REVIEW ARTICLE

CRITICAL CARE MEDICINE

Simon R. Finfer, M.D., and Jean-Louis Vincent, M.D., Ph.D., *Editors*

Resuscitation Fluids

John A. Myburgh, M.B., B.Ch., Ph.D., and Michael G. Mythen, M.D., M.B., B.S.

Fluid resuscitation with colloid and crystalloid solutions is a ubiquitous intervention in acute medicine. The selection and use of resuscitation fluids is based on physiological principles, but clinical practice is determined largely by clinician preference, with marked regional variation. No ideal resuscitation fluid exists. There is emerging evidence that the type and dose of resuscitation fluid may affect patient-centered outcomes.

Despite what may be inferred from physiological principles, colloid solutions do not offer substantive advantages over crystalloid solutions with respect to hemodynamic effects. Albumin is regarded as the reference colloid solution, but its cost is a limitation to its use. Although albumin has been determined to be safe for use as a resuscitation fluid in most critically ill patients and may have a role in early sepsis, its use is associated with increased mortality among patients with traumatic brain injury. The use of hydroxyethyl starch (HES) solutions is associated with increased rates of renal-replacement therapy and adverse events among patients in the intensive care unit (ICU). There is no evidence to recommend the use of other semisynthetic colloid solutions.

Balanced salt solutions are pragmatic initial resuscitation fluids, although there is little direct evidence regarding their comparative safety and efficacy. The use of normal saline has been associated with the development of metabolic acidosis and acute kidney injury. The safety of hypertonic solutions has not been established.

All resuscitation fluids can contribute to the formation of interstitial edema, particularly under inflammatory conditions in which resuscitation fluids are used excessively. Critical care physicians should consider the use of resuscitation fluids as they would the use of any other intravenous drug. The selection of the specific fluid should be based on indications, contraindications, and potential toxic effects in order to maximize efficacy and minimize toxicity.

From the University of New South Wales, the Division of Critical Care and Trauma, George Institute for Global Health, and the Department of Intensive Care Medicine, St. George Hospital — all in Sydney (J.A.M.); and the National Institute for Health Research, University College London Hospitals Biomedical Research Centre, London (M.G.M.). Address reprint requests to Dr. Myburgh at the Department of Intensive Care Medicine, St. George Hospital, Gray St., Kogarah 2217, Sydney, NSW, Australia, or at jmyburgh@georgeinstitute.org.au.

N Engl J Med 2013;369:1243-51.
DOI: 10.1056/NEJMra1208627

HISTORY OF FLUID RESUSCITATION

In 1832, Robert Lewins described the effects of the intravenous administration of an alkalinized salt solution in treating patients during the cholera pandemic. He observed that "the quantity necessary to be injected will probably be found to depend upon on the quantity of serum lost; the object being to place the patient in nearly his ordinary state as to the quantity of blood circulating in the vessels."[1] The observations of Lewins are as relevant today as they were nearly 200 years ago.

Asanguinous fluid resuscitation in the modern era was advanced by Alexis Hartmann, who modified a physiologic salt solution developed in 1885 by Sidney Ringer for rehydration of children with gastroenteritis.[2] With the development of blood fractionation in 1941, human albumin was used for the first time in large quantities for resuscitation of patients who were burned during the attack on Pearl Harbor in the same year.

