Fluid Resuscitation

History, Physiology, and Modern Fluid Resuscitation Strategies

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KEYWORDS

• Crystalloid • Colloid • Balanced solutions • Fluid resuscitation • Fluid administration

KEY POINTS

- Balanced crystalloid offers theoretic benefits over normal saline, but to date large studies demonstrate only minimal benefits. Rather than the choice of crystalloid, clinicians should focus on the volume of fluid administered.
- The use of colloids has never been found to improve patient-centered outcomes. Initial volume repletion in the emergency department should be performed primarily with intravenous crystalloids.
- Fluid administration should be seen in the greater scheme of a patient resuscitation, modeled after trauma resuscitation, damage control resuscitation with the primary goal of controlling the underlying cause of the patients' shock.
- Although fluids can play a pivotal role in resuscitating patients, patients should be evaluated for potential harms of additional fluids prior to their administration.
- Early use of low-dose vasopressors has the potential to increase venous tone, limiting the volume of fluid required during initial resuscitative efforts.

INTRODUCTION

The repletion of patients' intravascular volume through the use of an intravenous (IV) electrolyte solution was first described by a young Irish physician, William Brooke O'Shaughnessy, in 1831. Immersing himself in the middle of a cholera outbreak in Sutherland, England, O'Shaughnessy observed that large amounts of water, sodium, chloride, and bicarbonate were being lost in these patients' stool.

> *The indications of cure … are two in number –first to restore the blood to its natural specific gravity; second to restore its deficient saline matters*[1] *… The first of these can only be affected by absorption, by imbibition, or by the injection of aqueous fluid into the veins.*[1]

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Since these humble beginnings, IV fluid therapy has become a key component of the initial management of shock in the emergency department. This article will discuss types of fluid, their physiologic effects, and current strategies on how best to utilize fluids when resuscitating patients in shock.

THE GREAT FLUID DEBATE

Normal Saline Versus Balanced Solutions

Lactated Ringers (LR), was discovered by Sydney Ringer and his laboratory assistant in 1883, when a saline solution mistakenly made with tap water rather than a distilled solution was used while studying frog hearts.[2] They noted cardiac activity was sustained for longer periods with the fortuitous tap water solution.[2] This prompted Ringer to further investigate the inorganic compounds present in the water, and to create his own solution.[2] His solution has undergone multiple revisions, the most famous of which was made by Alexis Hartmann, who in 1930 added lactate in the hopes of limiting the acidosis observed with previous iterations.[2]

Normal saline (NS) in its current form seems to originate from Joseph Hamburger, a Dutch physiologist, who in 1896 observed that a 0.9% sodium-chloride (NaCl) solution was more similar to human blood's freezing point than fluids of alternate tonicities.[3]

The debate over the appropriate crystalloid has been going on since Hartman first proposed his modified sodium-lactate solution as a means of preventing the acidosis observed with large-volume infusions of normal saline.[4–6] Because of its high chloride (Cl) content, normal saline is an acidotic solution with a pH of 5.6.[7] Solutions such as LR or PlasmaLyte replace a portion of their chloride content with an alternative anion that is metabolized to bicarbonate after its administration (**Table 1**). These chloride poor solutions are considered balanced solutions because of their more neutral effects on the acid-base physiology and chemical composure more similar to plasma.

Although the administration of NS will lead to a hyperchloremic, nonanion gap metabolic acidosis, it is unclear whether this acidosis has detrimental effects clinically.

Table 1
Electrolyte concentrations of various crystalloid solutions

	0.9% NS	0.45% NS	3% NS[a]	Lactate Ringers	PlasmaLyte	$D5^+$ 0.9% NS[a]	$D5^+$ 0.45% NS[a]
Na mEq/L	154	77	513	130	140	154	77
Cl mEq/L	154	77	513	109	93	154	77
K mEq/L	—	—	—	4	5	—	—
Ca mEq/L	—	—	—	217	—	—	—
Mg mEq/L	—	—	—	—	3	—	—
Acetate	—	—	—	—	27	—	—
Gluconate	—	—	—	—	23	—	—
Glucose g	—	—	—	—	—	50	50
Lactate mEq/L	—	—	—	—28	—	—	—
Glucose	—	—	—	—	—	—	—
mOsm/L	308	154	1027	273	294	560	406
SID	0	0	0	21	12	0	0
pH	5.6	5.6	50	6.5	7.4	4.0	4.0

[a] Specifically for Baxter products.

