CHAPTER 59

Principles of Fluid Therapy

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OBJECTIVES

This chapter will:

1. Describe the physiologic rationale for fluid resuscitation in the intensive care unit.
2. Discuss choice of fluid, volume, and end points for intravenous fluid resuscitation.

Administering intravenous (IV) fluid is one of the most common interventions in the intensive care unit (ICU). Although IV fluid can be used to replace free water, electrolytes, glucose, and plasma constituents (e.g., albumin), most IV fluid in the ICU is given to increase intravascular volume. Critically ill adults frequently experience either absolute hypovolemia (resulting from blood loss, diarrhea, decreased oral intake) or effective hypovolemia (increased venous capacitance resulting from sepsis, medications, adrenal insufficiency). IV fluid resuscitation can increase ventricular preload, cardiac output, and oxygen delivery, restoring hemodynamic stability and tissue perfusion. This chapter discusses the physiologic rationale for fluid therapy in the ICU; the volume, rate, and end points of fluid resuscitation; choice of fluid; and areas of ongoing controversy.

PHYSIOLOGIC RATIONALE FOR FLUID ADMINISTRATION

Hypovolemia reduces effective circulating blood volume. With mild hypovolemia, compensatory increases in heart rate, cardiac contractility, and peripheral vasoconstriction maintain systemic blood pressure and tissue perfusion. Healthy organs autoregulate their blood flow, redistributing perfusion toward the brain, heart, and kidneys and away from the skin and splanchnic bed. With more severe hypovolemia, activation of the sympathetic, renin-angiotensin, and antidiuretic hormone systems is inadequate to maintain blood pressure.[1] Overt hypotension may be accompanied by signs of end-organ dysfunction (skin mottling, decreased urine output, altered mental status), and decreased oxygen delivery may precipitate anaerobic metabolism and lactic acidosis. Rapid administration of IV fluid to patients with hypovolemia is intended to increase intravascular volume, improve venous return and ventricular filling, and ultimately restore cardiac output, perfusion pressure, and oxygen delivery.

Resuscitation volume, end points, and fluid choice have been predicated largely on this classic physiologic model. However, evolving understanding suggests that the hemodynamic response to fluid administration depends on an intricate interaction of mean systemic filling pressure, right atrial pressure, venous resistance, and ventricular compliance, many of which are deranged during critical illness.[2] Moreover, the traditional Starling model, in which fluid movement across the capillary membrane is governed by the balance of hydrostatic and oncotic pressure, has been challenged by increasing insight into the function of the endothelial glycocalyx. This dynamic network of glycoproteins and proteoglycans bound to the luminal side of endothelial cells regulates the movement of colloids from the intravascular to interstitial space, governing oncotic pressure and endothelial permeability.[3] Damage to the glycocalyx during critical illness disrupts these functions, allowing outflow of protein and fluid into the interstitial space and altering the expected response to colloid and crystalloid administration. Simplistic approaches to fluid resuscitation end points ("central venous pressure > 8 mm Hg") and fluid choice ("colloids stay in the vascular space") are evolving to recognize that effects of fluid therapy may vary widely among patients with different pathophysiologic conditions in different phases of critical illness.[4]

VOLUME, RATE, AND END POINT OF FLUID ADMINISTRATION

Initial Assessment and Management

Determining intravascular volume in critically ill patients is challenging. Physical exam findings such as tachycardia and hypotension are nonspecific and, because of aberrant vascular permeability and oncotic pressure, some critically ill patients with marked peripheral edema may be intravascularly deplete. For patients with a clinical history, physical examination, and laboratory evaluation suggestive of volume depletion, current clinical practice guidelines suggest the initial administration of 20 mL/kg of IV crystalloid, given as boluses of at least 250 to 500 mL over 10 to 30 minutes, with careful monitoring of the patient's hemodynamic response.[5–7]

The optimal approach to fluid management after an initial empiric fluid bolus is an area of current controversy. Patients with ongoing fluid losses (e.g., severe pancreatitis, burns) may benefit from repeated fluid boluses, sometimes receiving upwards of 10 to 20 L of IV fluid in the days after ICU admission. However, increasing recognition of the detrimental effects of fluid overload on organ function[8] and the potential toxicities of the IV fluids[9] has generated intense interest in objective measures to guide the volume of fluid administered.