Today, asanguinous fluids are used in almost all patients undergoing general

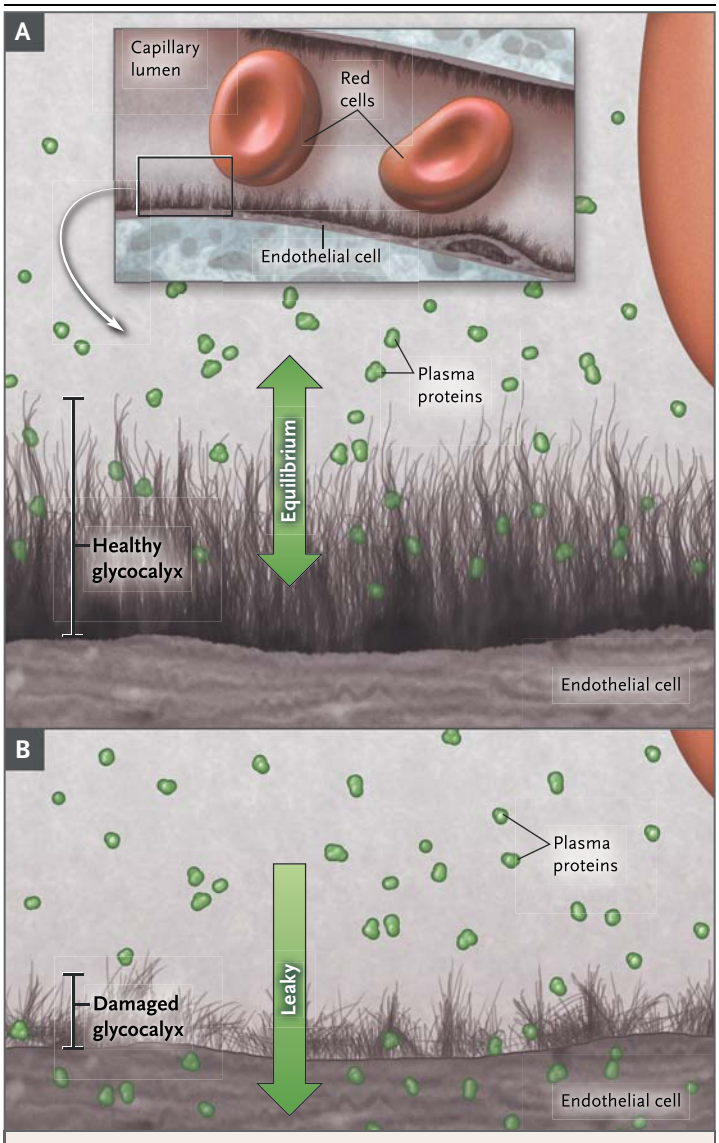

Figure 1. Role of the Endothelial Glycocalyx Layer in the Use of Resuscitation Fluids.

The structure and function of the endothelial glycocalyx layer, a web of membrane-bound glycoproteins and proteoglycans on endothelial cells, are key determinants of membrane permeability in various vascular organ systems. Panel A shows a healthy endothelial glycocalyx layer, and Panel B shows a damaged endothelial glycocalyx layer and resultant effect on permeability, including the development of interstitial edema in some patients, particularly those with inflammatory conditions (e.g., sepsis).

anesthesia for major surgery, in patients with severe trauma and burns, and in patients in the ICU. It is one of the most ubiquitous interventions in acute medicine.

Fluid therapy is only one component of a complex hemodynamic resuscitation strategy. It is targeted primarily at restoring intravascular volume. Since venous return is in equilibrium with cardiac output, sympathetically mediated responses regulate both efferent capacitance (venous) and afferent conductance (arterial) circulations in addition to myocardial contractility.[3] Adjunctive therapies to fluid resuscitation, such as the use of catecholamines to augment cardiac contraction and venous return, need to be considered early to support the failing circulation.[4] In addition, changes to the microcirculation in vital organs vary widely over time and under different pathologic states, and the effects of fluid administration on end-organ function should be considered along with effects on intravascular volume.

THE PHYSIOLOGY OF FLUID RESUSCITATION

For decades, clinicians have based their selection of resuscitation fluids on the classic compartment model — specifically, the intracellular fluid compartment and the interstitial and intravascular components of the extracellular fluid compartment and the factors that dictate fluid distribution across these compartments. In 1896, English physiologist Ernest Starling found that capillaries and postcapillary venules acted as a semipermeable membrane absorbing fluid from the interstitial space.[5] This principle was adapted to identify the hydrostatic and oncotic pressure gradients across the semipermeable membrane as the principal determinants of transvascular exchange.[6]

Recent descriptions have questioned these classic models.[7] A web of membrane-bound glycoproteins and proteoglycans on the luminal side of endothelial cells has been identified as the endothelial glycocalyx layer[8] (Fig. 1). The subglycocalyx space produces a colloid oncotic pressure that is an important determinant of transcapillary flow. Nonfenestrated capillaries throughout the interstitial space have been identified, indicating that absorption of fluid does not occur through venous capillaries but that fluid from the interstitial space, which enters through a small number of large pores, is returned to the circulation primarily as lymph that is regulated through sympathetically mediated responses.[9]

The structure and function of the endothelial glycocalyx layer are key determinants of membrane permeability in various vascular organ sys-

tems. The integrity, or "leakiness," of this layer, and thereby the potential for the development of interstitial edema, varies substantially among organ systems, particularly under inflammatory conditions, such as sepsis,[10] and after surgery or trauma, when resuscitation fluids are commonly used.