Several small nonrandomized and animal studies have found increased inflammation, impaired kidney function, increased pressor requirement, higher transfusion requirements, and even increased mortality associated with the administration of high chloride solutions.[8] The SPLIT Trial, a large, multicenter, cluster-randomized control trial comparing the use of NS with PlasmaLyte, by Young and colleagues,[9] did not demonstrate these harms.

Recently, 2 large single-center, pragmatic, cluster-randomized, multiple crossover trials were published to evaluate NS versus balanced solutions.[10,11] Both studies demonstrated greater derangement of serum Cl and bicarbonate concentrations in the normal saline groups. The study of noncritically ill emergency department patients also noted an improvement in the rate of major adverse kidney events (MAKE-30), a composite outcome including death, new renal replacement therapy, or persistent renal dysfunction at 30 days in patients randomized to balanced fluids.[10] Similarly, the SMART Trial, enrolling patients admitted to the intensive care unit (ICU), observed a 1.1% absolute decrease in the rate of MAKE-30 in patients who received balanced solutions.[11] Importantly, while both studies found a statistical difference in the rate of MAKE-30, the absolute difference was small (approximately 1% in either study), and no single individual endpoint was significantly different, including mortality.[11] A subgroup analysis reported a statistically significant improvement in both the composite outcome MAKE-30 and mortality in isolation in the cohort of patients admitted with sepsis.[12] Although interesting, this subgroup analysis should be viewed as hypothesis generating, requiring further validation. A recent Cochrane review examining over 20,000 patients in randomized controlled trials (RCTs) comparing normal saline with balanced solutions identified no difference in the rate of renal failure or death at 30 days.[13] Although the acid-base consequences of normal saline may indeed be real, the patient-centered consequences of using normal saline instead of a more balanced solution seems to be mostly a theoretic concern.

Colloid Versus Crystalloid

The second major consideration when determining what fluid to administer is whether to use a crystalloid or colloid solution. Colloids are defined as: "protein or polysaccharide solution that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment such as albumin, dextran, Hetastarch; or certain blood components such as plasma and platelets."[14] This discussion of colloids as resuscitative fluids will focus on albumin, as studies examining Hetastarch found an associated risk of renal failure and death.[15] Additionally, specific indications for albumin beyond resuscitation, such as hepatorenal syndrome and spontaneous bacterial peritonitis,[16] are beyond the scope of this article.

The physiologic defense for the use of colloids rests primarily on the Starling equation, or the ability to increase plasma oncotic pressure, increasing fluid reabsorption, thereby increasing circulating volume. The classic teaching is that fluid exchange occurs at the level of the capillary and is governed predominantly by 4 variables: the capillary oncotic pressure, the interstitial oncotic pressure, the capillary hydrostatic pressure, and interstitial hydrostatic pressure.[17,18] Over the course of the capillary, the forces begin to balance out such that the arterial side favors filtration, and the venous side favors reabsorption (**Fig. 1**A).[18]

Recent experimental evidence has challenged this view in favor of the revised Starling equation. In the revised Starling equation, plasma hydrostatic pressure is the dominant force. This results in net filtration occurring throughout the capillary without any reabsorption (**Fig. 1**B).[18] The lymphatic system then serves as the major pathway for filtered fluid to return to the vascular circulation.[18] In this model, the major

