin-Ceba R, et al. Fluid overload in patients with severe sepsis and septic shock treated with early goal-directed therapy is associated with increased acute need for fluid-related medical interventions and hospital death. *Shock (Augusta, GA)*. 2015;43(1):68-73.
9. Brotfain E, Koyfman L, Toledano R, et al. Positive fluid balance as a major predictor of clinical outcome of patients with sepsis/septic shock after ICU discharge. *Am J Emerg Med*. 2016;34(11): 2122-2126.
10. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354(24):2564-2575.
11. Patel DM, Connor MJ Jr. Intra-abdominal hypertension and abdominal compartment syndrome: an underappreciated cause of acute kidney injury. *Adv Chronic Kidney Dis*. 2016;23(3): 160-166.
12. Claure-Del Granado R, Mehta RL. Fluid overload in the ICU: evaluation and management. *BMC Nephrol*. 2016;17(1):109.
13. Neyra JA, Li X, Canepa-Escaro F, et al. Cumulative fluid balance and mortality in septic patients with or without acute kidney injury and chronic kidney disease. *Crit Care Med*. 2016;44(10): 1891-1900.
14. Child DL, Cao Z, Seiberlich LE, et al. The costs of fluid overload in the adult intensive care unit: is a small-volume infusion model a proactive solution? *Clinicoecon Outcomes Res*. 2015;7:1-8.
15. Barmparas G, Liou D, Lee D, et al. Impact of positive fluid balance on critically ill surgical patients: a prospective observational study. *J Crit Care*. 2014;29(6):936-941.

16. Stein A, de Souza LV, Belettini CR, et al. Fluid overload and changes in serum creatinine after cardiac surgery: predictors of mortality and longer intensive care stay. A prospective cohort study. *Crit Care*. 2012;16(3):R99.
17. Magee G, Zbrozek A. Fluid overload is associated with increases in length of stay and hospital costs: pooled analysis of data from more than 600 US hospitals. *Clinicoecon Outcomes Res*. 2013;5: 289-296.
18. Ostermann M, Straaten HM, Forni LG. Fluid overload and acute kidney injury: cause or consequence? *Crit Care*. 2015;19: 443.
19. Wise R, Jacobs J, Pilate S, et al. Incidence and prognosis of intra-abdominal hypertension and abdominal compartment syndrome in severely burned patients: pilot study and review of the literature. *Anaesthesiol Intensive Ther*. 2016;48(2):95-109.
20. Payen D, de Pont AC, Sakr Y, et al. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care*. 2008;12(3): R74.
21. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med*. 2017;43(3):304-377.
22. Centers for Medicare and Medicaid Services TJC. Specifications manual for national hospital inpatient quality measures discharges 10-01-15 (4Q15) through 06-30-16 (2Q16). Published March 9, 2015. Accessed Febuary13, 2018. https://www.jointcommission.org/assets/1/6/IQRManualReleaseNotes_V5_01.pdf
23. Marik P. iSepsis—a 30 ml/kg bolus: yes or no—the results. 2017. Accessed March 7, 2018. https://emcrit.org/isepsis/isepsis-30ml-kg-bolus-yes-no-results/
24. Arabi YM, Dara SI, Tamim HM, et al. Clinical characteristics, sepsis interventions and outcomes in the obese patients with septic shock: an international multicenter cohort study. *Crit Care*. 2013;17(2):R72.
25. Self WH, Semler MW, Bellomo R, et al. Liberal versus restrictive intravenous fluid therapy for early septic shock: rationale for a randomized trial. *Ann Emerg Med*. 2018;72(4):457-466.
26. Macdonald SPJ, Taylor DM, Keijzers G, et al. REstricted Fluid REsuscitation in Sepsis-associated Hypotension (REFRESH): study protocol for a pilot randomised controlled trial. *Trials*. 2017;18(1):399.
27. Cecconi M, Hofer C, Teboul JL, et al. Fluid challenges in intensive care: the FENICE study: a global inception cohort study. *Intensive Care Med*. 2015;41(9):1529-1537.
28. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*. 2002;121(6): 2000-2008.
29. Cannesson M, Pestel G, Ricks C, et al. Hemodynamic monitoring and management in patients undergoing high risk surgery: a survey among North American and European anesthesiologists. *Crit Care*. 2011;15(4):R197.