THE IDEAL RESUSCITATION FLUID

The ideal resuscitation fluid should be one that produces a predictable and sustained increase in intravascular volume, has a chemical composition as close as possible to that of extracellular fluid, is metabolized and completely excreted without accumulation in tissues, does not produce adverse metabolic or systemic effects, and is cost-effective in terms of improving patient outcomes. Currently, there is no such fluid available for clinical use.

Resuscitation fluids are broadly categorized into colloid and crystalloid solutions (Table 1). Colloid solutions are suspensions of molecules within a carrier solution that are relatively incapable of crossing the healthy semipermeable capillary membrane owing to the molecular weight of the molecules. Crystalloids are solutions of ions that are freely permeable but contain concentrations of sodium and chloride that determine the tonicity of the fluid.

Proponents of colloid solutions have argued that colloids are more effective in expanding intravascular volume because they are retained within the intravascular space and maintain colloid oncotic pressure. The volume-sparing effect of colloids, as compared with crystalloids, is considered to be an advantage, which is conventionally described in a 1:3 ratio of colloids to crystalloids to maintain intravascular volume. Semisynthetic colloids have a shorter duration of effect than human albumin solutions but are actively metabolized and excreted.

Proponents of crystalloid solutions have argued that colloids, in particular human albumin, are expensive and impractical to use as resuscitation fluids, particularly under field-type conditions. Crystalloids are inexpensive and widely available and have an established, although unproven, role as first-line resuscitation fluids. However, the use of crystalloids has classically been associated with the development of clinically significant interstitial edema.

TYPES OF RESUSCITATION FLUID

Globally, there is wide variation in clinical practice with respect to the selection of resuscitation fluid. The choice is determined largely by regional and clinician preferences that are based on institutional protocols, availability, cost, and commercial marketing.[11] Consensus documents about the use of resuscitation fluids have been developed and directed primarily at specific patient populations,[12-14] but such recommendations have been based largely on expert opinion or low-quality clinical evidence. Systematic reviews of randomized, controlled trials have consistently shown that there is little evidence that resuscitation with one type of fluid as compared with another reduces the risk of death[15] or that any solution is more effective or safer than any other.[16]

ALBUMIN

Human albumin (4 to 5%) in saline is considered to be the reference colloidal solution. It is produced by the fractionation of blood and is heat-treated to prevent transmission of pathogenic viruses. It is an expensive solution to produce and distribute, and its availability is limited in low- and middle-income countries.

In 1998, the Cochrane Injuries Group Albumin Reviewers published a meta-analysis comparing the effects of albumin with those of a range of crystalloid solutions in patients with hypovolemia, burns, or hypoalbuminemia and concluded that the administration of albumin was associated with a significant increase in the rate of death (relative risk, 1.68; 95% confidence interval [CI], 1.26 to 2.23; $P<0.01$).[17] Despite its limitations, including the small size of the included studies, this meta-analysis caused substantial alarm, particularly in countries that used large amounts of albumin for resuscitation.

As a result, investigators in Australia and New Zealand conducted the Saline versus Albumin Fluid Evaluation (SAFE) study, a blinded, randomized, controlled trial, to examine the safety of albumin in 6997 adults in the ICU.[18] The study assessed the effect of resuscitation with 4% albumin, as compared with saline, on the rate of death at 28 days. The study showed no significant difference between albumin and saline with respect to the rate of death (relative risk, 0.99; 95% CI, 0.91 to 1.09; $P=0.87$) or the development of new organ failure.

Table 1. Types and Compositions of Resuscitation Fluids.*

Variable	Human Plasma	Colloids									Crystalloids		
		4% Albumin	Hydroxyethyl Starch						4% Succinylated Modified Fluid Gelatin	3.5% Urea-Linked Gelatin	0.9% Saline	Compounded Sodium Lactate	Balanced Salt Solution
			10% (200/0.5)	6% (450/0.7)	6% (130/0.4)		6% (130/0.42)						
Trade name		Albumex	Hemohes	Hextend	Voluven	Volulyte	Venofundin	Tetraspan	Gelofusine	Haemaccel	Normal saline	Hartmann's or Ringer's lactate	PlasmaLyte
Colloid source		Human donor	Potato starch	Maize starch	Maize starch	Maize starch	Potato starch	Potato starch	Bovine gelatin	Bovine gelatin			
Osmolarity (mOsm/liter)	291	250	308	304	308	286	308	296	274	301	308	280.6	294
Sodium (mmol/liter)	135–145	148	154	143	154	137	154	140	154	145	154	131	140
Potassium (mmol/liter)	4.5–5.0			3.0		4.0		4.0		5.1		5.4	5.0
Calcium (mmol/liter)	2.2–2.6			5.0				2.5		6.25		2.0	
Magnesium (mmol/liter)	0.8–1.0			0.9		1.5		1.0					3.0
Chloride (mmol/liter)	94–111	128	154	124	154	110	154	118	120	145	154	111	98
Acetate (mmol/liter)						34		24					27
Lactate (mmol/liter)	1–2			28								29	
Malate (mmol/liter)								5					
Gluconate (mmol/liter)													23
Bicarbonate (mmol/liter)	23–27												
Octanoate (mmol/liter)		6.4											