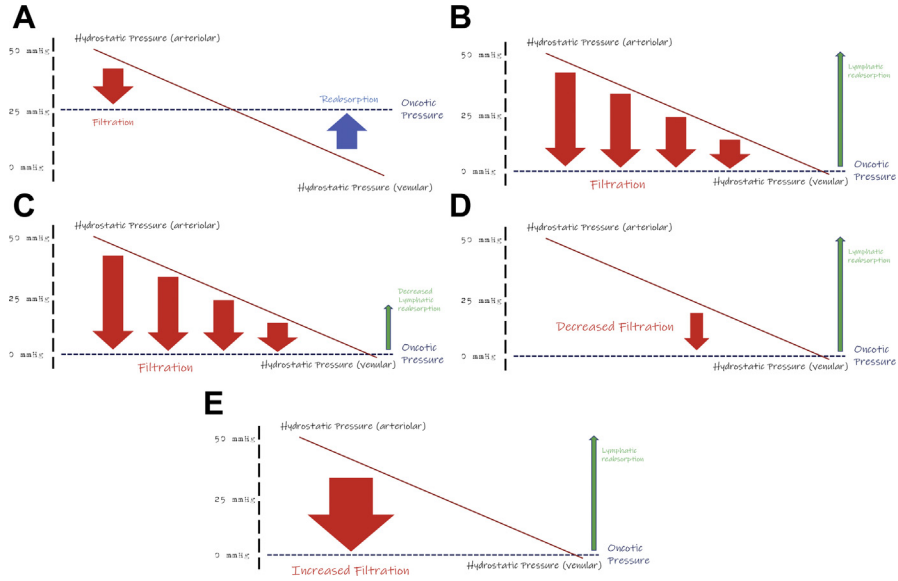

Fig. 1. (*A*) Classic starling equation. (*B*) Revised starling equation. (*C*) Revised starling equation in congestive heart failure patient. (*D*) Revised starling equation in patient in septic shock before resuscitation. (*E*) Revised starling equation in patient in septic shock after resuscitation.

determinants of the of filtration are the plasma hydrostatic pressure and vascular integrity.[18] The dominant forces of reabsorption are the lymphatic tone and right atrial pressure. Because most reabsorption occurs through the lymphatic system, the major determinants of reabsorption are lymphatic tone and right atrial pressure, the eventual basin for the lymphatic system.[18]

Although the lymphatic system can accommodate the volume of fluid filtered out of the vascular beds under normal conditions,[17] a decrease in lymphatic drainage or an increase in vascular filtration can result in interstitial edema. In a patient with congestive heart failure, filtration at the capillaries occurs at a normal rate, but lymphatic drainage is impaired because of elevated right atrial pressure, leading to interstitial edema (**Fig. 1**C). Conversely, in sepsis, because of systemic inflammation, there is a decrease in glycocalyx integrity, leading to the potential for an increase in net filtration.[19] Patients in septic shock are typically hypotensive, leading to a decrease in hydrostatic pressure and vascular filtration (**Fig. 1**D). It is only after the restoration of hydrostatic pressure through aggressive IV fluid administration that the loss of integrity of the glycocalyx becomes evident, and extravascular fluid accumulation is observed (**Fig. 1**E).

RCT data examining the use of colloids as resuscitative fluids have not consistently demonstrated fluid-sparing outcomes that would support the classic Starling theory. These trials observed small differences in overall fluid administration and early improvements in hemodynamic parameters; however, the differences were clinically inconsequential and failed to translate into an improvement in mortality.[20,21]

Outside the confines of specific disease states, where clinically relevant improvements in patient outcomes have been demonstrated, clinicians should limit the use of colloids in their resuscitative efforts. In fact, despite many physiologic theories expounding on the benefits of various fluid choices (both colloids and crystalloids)

over others, evidence has failed to identify the existence of an ideal IV fluid. The choice of solution matters far less than the quantity of fluid that is given. Thus, clinicians should feel free to use whichever solution is most convenient to them and refocus their attention on strategies to limit over-resuscitation and the downstream harms of fluid administration.

THE FORGOTTEN PHYSIOLOGY OF VENOUS RETURN

The current management of shock has been focused on the restoration of arterial blood pressure, end-organ perfusion, and oxygen delivery. Most resuscitative models focus on methods for optimizing cardiac output, but this is a limited view of the circulatory system. Venous return physiology plays a large role in determining the cardiac output, and the variables that determine the venous return are often overlooked. Understanding of the determinants of venous return is vital to understanding the safe and effective use of IV fluids.

The 3 variables that determine venous return are the right atrial pressure, the mean systemic filling pressure (Pms), and the vascular resistance. Under most clinical circumstances, vascular resistance minimally influences venous return; thus right atrial pressure and Pms are the major determinants of venous return.[22]

Pms is an elusive concept, primarily because of the difficulties encountered when attempting to measure its existence. Technically it is defined as the pressure in the vascular system if blood flow were to cease.[23] Functionally the Pms is the pressure driving blood back to the heart. It is in direct competition with the right atrial pressure and is determined by the volume of blood in the venous circulation and the intrinsic compliance of the vascular bed. Essentially a certain volume of fluid is required to fill the vascular bed to exert force on the vessel walls. This volume is called the unstressed volume. The volume of blood above this level is the stressed volume, or the volume that will increase Pms and venous return (**Fig. 2**).[23]