Fluid Resuscitation Targets

End point–targeted fluid resuscitation became routine practice for many ICU providers after a 2001 trial of early goal-directed therapy (EGDT) for sepsis.[10] Among 263 patients with sepsis and hypoperfusion, the protocolized administration of 500 mL IV crystalloid boluses every 30 minutes to achieve a central venous pressure (CVP) of 8 to 12 mm Hg, vasopressors to maintain a mean arterial pressure (MAP) of 65 mm Hg, and dobutamine and blood transfusion to attain a mixed venous oxygen saturation of at least 70% resulted in a 16% absolute reduction in mortality. Based on this study, and on related trials of goal-directed fluid therapy in the operating room,[11] protocolized fluid resuscitation targeting CVP, MAP, and venous oxygen saturation or lactate was incorporated into international guidelines and widely adopted as standard-of-care for fluid management in ICU patients with tissue hypoperfusion.[5]

Recently, however, three multicenter trials compared EGDT with care in which invasive resuscitation end points were optional (CVP) or forbidden (venous oxygen saturation) and did not find a benefit for EGDT.[12] Because patients in the recent trials were less severely ill and the volume of fluid was more similar between study arms than in the original EGDT trial, the implications for the volume of fluid that should be administered during early sepsis resuscitation are unclear. Provocative studies from regions in which EGDT is not standard-of-care have shown worse outcomes with early fluid resuscitation among children with severe infection[13] and septic adults.[14] In these trials, administration of IV fluid appeared to precipitate respiratory failure[14] and cardiovascular decompensation,[15] but limited access to hemodynamic monitoring and mechanical ventilation in these studies makes extrapolation challenging. Ongoing trials comparing liberal to conservative fluid management in early septic shock may help determine the optimal volume of early fluid resuscitation (NCT02079402, NCT01663701).

These studies[8,12,14] highlight the difficulty of assessing the risks and benefits of IV fluid administration for a given patient, and the limitations of static predictors of a patient's response to fluid (e.g., venous oxygen, lactate, or CVP). Venous oxygen and lactate levels are not sensitive or specific enough to predict whether a patient will experience hemodynamic improvement with an IV fluid bolus.[16] Use of CVP or pulmonary artery occlusion pressure (PAOP) as surrogates for ventricular end-diastolic volume may be confounded by right ventricular compliance, valve regurgitation, and changing intrathoracic pressures.[17] Although a very low or a very high intravascular pressure may provide some information, CVP and PAOP do not accurately or reliably predict patients' hemodynamic response to fluid challenges.[17] In view of the numerous trials demonstrating no outcome benefit from invasive intravascular pressure measurement,[12,18] focus has shifted to alternative, dynamic measures of "fluid responsiveness."

Assessment of "Fluid Responsiveness"

"Fluid responsiveness" has been defined as an increase in stroke volume or cardiac output of at least 10% to 15% in the 10 to 15 minutes after administration of a 250 to 500 mL bolus of crystalloid.[17] The goal in attempting to predict "fluid responsiveness" is to reserve fluid administration (after initial resuscitation) for those patients for whom the hemodynamic benefits outweigh potential harms (although whether guiding fluid administration based on "fluid responsiveness" improves patient outcomes is currently unknown). Importantly, "fluid responsiveness" and fluid deficiency are not the same. Measurement of "fluid responsiveness" has become widespread in part because we do not have a tool for real-time measurement of absolute intravascular volume status. It is critical to remember that most healthy volunteers meet criteria for "fluid responsiveness,"[19] and "fluid responsiveness" by itself is not an indication to administer fluid.

Systolic pressure variation, pulse pressure variation,[20] and stroke volume variation derived from the arterial or pulse oximetry wave forms are dynamic predictors of "fluid responsiveness" that use respiratory variation in intrathoracic pressure to gauge a patient's expected hemodynamic response to fluid bolus administration. In mechanically ventilated patients who are not spontaneously breathing, delivery of a positive pressure breath increases intrathoracic pressure and decreases venous return, ventricular filling, and stroke volume. Variation in systolic pressure, pulse pressure, or stroke volume greater than 10% to 15% between inspiration and expiration suggests that administration of IV fluid may increase stroke volume and cardiac output.