* To convert the values for potassium to milligrams per deciliter, divide by 0.2558. To convert the values for calcium to milligrams per deciliter, divide by 0.250. To convert the values for magnesium to milligrams per deciliter, divide by 0.4114.

Additional analyses from the SAFE study provided new insights into fluid resuscitation among patients in the ICU. Resuscitation with albumin was associated with a significant increase in the rate of death at 2 years among patients with traumatic brain injury (relative risk, 1.63; 95% CI, 1.17 to 2.26; P=0.003).[19] This outcome has been attributed to increased intracranial pressure, particularly during the first week after injury.[20] Resuscitation with albumin was associated with a decrease in the adjusted risk of death at 28 days in patients with severe sepsis (odds ratio, 0.71; 95% CI, 0.52 to 0.97; P=0.03), suggesting a potential, but unsubstantiated, benefit in patients with severe sepsis.[21] No significant between-group difference in the rate of death at 28 days was observed among patients with hypoalbuminemia (albumin level, ≤25 g per liter) (odds ratio, 0.87; 95% CI, 0.73 to 1.05).[22]

In the SAFE study, no significant difference in hemodynamic resuscitation end points, such as mean arterial pressure or heart rate, was observed between the albumin and saline groups, although the use of albumin was associated with a significant but clinically small increase in central venous pressure. The ratio of the volumes of albumin to the volumes of saline administered to achieve these end points was observed to be 1:1.4.

In 2011, investigators in sub-Saharan Africa reported the results of a randomized, controlled trial — the Fluid Expansion as Supportive Therapy (FEAST) study[23] — comparing the use of boluses of albumin or saline with no boluses of resuscitation fluid in 3141 febrile children with impaired perfusion. In this study, bolus resuscitation with albumin or saline resulted in similar rates of death at 48 hours, but there was a significant increase in the rate of death at 48 hours associated with both therapies, as compared with no bolus therapy (relative risk, 1.45; 95% CI, 1.13 to 1.86; P=0.003). The principal cause of death in these patients was cardiovascular collapse rather than fluid overload or neurologic causes, suggesting a potentially adverse interaction between bolus fluid resuscitation and compensatory neurohormonal responses.[24] Although this trial was conducted in a specific pediatric population in an environment in which critical care facilities were limited or absent, the results call into question the role of bolus fluid resuscitation with either albumin or saline in other populations of critically ill patients.

The observations in these key studies challenge physiologically based concepts about the efficacy of albumin and its role as a resuscitation solution. In acute illness, it appears that the hemodynamic effects and effects on patient-centered outcomes of albumin are largely equivalent to those of saline. Whether specific populations of patients, particularly those with severe sepsis, may benefit from albumin resuscitation remains to be determined.

SEMISYNTHETIC COLLOIDS

The limited availability and relative expense of human albumin have prompted the development and increasing use of semisynthetic colloid solutions during the past 40 years. Globally, HES solutions are the most commonly used semisynthetic colloids, particularly in Europe.[11] Other semisynthetic colloids include succinylated gelatin, urea-linked gelatin–polygeline preparations, and dextran solutions. The use of dextran solutions has largely been superseded by the use of other semisynthetic solutions.

HES solutions are produced by hydroxyethyl substitution of amylopectin obtained from sorghum, maize, or potatoes. A high degree of substitution on glucose molecules protects against hydrolysis by nonspecific amylases in the blood, thereby prolonging intravascular expansion, but this action increases the potential for HES to accumulate in reticuloendothelial tissues, such as skin (resulting in pruritus), liver, and kidney.