For example, in a patient with distributive shock from sepsis, the total volume of blood has not changed. Instead, vasodilation has led to an increase in vascular compliance, shifting a portion of the stressed volume to an unstressed state. This in turn leads to a decrease in the Pms and venous return.[24] Conversely, in a patient with hemorrhagic shock, there is also a decrease in the stressed volume. In this instance, however, it is not because of a change in vascular compliance, but rather a decrease in absolute blood volume. The physiologic response is to increase catecholamine levels, inducing venoconstriction, shifting blood from the unstressed to the stressed volume, increasing the Pms and temporarily maintaining the venous return. If bleeding is not controlled, however, blood loss will outpace venoconstrictive compensation, and further attempts to augment preload through the shifting of unstressed to stressed volume will be futile.

In septic shock, resuscitative efforts typically occur in a 2-stage process. First, adding volume to the system (in the form of a fluid bolus), will increase both the stressed volume and the total volume. Once an appropriate amount of fluid is given, attempts are made to reduce the vessel wall compliance, with the addition of vasopressor agents, causing a change in the ratio of volume in the stressed and unstressed states. In this case the total volume would stay constant, while the unstressed volume decreases, and the stressed volume increases. In contrast, for patients in hemorrhagic shock, intrinsic catecholamines have already constricted the venous system, maximally recruiting unstressed to stressed volume. The administration of IV fluids, in this case blood products, to replace the lost blood, is an attempt to restore the total volume and stressed volume to a more physiologic state.

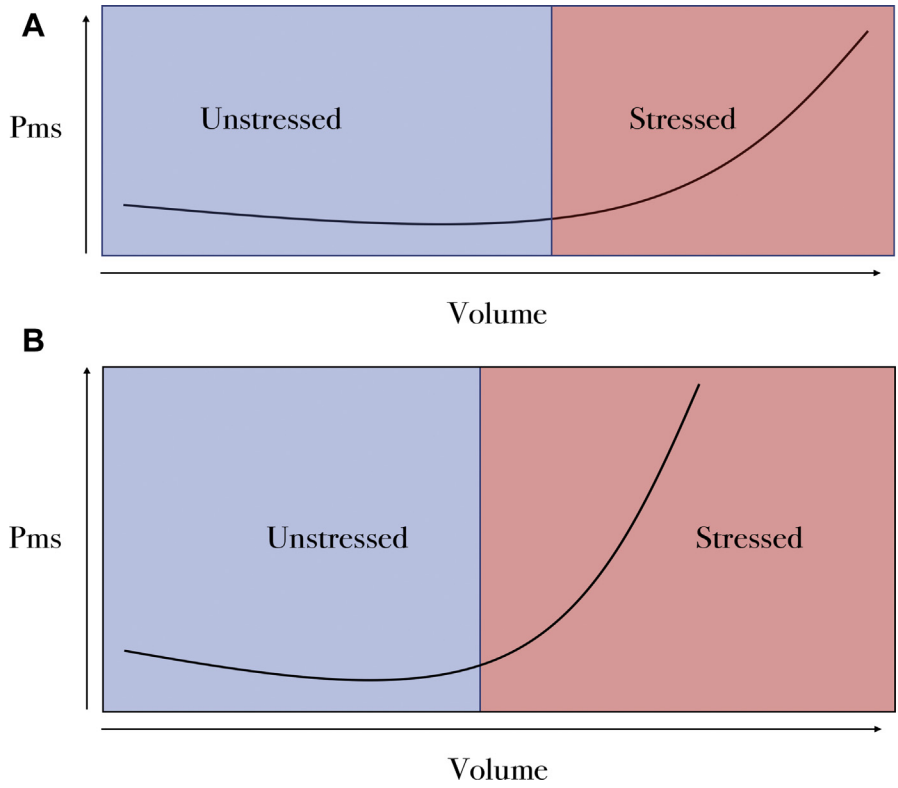

Fig. 2. (*A*) Unstressed and stressed volume. (*B*) Unstressed and stressed volume following and increase in vascular compliance.