Ultrasound also may be used to assess "fluid responsiveness" in the ICU. Inferior vena cava (IVC) diameter, collapsibility, size relative to the aorta, and distention with positive pressure ventilation[21] have been proposed as potential predictors of a patient's response to fluid administration. Left ventricular cavity size and aortic flow velocity on transthoracic or transesophageal echocardiography may predict "fluid responsiveness."[22] In patients for whom a real-time measure of stroke volume or cardiac output is available, monitoring the change in these variables after increasing venous return by passively raising the patient's legs to 45 degrees for 30 to 90 seconds may serve as an easily reversible test of "fluid responsiveness."[23]

Fluid Challenge

For many ICU patients, advanced measures of "fluid responsiveness" remain unavailable (because of absence of stroke volume or cardiac output monitoring, spontaneous breathing, low-tidal volume ventilation, or arrhythmia). For these patients, a "fluid challenge" approach is frequently employed: approximately 250 mL of colloid or crystalloid is administered over 10 minutes with careful monitoring for efficacy (improved heart rate, blood pressure, urine output, mental status) and safety (development of pulmonary edema, elevation in intravascular pressures). This process may be repeated serially for patients who appear to be responding clinically to fluid administration. For patients who do not respond, or who encounter safety concerns, further fluid administration is withheld and alternative therapies to improve hemodynamics (e.g., vasopressors) are considered.

Fluid Management After Resuscitation

Optimal fluid management differs in different phases of critical illness.[4] During initial rescue and optimization, fluid boluses are given to reverse hypotension and restore perfusion. After stabilization, the goals shift toward replacing ongoing losses and maintaining net zero or negative fluid balance.[4] Fluids should be titrated to patient need and excessive "maintenance fluids" should be avoided.[8] Finally, as patients experience organ recovery, oral

intake should be emphasized, IV fluid minimized, and fluid mobilization encouraged with diuretics if needed. Although useful as a conceptual framework, these phases may be challenging to delineate in practice and may not be experienced linearly by patients moving through their ICU course.

In summary, fluid status assessment in critical illness is challenging. Initial resuscitation for patients with hypovolemia frequently involves administration of 20 mL/kg of IV crystalloid in the form of fluid boluses. Additional fluid administration should be titrated to patient need using all available clinical data, including hemodynamics, urine output, and static or dynamic predictors of "fluid responsiveness." The ideal volume and end points of fluid resuscitation remain uncertain, and the potential harms of fluid overload are increasingly recognized. After stabilization, focus should shift toward maintaining a net even fluid balance and ultimately fluid removal during recovery.

SELECTION OF FLUID

The optimal IV fluid to administer in critically ill patients has been a subject of debate for decades. The ideal IV fluid for resuscitation would (1) increase intravascular volume without accumulating in the extravascular space, (2) deliver a chemical composition similar to plasma, and (3) improve patient outcomes cost effectively. No such fluid currently exists. Available IV fluids include colloid solutions (human albumin and semisynthetic colloids) and crystalloid solutions (saline and "balanced" crystalloids). How the exact choice among these fluids influences patient outcomes remains unclear.

Crystalloids

Crystalloids, which are solutions of ions freely permeable through capillary membranes, are the most commonly administered IV fluid globally and the first line for fluid resuscitation in the ICU.[5–7] Two basic categories of "isotonic" crystalloid exist: saline and "physiologically balanced" solutions. Saline (0.9% sodium chloride) comprises 154 mmol/L each of sodium and chloride, achieving isotonicity to the extracellular fluid by means of a chloride concentration considerably higher than that of the plasma. "Physiologically balanced" crystalloids (lactated Ringer's, Hartmann's solution, Plasma-Lyte) can be slightly hypotonic to extracellular fluid but provide anions that more closely approximate plasma pH.

Fluid resuscitation with saline causes hyperchloremic metabolic acidosis among critically ill patients.[24] Whether saline-induced hyperchloremia or metabolic acidosis affect patient outcomes remains unclear. The chloride contained in IV crystalloids also has been hypothesized to regulate renal blood flow via tubuloglomerular feedback,[25] and observational studies have suggested use of saline is associated with increased acute kidney injury and death among ICU patients.[26,27] Although a recent pilot trial among more than 2000 critically ill adults did not observe a difference in outcomes between patients assigned to saline versus Plasma-Lyte, the patients' severity of illness was low and the median volume of crystalloid received was only 2 L. Additional trials are needed to definitively determine whether choice of crystalloid affects clinical outcomes among critically ill adults.