The use of HES, particularly high-molecular-weight preparations, is associated with alterations in coagulation — specifically, changes in viscoelastic measurements and fibrinolysis — although the clinical consequences of these effects in specific patient populations, such as those undergoing surgery or patients with trauma, are undetermined.[25] Study reports have questioned the safety of concentrated (10%) HES solutions with a molecular weight of more than 200 kD and a molar substitution ratio of more than 0.5 in patients with severe sepsis, citing increased rates of death, acute kidney injury, and use of renal-replacement therapy.[26,27]

Currently used HES solutions have reduced concentrations (6%) with a molecular weight of 130 kD and molar substitution ratios of 0.38 to 0.45. They are available in various types of crystalloid carrier solutions. HES solutions are widely used in patients undergoing anesthesia for major surgery, particularly as a component of goal-directed perioperative fluid strategies,[28] as

a first-line resuscitation fluid in military theaters,[29] and in patients in the ICU.[11] Because of the potential that such solutions may accumulate in tissues, the recommended maximal daily dose of HES is 33 to 50 ml per kilogram of body weight per day.

In a blinded, randomized, controlled trial involving 800 patients with severe sepsis in the ICU,[30] Scandinavian investigators reported that the use of 6% HES (130/0.42), as compared with Ringer's acetate, was associated with a significant increase in the rate of death at 90 days (relative risk, 1.17; 95% CI, 1.01 to 1.30; P=0.03) and a significant 35% relative increase in the rate of renal-replacement therapy. These results are consistent with previous trials of 10% HES (200/0.5) in similar patient populations.[27]

In a blinded, randomized, controlled study, called the Crystalloid versus Hydroxyethyl Starch Trial (CHEST), involving 7000 adults in the ICU, the use of 6% HES (130/0.4), as compared with saline, was not associated with a significant difference in the rate of death at 90 days (relative risk, 1.06; 95% CI, 0.96 to 1.18; P=0.26). However, the use of HES was associated with a significant 21% relative increase in the rate of renal-replacement therapy.[31]

Both the Scandinavian trial and CHEST showed no significant difference in short-term hemodynamic resuscitation end points, apart from transient increases in central venous pressure and lower vasopressor requirements with HES in CHEST. The observed ratio of HES to crystalloid in these trials was approximately 1:1.3, which is consistent with the ratio of albumin to saline reported in the SAFE study[18] and in other recent blinded, randomized, controlled trials of HES.[32,33]

In CHEST, HES was associated with increases in urine output in patients at low risk for acute kidney injury but with parallel increases in serum creatinine levels in patients at increased risk for acute kidney injury. In addition, the use of HES was associated with an increased use of blood products and an increased rate of adverse events, particularly pruritus.[31]

Whether these results are generalizable to the use of other semisynthetic colloid solutions, such as gelatin or polygeline preparations, is unknown. A recent observational study has raised concern about the risk of acute kidney injury associated with the use of gelatin solutions.[34] However, these solutions have not been studied in high-quality randomized, controlled trials to date. In light of current evidence of the lack of clinical benefit, potential nephrotoxicity, and increased cost, the use of semisynthetic colloids for fluid resuscitation in critically ill patients is difficult to justify.

CRYSTALLOIDS

Sodium chloride (saline) is the most commonly used crystalloid solution on a global basis, particularly in the United States. Normal (0.9%) saline contains sodium and chloride in equal concentrations, which makes it isotonic as compared with extracellular fluid. The term "normal saline" comes from the studies of red-cell lysis by Dutch physiologist Hartog Hamburger in 1882 and 1883, which suggested that 0.9% was the concentration of salt in human blood, rather than the actual concentration of 0.6%.[35]

The strong ion difference of 0.9% saline is zero, with the result that the administration of large volumes of saline results in a hyperchloremic metabolic acidosis.[36] Adverse effects such as immune[37] and renal[38] dysfunction have been attributed to this phenomenon, although the clinical consequences of these effects is unclear.[39]

Concern about sodium and water overload associated with saline resuscitation has resulted in the concept of "small volume" crystalloid resuscitation with the use of hypertonic saline (3%, 5%, and 7.5%) solutions. However, the early use of hypertonic saline for resuscitation, particularly in patients with traumatic brain injury, has not improved either short-term or long-term outcomes.[40]

Crystalloids with a chemical composition that approximates extracellular fluid have been termed "balanced" or "physiologic" solutions and are derivatives of the original Hartmann's and Ringer's solutions. However, none of the proprietary solutions are either truly balanced or physiologic[41] (Table 1).