With these principles in mind, it is important to remember the intended goals of a fluid bolus, to increase cardiac output and oxygen delivery to the end-organs. But it equally important to remember this is only achieved if the fluid bolus results in an augmentation of Pms and increases venous return.

THE CLINICAL REALITY OF A FLUID BOLUS

Traditionally it has been taught that a fluid bolus of 500 to 1000 mL should be rapidly infused into the circulation to assess for an adequate hemodynamic response prior to deciding whether to administer further volume challenges. Studies describing the effects of the administration of IV fluids in a rapid bolus have observed the desired increase in cardiac output lasts for approximately 120 minutes, at which point cardiac function seems to return to prior levels.[25] Studies indicate a more rapid administration of the fluid bolus leads to a shorter period of observed effects on cardiac output.[25] This phenomenon is likely caused by the rapid increase in hydrostatic pressure induced by the bolus, leading to an increase in filtration of fluid from the intravascular space. The central venous pressure (CVP), however, remains elevated for much longer.[25]

A MODERN-DAY RESUSCITATIVE STRATEGY

Typically, a fluid responsiveness strategy is recommended as the gold standard to guide fluid administration, defined as a response of 10% to 15% increase in a patient's

cardiac output.[26] Recent data suggest that the use of a passive leg raise and some form of noninvasive cardiac output monitoring (ie ultrasound or pulse pressure variation) is the most accurate measure to predict whether an individual patient will respond to a fluid bolus.[26] Although PLR seems to adequately predict a patient's response to fluid, no data suggest that a fluid responsiveness strategy improves patient-important outcomes. Approximately 90% of healthy volunteers will respond to a fluid bolus by increasing their cardiac output.[27] One may conclude that people exist naturally in a fluid responsive state, and to iatrogenically drive someone to the flat portion of their Frank-Starling curve is by definition over-resuscitation. Because of the effects of a fluid bolus on cardiac output are short-lived, and the effects on CVP and venous congestion are more enduring, a resuscitative strategy that encourages multiple fluid boluses based on the response of cardiac output may cause harm. A growing body of evidence suggests aggressive fluid resuscitative strategies are harmful, leading to increased rates of acute kidney injury (AKI), pulmonary edema, acute respiratory distress syndrome, and even death.[28]

In a trial of African children in septic shock, those randomized to IV fluid bolus therapy resolved shock quicker but died more frequently than those randomized to maintenance fluid alone.[29,30] Despite concerns with this trial's external validity (eg, pediatric patients treated in nonindustrialized countries), similar results have been demonstrated in multiple trials in varied patient populations. Adult septic shock patients in Zambia randomized to a resuscitation strategy of correcting early hemodynamic abnormalities with IV fluid therapy had a more rapid resolution of shock, but this strategy was also associated with increased mortality.[31] Hjortrup and colleagues[32] found that an aggressive response to hemodynamic perturbations led to an increase in the frequency of AKI. Although these vigorous resuscitative strategies were all associated with timelier improvements in early hemodynamic markers, this came at the cost of downstream morbidity and mortality.

It is not hard to imagine the physiologic underpinning of such observations. As discussed, sepsis leads to increases in venodilation, a decrease in stressed volume, and in turn a decrease in venous return and cardiac output. In addition, the inflammatory milieu increases capillary permeability, increasing the filtration at the capillary level. Prior to resuscitative efforts, extravascular fluid accumulation is limited by the decreased hydrostatic pressure of the hypotensive state. Only after active resuscitation with IV fluid boluses is the loss of vascular integrity fully realized, creating a circular feedback loop. IV fluids are administered to increase blood pressure, and this increase in blood pressure leads to an increase in hydrostatic forces, increasing the rate of fluid leaving the capillaries. This capillary leak leads to an increase in tissue edema, a decrease in intravascular volume, and hypotension. In response, more fluids are administered, leading to more third spacing of fluids and tissue edema.

Clearly there are harms associated with the use of IV fluids. Optimal resuscitative strategies take these risks into account when administering IV fluids to patients in shock. The first step is the understanding that resuscitation alone does not correct shock. Studies examining interventions intended to optimize patients' hemodynamic abnormalities, in any type of shock, have failed to demonstrate an improvement in patient outcomes.[33,34] The only beneficial therapies have been ones that focus on the correction of the underlying cause or strategies that seek to limit resuscitative interventions until source control is achieved. Given this understanding, fluids should be viewed as a bridge, intended to support patients until control of the underlying shock state can be achieved.