30. Monnet X, Marik PE, Teboul JL. Prediction of fluid responsiveness: an update. *Ann Intensive Care*. 2016;6(1):111.
31. Bashir MU, Tawil A, Mani VR, et al. Hidden obligatory fluid intake in critical care patients. *J Intensive Care Med*. 2017; 32(3):223-227.
32. Bihari S, Watts NR, Seppelt I, et al. Maintenance fluid practices in intensive care units in Australia and New Zealand. *Crit Care Resusc*.2016;18(2):89-94.
33. Barmparas G, Ko A, Harada MY, et al. Decreasing maintenance fluids in normotensive trauma patients may reduce intensive care unit stay and ventilator days. *J Crit Care*. 2016;31(1): 201-205.
34. Moritz ML, Ayus JC. Maintenance intravenous fluids in acutely Ill patients. *N Engl J Med*. 2015;373(14):1350-1360.
35. Lief L. Maintenance intravenous fluids in acutely Ill patients. *N Engl J Med*. 2016;374(3):289-290.
36. Padhi S, Bullock I, Li L, Stroud M. Intravenous fluid therapy for adults in hospital: summary of NICE guidance. *BMJ: Br Medl J (Online)*. 2013;347.
37. Alvarado Sanchez JI, Amaya Zuniga WF, Monge Garcia MI. Predictors to intravenous fluid responsiveness. *J Intensive Care Med*. 2018;33(4):227-240.
38. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med*. 2013;369(13):1243-1251.
39. Reddi AS. *Fluid, electrolyte and acid-base disorders*. 2nded. New York, NY: Springer Science+Business Media; 2017.
40. Marino PL, Sutin KM. *The ICU book*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.
41. Hahn RG, Drobin D, Stahle L. Volume kinetics of Ringer's solution in female volunteers. *Br J Anaesth*. 1997;78(2):144-148.
42. Stewart PA. Independent and dependent variables of acid-base control. *Respir Physiol*. 1978;33(1):9-26.
43. Carlesso E, Maiocchi G, Tallarini F, et al. The rule regulating pH changes during crystalloid infusion. *Intensive Care Med*. 2011; 37(3):461-468.
44. Raghunathan K, Murray PT, Beattie WS, et al. Choice of fluid in acute illness: what should be given? An international consensus. *Br J Anaesth*. 2014;113(5):772-783.
45. Lobo DN, Awad S. Should chloride-rich crystalloids remain the mainstay of fluid resuscitation to prevent 'pre-renal' acute kidney injury?: con. *Kidney Int*. 2014;86(6):1096-1105.
46. Suetrong B, Pisitsak C, Boyd JH, et al. Hyperchloremia and moderate increase in serum chloride are associated with acute kidney injury in severe sepsis and septic shock patients. *Critl care*. 2016; 20(1):315.
47. Young P, Bailey M, Beasley R, et al. Effect of a buffered crystalloid solution vs saline on acute kidney injury among patients in the intensive care unit: the split randomized clinical trial. *Jama*. 2015;314(16):1701-1710.
48. Semler MW, Wanderer JP, Ehrenfeld JM, et al. Balanced crystalloids versus saline in the intensive care unit. the salt randomized trial. *Am J Respir Crit Care Med*. 2017;195(10):1362-1372.
49. Self WH, Semler MW, Wanderer JP, et al. Balanced crystalloids versus saline in noncritically Ill adults. *N Engl J Med*. 2018; 378(9):819-828.
50. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically Ill adults. *N Engl J Med*. 2018;378(9): 829-839.
51. Oddo M, Poole D, Helbok R, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. *Intensive Care Med*. 2018;44(4):449-463.

52. Pfortmueller CA, Schefold JC. Hypertonic saline in critical illness—a systematic review. *J Crit Care*. 2017;42:168-177.
53. Wu MC, Liao TY, Lee EM, et al. Administration of hypertonic solutions for hemorrhagic shock: a systematic review and meta-analysis of clinical trials. *Anesth Analg*. 2017;125(5):1549-1557.
54. Van Regenmortel N, De Weerdt T, Van Craenenbroeck AH, et al. Effect of isotonic versus hypotonic maintenance fluid therapy on urine output, fluid balance, and electrolyte homeostasis: a crossover study in fasting adult volunteers. *Br J Anaesth*. 2017;118(6):892-900.
55. Hendrickx S, Van Vlimmeren K, Baar I, et al. Introducing TOPMAST, the first double-blind randomized clinical trial specifically dedicated to perioperative maintenance fluid therapy in adults. *Anaesthesiol Intensive Ther*. 2017;49(5):366-372.