Balanced salt solutions are relatively hypotonic because they have a lower sodium concentration than extracellular fluid. Because of the instability of bicarbonate-containing solutions in plastic containers, alternative anions, such as lactate, acetate, gluconate, and malate, have been used. Excessive administration of balanced salt solutions may result in hyperlactatemia, metabolic alkalosis, and hypotonicity (with compounded sodium lactate) and cardiotoxicity (with acetate). The addition of calcium in some solu-

tions may generate microthrombi with citrate-containing red-cell transfusions.

Given the concern regarding an excess of sodium and chloride associated with normal saline, balanced salt solutions are increasingly recommended as first-line resuscitation fluids in patients undergoing surgery,[13] patients with trauma,[14] and patients with diabetic ketoacidosis.[42] Resuscitation with balanced salt solutions is a key element in the initial treatment of patients with burns, although there is increasing concern about the adverse effects of fluid overload, and a strategy of "permissive hypovolemia" in such patients has been advocated.[43]

A matched-cohort observational study compared the rate of major complications in 213 patients who received only 0.9% saline and 714 patients who received only a calcium-free balanced salt solution (PlasmaLyte) for replacement of fluid losses on the day of surgery.[44] The use of balanced salt solution was associated with a significant decrease in the rate of major complications (odds ratio, 0.79; 95% CI, 0.66 to 0.97; P<0.05), including a lower incidence of postoperative infection, renal-replacement therapy, blood transfusion, and acidosis-associated investigations.

In a single-center, sequential, observational ICU study,[45] the use of a chloride-restrictive fluid strategy (using lactated and calcium-free balanced solutions) to replace chloride-rich intravenous fluids (0.9% saline, succinylated gelatin, or 4% albumin) was associated with a significant decrease in the incidence of acute kidney injury and the rate of renal-replacement therapy. Given the widespread use of saline (>200 million liters per year in the United States alone), these data suggest that a randomized, controlled trial examining the safety and efficacy of saline, as compared with a balanced salt solution, is warranted.

DOSE AND VOLUMES

The requirements for and response to fluid resuscitation vary greatly during the course of any critical illness. No single physiological or biochemical measurement adequately reflects the complexity of fluid depletion or the response to

Table 2. Recommendations for Fluid Resuscitation in Acutely Ill Patients.

Fluids should be administered with the same caution that is used with any intravenous drug.
Consider the type, dose, indications, contraindications, potential for toxicity, and cost.
Fluid resuscitation is a component of a complex physiological process.
Identify the fluid that is most likely to be lost and replace the fluid lost in equivalent volumes.
Consider serum sodium, osmolarity, and acid–base status when selecting a resuscitation fluid.
Consider cumulative fluid balance and actual body weight when selecting the dose of resuscitation fluid.
Consider the early use of catecholamines as concomitant treatment of shock.
Fluid requirements change over time in critically ill patients.
The cumulative dose of resuscitation and maintenance fluids is associated with interstitial edema.
Pathological edema is associated with an adverse outcome.
Oliguria is a normal response to hypovolemia and should not be used solely as a trigger or end point for fluid resuscitation, particularly in the post-resuscitation period.
The use of a fluid challenge in the post-resuscitation period (≥24 hours) is questionable.
The use of hypotonic maintenance fluids is questionable once dehydration has been corrected.
Specific considerations apply to different categories of patients.
Bleeding patients require control of hemorrhage and transfusion with red cells and blood components as indicated.
Isotonic, balanced salt solutions are a pragmatic initial resuscitation fluid for the majority of acutely ill patients.
Consider saline in patients with hypovolemia and alkalosis.
Consider albumin during the early resuscitation of patients with severe sepsis.
Saline or isotonic crystalloids are indicated in patients with traumatic brain injury.
Albumin is not indicated in patients with traumatic brain injury.
Hydroxyethyl starch is not indicated in patients with sepsis or those at risk for acute kidney injury.
The safety of other semisynthetic colloids has not been established, so the use of these solutions is not recommended.
The safety of hypertonic saline has not been established.
The appropriate type and dose of resuscitation fluid in patients with burns has not been determined.

fluid resuscitation in acute illness. However, systolic hypotension and particularly oliguria are widely used as triggers to administer a "fluid challenge," ranging from 200 to 1000 ml of crystalloid or colloid for an adult patient.