The concept of damage control resuscitation has been successfully implemented in patients with traumatic injuries leading to hemorrhagic shock.[35] In fact, for patients in

hemorrhagic shock, aggressive resuscitation prior to achieving hemorrhage control is detrimental. Rather, a damage control strategy (DCS) focusing on maintaining the minimal blood pressure to maintain end-organ perfusion until hemorrhage control is achieved improves overall survival.[36–38] The authors believe that all resuscitative efforts, no matter the source of shock, should be viewed from a similar perspective. Any resuscitative strategy should attempt to define the cause of the patients' hemodynamic collapse. Once identified, measures to control the etiology of shock should be undertaken in parallel to the hemodynamic resuscitation. Classically in septic shock, a prescribed volume of fluids is administered regardless of the patient's volume status. However, in the authors' view of DCS, fluids would be administered as thoughtfully as vasopressors.

The authors advocate for a fluid tolerance strategy that assesses an individual patient's fluid tolerance by examining the potential benefit or harm associated with additional fluid administration. Unlike fluid responsiveness, fluid tolerance is not based on a single measure, but rather is a holistic approach, examining the patient's history, current presentation, and bedside ultrasound to determine whether a patient is more likely to be helped or harmed from IV fluids. For example, a history of pulmonary hypertension or congestive heart failure would indicate that the patient may be fluid intolerant. Likewise, a patient presenting with septic shock is more likely to have increased capillary leak compared to a patient with hypovolemia caused by diabetic ketoacidosis.

The authors caution against the use of serum lactate as an indicator of a patient's fluid requirements.[39] There is a growing body of evidence that lactate is a poor surrogate for tissue hypoperfusion and hypovolemia. A recently published RCT[40] examining a lactate-guided resuscitation strategy suggested harms associated with this approach. Rather, a nonclearing lactate level should alert clinicians of the ongoing stress experienced by the patient, prompting an inquiry into whether the source of the patient's shock is truly controlled. It is the authors' opinion that the interpretation of lactate should be separate from decisions regarding ongoing fluid resuscitation.

Both physical examination and point of care ultrasound should focus on signs indicating that further fluid administration is likely to be detrimental to the patient. Signs concerning for heart failure, such as jugular vein distension, orthopnea, and decreased pulse pressure are all indicative of potential fluid intolerance, but they are fairly late findings and often not present despite significant volume overload.[26,41] An elevated CVP (a level > 8 mm Hg or a rising level with ongoing fluid administration), although much maligned for its inability to predict fluid responsiveness, is a fairly reliable marker of fluid intolerance.[28,42] Echocardiographic markers of fluid intolerance, including a reduction in left-sided systolic function or ejection fraction,[26] a decrease in right-sided function as indicated by a low tricuspid annular plane excursion,[43] and a large inferior vena cava without respiratory variation are also fairly sensitive markers that further fluid is likely to be harmful.[26,44]

An assessment of fluid tolerance should not be based on cardiac function in isolation, but should also include a determination of capillary integrity and accumulation of extravascular fluid. This includes extremity edema and pulmonary edema seen in a standard chest radiograph or on ultrasound. Ultrasonographic signs of venous congestion present on the hepatic, portal, or intrarenal veins have been demonstrated to be strong markers of fluid intolerance in critically ill patients.[45–48]

Finally, it is important to continue to reassess patients' ultrasonographic and physical examination signs of volume intolerance, as they may be absent during an initial assessment, only to become obvious as the physiology evolves. Similar to fluid

responsiveness strategies, assessments of fluid intolerance should be made prior to the administration of each IV fluid bolus and not only during the initial assessment.

SUMMARY

It is important to note that the discovery of IV fluids failed to have a significant impact in limiting the mortality during subsequent cholera outbreaks. It was not until Dr. John Snow discovered that contaminated drinking water from the Broad Street pump was the source of 1 specific deadly outbreak that control of future epidemics was achieved. This observation should serve as a clear reminder that IV fluid therapy is not a cure but rather a bridge until definitive control of the patient's source of shock can be controlled. Moreover, there are clear harms associated with the aggressive use IV fluid administration. Clinicians should strive to identify signs of these harms and limit fluid administration in patients when fluid intolerance is present.

DISCLOSURE

The authors have nothing to disclose.

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