56. Semler MW, Rice TW. Sepsis resuscitation: fluid choice and dose. *Clin Chest Med*. 2016;37(2):241-250.
57. Ayus JC, Wheeler JM, Arieff AI. Postoperative hyponatremic encephalopathy in menstruant women. *Ann Intern Med*. 1992;117(11):891-897.
58. Khajavi MR, Etezadi F, Moharari RS, et al. Effects of normal saline vs. lactated ringer's during renal transplantation. *Ren Fail*. 2008;30(5):535-539.
59. Lorenzo M, Davis JW, Negin S, et al. Can Ringer's lactate be used safely with blood transfusions? *Am J Surg*. 1998;175(4):308-310.
60. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247-2256.
61. Annane D, Siami S, Jaber S, et al. Effects of fluid resuscitation with colloids vs crystalloids on mortality in critically ill patients presenting with hypovolemic shock: the CRISTAL randomized trial. *JAMA*. 2013;310(17):1809-1817.
62. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med*. 2014;370(15):1412-1421.
63. Scallan J, Huxley VH, Korthuis RJ. *Fluid movement across the endothelial barrier*. In: *Capillary Fluid Exchange: Regulation, Functions, and Pathology*. San Rafael, CA: Morgan & Claypool Life Sciences; 2010. Chapter 1.
64. Caironi P. POINT: should intravenous albumin be used for volume resuscitation in severe sepsis/septic shock? Yes. *Chest*. 2016;149(6):1365-1367.
65. Jahangirifard A, Razavi MR, Ahmadi ZH, et al. Effect of desmopressin on the amount of bleeding and transfusion requirements in patients undergoing heart transplant surgery. *Basic Clin Pharmacol Toxicol*. 2017;121(3):175-180.
66. Desborough MJ, Oakland KA, Landoni G, et al. Desmopressin for treatment of platelet dysfunction and reversal of antiplatelet agents: a systematic review and meta-analysis of randomized controlled trials. *J Thromb Haemost*. 2017;15(2):263-272.
67. Mazer CD, Whitlock RP, Fergusson DA, et al. Restrictive or liberal red-cell transfusion for cardiac surgery. *N Engl J Med*. 2017;377(22):2133-2144.
68. Gomez BI, McIntyre MK, Gurney JM, et al. Enteral resuscitation with oral rehydration solution to reduce acute kidney injury in burn victims: evidence from a porcine model. *PloS one*. 2018;13(5):e0195615.
69. Van Regenmortel N, Verbrugghe W, Roelant E, et al. Maintenance fluid therapy and fluid creep impose more significant fluid, sodium, and chloride burdens than resuscitation fluids in critically ill patients: a retrospective study in a tertiary mixed ICU population. *Intensive Care Med*. 2018;44(4):409-417.
70. Magee CA, Bastin MLT, Laine ME, et al. Insidious harm of medication diluents as a contributor to cumulative volume and hyperchloremia: a prospective, open-label, sequential period pilot study. *Crit Care Med*. 2018;46(8):1217-1223.
71. Society for Healthcare Epidemiology of A, Infectious Diseases Society of A, Pediatric Infectious Diseases S. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infect Control Hosp Epidemiol*. 2012;33(4):322-327.
72. Levine AR, Meyer MJ, Bittner EA, et al. Oral midodrine treatment accelerates the liberation of intensive care unit patients from intravenous vasopressor infusions. *J Crit Care*. 2013;28(5):756-762.
73. Gagnon DJ, Fontaine GV, Riker RR, et al. Repurposing valproate, enteral clonidine, and phenobarbital for comfort in adult ICU patients: a literature review with practical considerations.*Pharmacotherapy*. 2017;37(10):1309-1321.
74. Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. *N Engl J Med*. 2017;376(23):2235-2244.
75. Bulger J, Nickel W, Messler J, et al. Choosing wisely in adult hospital medicine: five opportunities for improved healthcare value. *J Hosp Med*. 2013;8(9):486-492.
76. Hébert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. *N Engl J Med*. 1999;340(6):409-417.
77. Carson JL, Grossman BJ, Kleinman S, et al. Red blood cell transfusion: a clinical practice guideline from the AABB. *Ann Intern Med*. 2012;157(1):49-58.
78. Vincent WR, Hatton KW. Critically ill patients need "FAST HUGS BID"(an updated mnemonic). *Crit Care Med*. 2009;37(7):2326-2327.