The use of crystalloid and colloid resuscitation fluids, often prescribed by the most junior members of the clinical team, in addition to hypotonic "maintenance" fluids, results in increased cumulative doses of sodium and water over time.[46] These increases are associated with the development of interstitial edema with resultant organ dysfunction.[47]

Associations between increased cumulative positive fluid balance and long-term adverse outcomes have been reported in patients with sepsis.[48] In trials of liberal versus goal-directed or restrictive fluid strategies in patients with the acute respiratory distress syndrome (particularly in perioperative patients),[49,50] restrictive fluid strategies were associated with reduced morbidity. However, since there is no consensus on the definition of these strategies, high-quality trials in specific patient populations are required.[46]

Although the use of resuscitation fluids is one of the most common interventions in medicine, no currently available resuscitation fluid can be considered to be ideal. In light of recent high-quality evidence, a reappraisal of how resuscitation fluids are used in acutely ill patients is now required (Table 2). The selection, timing, and doses of intravenous fluids should be evaluated as carefully as they are in the case of any other intravenous drug, with the aim of maximizing efficacy and minimizing iatrogenic toxicity.

Dr. Myburgh reports receiving travel support and lecture fees, as well as grant support to his institution, from Fresenius Kabi; and Dr. Mythen, receiving consulting fees paid to himself and his institution by Aqix, grant support to his institution from Fresenius Kabi, lecture fees and travel support from Baxter, B. Braun, and Fresenius Kabi, and fees for the development and presentation of educational materials from B. Braun. Dr. Mythen also reports organizing nonprofit educational conferences for the Evidence-Based Perioperative Medicine (EBPOM) project, which has received financial support from Baxter, B. Braun, Beacon Pharmaceuticals, Cosmed, Cranlea, Deltex, Edwards, Fresenius Kabi, Imacor, LiDCO, Masimo, Medgraphics, Orion Pharma, Pulsion, and Vitalograph. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Lewins R. Saline injections into the veins. London Medical Gazette. April 7, 1832:257-68.
2. Lee JA. Sydney Ringer (1834-1910) and Alexis Hartmann (1898-1964). Anaesthesia 1981;36:1115-21.
3. Funk DJ, Jacobsohn E, Kumar A. The role of venous return in critical illness and shock. I. Physiology. Crit Care Med 2013;41:255-62.
4. Persichini R, Silva S, Teboul JL, et al. Effects of norepinephrine on mean systemic pressure and venous return in human septic shock. Crit Care Med 2012;40:3146-53.
5. Starling EH. On the absorption of fluids from connective tissue spaces. J Physiol 1896;19:312-26.
6. Krogh A, Landis EM, Turner AH. The movement of fluid through the human capillary wall in relation to venous pressure and to the colloid osmotic pressure of the blood. J Clin Invest 1932;11:63-95.
7. Levick JR, Michel CC. Microvascular fluid exchange and the revised Starling principle. Cardiovasc Res 2010;87:198-210.
8. Weinbaum S, Tarbell JM, Damiano ER. The structure and function of the endothelial glycocalyx layer. Annu Rev Biomed Eng 2007;9:121-67.
9. Woodcock TE, Woodcock TM. Revised Starling equation and the glycocalyx model of transvascular fluid exchange: an improved paradigm for prescribing intravenous fluid therapy. Br J Anaesth 2012;108:384-94.
10. Lee WL, Slutsky AS. Sepsis and endothelial permeability. N Engl J Med 2010;363:689-91.
11. 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:R185.
12. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36:296-327. [Erratum, Crit Care Med 2008;36:1394-6.]
13. Powell-Tuck J, Gosling P, Lobo DN, et al. British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients (GIFTASUP). March 2011 (http://www.bapen.org.uk/pdfs/bapen_pubs/giftasup.pdf).
14. Advanced Trauma Life Support (ATLS) for doctors. Chicago: American College of Surgeons Committee on Trauma, 2012 (http://www.facs.org/trauma/atls/index.html).
15. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. Cochrane Database Syst Rev 2012;6:CD000567.
16. Bunn F, Trivedi D. Colloid solutions for fluid resuscitation. Cochrane Database Syst Rev 2012;7:CD001319.
17. Cochrane Injuries Group Albumin Reviewers. Human albumin administration in critically ill patients: systematic review of randomised controlled trials. BMJ 1998;317:235-40.
18. The SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247-56.
19. *Idem.* Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007;357:874-84.
20. Cooper DJ, Myburgh J, Finfer S, et al. Albumin resuscitation for traumatic brain injury: is intracranial hypertension the cause of increased mortality? J Neurotrauma 2013 March 21 (Epub ahead of print).
21. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. Intensive Care Med 2011;37:86-96.
22. Finfer S, Bellomo R, McEvoy S, et al. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the Saline versus Albumin Fluid Evaluation (SAFE) study. BMJ 2006;333:1044.
23. Maitland K, Kiguli S, Opoka R, et al.