Colloids

Colloids are suspensions of molecules with high enough molecular weights to limit passage across healthy capillary membranes. Available colloids include human albumin solutions, gelatins, dextrans, and starches. The traditional physiologic rationale that colloids more effectively expand intravascular volume by maintaining colloid oncotic pressure in the intravascular space has been challenged by improved understanding of the endothelial glycocalyx[3] and the similarity in fluid requirements among patients receiving colloids versus crystalloids in controlled trials.[28]

Albumin

Human serum albumin is a small protein synthesized by the liver that sustains plasma colloid oncotic pressure, binds nitric oxide, and regulates inflammation. Several large trials have examined the use of either 4% to 5% or 20% to 25% albumin solutions in critical illness.[28,29] The Saline versus Albumin Fluid Evaluation (SAFE) Study of nearly 7000 critically ill adults comparing 4% albumin to saline for fluid resuscitation in the ICU found no difference in 28-day mortality overall, with potential harm in the subgroup with traumatic brain injury and potential benefit among those with sepsis.[28] In the Albumin Italian Outcome Sepsis (ALBIOS) trial of nearly 2000 septic ICU patients, daily administration of 20% albumin targeting a serum albumin level of 3 g/L facilitated liberation from vasopressors but did not affect mortality, except possibly in patients with septic shock.[29] In the absence of clear improvement in patient outcomes, albumin's high cost will likely prevent it from replacing crystalloids as first-line therapy for patients requiring IV fluid resuscitation.

Semisynthetic Colloids

Semisynthetic colloids derived from bovine collagen (gelatins), sucrose (dextrans), and maize-derived glucose polymers (hydroxyethyl starch [HES]) have been used for intravascular volume expansion, but recent studies have raised concern about their safety.[9,30,31] HES, the most carefully studied semisynthetic colloid, has been linked to increased acute kidney injury[9,30,31] and mortality[9] in susceptible patient populations. Although some studies have suggested improved hemodynamic and clinical outcomes with use of colloids for critically ill adults,[32] cost and safety concerns argue against use of semisynthetic colloids as first-line for IV fluid resuscitation in critical illness.

In summary, IV crystalloids remain the first-line choice for fluid resuscitation in critical illness. Whether choice of crystalloid affects patient outcomes remains unknown. Albumin should be avoided in traumatic brain injury and otherwise reserved for the select patient populations most likely to benefit (e.g., advanced cirrhosis, septic shock with hypoalbuminemia). Hydroxyethyl starch is the only semisynthetic colloid rigorously studied and appears to increase acute kidney injury and potentially mortality in critically ill patients.

CONCLUSION

Fluid resuscitation remains a common and potentially lifesaving intervention for hypovolemic patients in the ICU.

Administration of 20 mL/kg of IV crystalloid in the form of rapid boluses with careful monitoring of hemodynamic response is the recommended approach to initial fluid management for patients whose clinical picture suggests hypovolemia. However, the optimal volume and end points of fluid administration throughout the phases of critical illness remain unclear. Although, for many providers, dynamic predictors of "fluid responsiveness" such as passive leg raising or pulse pressure variation have replaced static indices such as CVP, whether using such measures affects patient outcomes is unknown. For most ICU patients, fluid administration should be guided by a comprehensive approach to the available clinical data, including patient hemodynamics, urine output, and laboratory evaluation, in concert with static or dynamic measures of "fluid responsiveness." Whether the choice of IV fluid affects patient outcomes remains uncertain, but the cost of albumin solutions and the potential adverse effect of semisynthetic colloids make IV crystalloids the current first-line for fluid resuscitation in the ICU. Ultimately, deciding whether to administer fluid to an ICU patient (and which fluid to administer) requires an understanding of the underlying physiology, familiarity with the increasingly robust empiric data, and an individualized assessment of the risks and benefits for that patient at that particular point in his or her critical illness.

Key Points

1. Hypovolemic critically ill patients should receive early intravenous fluid resuscitation.
2. The physiologic rationale for fluid administration includes restoring ventricular preload, stroke volume, and organ perfusion.
3. The ideal volume and end point of fluid resuscitation is unknown. Static end points (e.g., central venous pressure), dynamic end points (e.g., passive leg raise), and measures of organ perfusion (e.g., venous oxygen or lactate) each have limitations in guiding fluid administration.
4. Crystalloids are currently first-line for IV fluid resuscitation because of albumin's high cost and concern for adverse effects associated with semisynthetic colloids.
5. Fluid administration must be individualized according to patient, condition, and phase of critical illness.

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A complete reference list can be found online at ExpertConsult.com.

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