Mortality after fluid bolus in African children with shock. N Engl J Med 2011;364:2483-95.
24. Maitland K, George E, Evans J, et al. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. BMC Med 2013;11:68.
25. Hartog CS, Reuter D, Loesche W, Hofmann M, Reinhart K. Influence of hydroxyethyl starch (HES) 130/0.4 on hemostasis as measured by viscoelastic device analysis: a systematic review. Intensive Care Med 2011;37:1725-37.
26. Schortgen F, Lacherade JC, Bruneel F, et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. Lancet 2001;357:911-6.
27. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med 2008;358:125-39.
28. Brandstrup B, Svendsen PE, Rasmussen M, et al. Which goal for fluid therapy during colorectal surgery is followed by the best outcome: near-maximal stroke volume or zero fluid balance? Br J Anaesth 2012;109:191-9.
29. McSwain NE, Champion HR, Fabian TC, et al. State of the art of fluid resuscitation 2010: prehospital and immediate transition to the hospital. J Trauma 2011;70:Suppl:S2-S10.
30. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012;367:124-34. [Erratum, N Engl J Med 2012;367:481.]
31. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. N Engl J Med 2012;367:1901-11.
32. James MF, Michell WL, Joubert IA, Nicol AJ, Navsaria PH, Gillespie RS. Resuscitation with hydroxyethyl starch improves renal function and lactate clearance in penetrating trauma in a randomized controlled study: the FIRST trial (Fluids in Resuscitation of Severe Trauma). Br J Anaesth 2011;107:693-702.
33. Guidet B, Martinet O, Boulain T, et al. Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: the CRYSTMAS study. Crit Care 2012;16(3):R94.
34. Bayer O, Reinhart K, Sakr Y, et al. Renal effects of synthetic colloids and crystalloids in patients with severe sepsis: a prospective sequential comparison. Crit Care Med 2011;39:1335-42.
35. Awad S, Allison SP, Lobo DN. The history of 0.9% saline. Clin Nutr 2008;27:179-88.
36. Morgan TJ, Venkatesh B, Hall J. Crystalloid strong ion difference determines metabolic acid-base change during acute normovolaemic haemodilution. Intensive Care Med 2004;30:1432-7.
37. Kellum JA, Song M, Li J. Science review: extracellular acidosis and the immune response: clinical and physiologic implications. Crit Care 2004;8:331-6.
38. Hadimioglu N, Saadawy I, Saglam T, Ertug Z, Dinckan A. The effect of different crystalloid solutions on acid-base balance and early kidney function after kidney transplantation. Anesth Analg 2008;107:264-9.
39. Handy JM, Soni N. Physiological effects of hyperchloraemia and acidosis. Br J Anaesth 2008;101:141-50.
40. Cooper DJ, Myles PS, McDermott FT, et al. Prehospital hypertonic saline resuscitation of patients with hypotension and severe traumatic brain injury: a randomized controlled trial. JAMA 2004;291:1350-7.
41. Guidet B, Soni N, Della Rocca G, et al. A balanced view of balanced solutions. Crit Care 2010;14:325.
42. Chua HR, Venkatesh B, Stachowski E, et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. J Crit Care 2012;27:138-45.
43. Arlati S, Storti E, Pradella V, Bucci L, Vitolo A, Pulici M. Decreased fluid volume to reduce organ damage: a new approach to burn shock resuscitation? A preliminary study. Resuscitation 2007;72:371-8.
44. Shaw AD, Bagshaw SM, Goldstein SL, et al. Major complications, mortality, and resource utilization after open abdominal surgery: 0.9% saline compared to Plasma-Lyte. Ann Surg 2012;255:821-9.
45. Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012;308:1566-72.
46. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. Anesth Analg 2012;114:640-51.
47. Cordemans C, De Laet I, Van Regenmortel N, et al. Fluid management in critically ill patients: the role of extravascular lung water, abdominal hypertension, capillary leak, and fluid balance. Ann Intensive Care 2012;2:Suppl 1:S1.
48. Boyd JH, Forbes J, Nakada TA, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. Crit Care Med 2011;39:259-65.
49. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564-75.
50. Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. Chest 2009;136:102-9.

2013 ICMJE RECOMMENDATIONS

The International Committee of Medical Journal Editors (ICMJE) has revised and renamed its Uniform Requirements. The new ICMJE Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals are available at www.icmje.org.