Estimates suggest that over half of critically ill patients receive fluid resuscitation early in the course of their illness; however, volumes and types of fluid vary substantially. Moreover, the association between overzealous fluid administration and numerous deleterious outcomes across variable patient populations has challenged the traditional reflexive instinct that fluids are the answer to all hemodynamic perturbations. Similarly, equivalent outcomes among anemic patients managed with either restrictive or liberal transfusion strategies has led to the growing adoption of the former. Clinicians must, however, reconcile this trend with the established roles of blood component therapy early in the course of resuscitation following hemorrhagic shock and in the prevention and treatment of coagulopathy.

**Physiological Underpinnings of Rational Fluid Management**

Four phases in the treatment of shock have been proposed by Vincent and De Backer and then further refined as outlined in Table 1. This framework of rescue, optimization, stabilization, and de-escalation (ROS-D) is useful conceptually in conjunction with our evolving understanding of the endothelium in critical illness. The human endothelium is lined with a complex proteinaceous meshwork consisting of glycoproteins, glycosaminoglycans, and other polymers. This endothelial glycocalyx layer is subject to degradation in shock states...
and complex both in structure and function, as has been extensively described elsewhere.10–14 Shortcomings in the classic Starling model are increasingly recognized and understood as knowledge develops about the endothelial glycocalyx layer, which has resulted in a revised model.15–17 Under the revised model, colloid oncotic pressure is a primarily intraendothelial force, whereas hydrostatic pressure is the primary driver of transcapillary filtration.18 The integration of these complex concepts into clinically actionable practice is beginning to coalesce, and key points are discussed subsequently.19,20 Greater appreciation for the complex nature of endothelial dysfunction and disharmony between the macrocirculation and microcirculation highlights the importance of context-sensitive resuscitation.20–22

### Intravenous Fluids

The discovery of an ideal asanguinous intravenous resuscitation fluid remains elusive, but broadly speaking such a fluid would yield a predictable increase in intravascular volume, not accumulate in tissues
via metabolism and/or excretion, mimic the composition of extracellular fluid, and produce no adverse effects. Modern crystalloid resuscitation fluids are aqueous salt solutions that contain sodium, chloride, and other constituents that thereby contribute to tonicity. Colloidal resuscitation fluids contain molecules in a carrier solution that are of a sufficient molecular weight such that their diffusion across a semipermeable membrane is hypothetically limited, thus generating an oncotic pressure under the classic Starling model.

**Isotonic Crystalloids**

**0.9% Saline**

The journey of 0.9% saline from the bench to widespread clinical adoption, including its labeling as normal saline, has been elucidated elsewhere.\(^2^3\) Despite its popularity, 0.9% saline is far from being physiological. Although 0.9% saline is isotonic to the extracellular fluid, considering its osmotic coefficient of 0.926, its equal sodium and chloride concentrations of 154 mmol/L equate to a strong ion difference of 0 and chloride concentration approximately 50% over that of human plasma. As a result, infusion of 0.9% saline inevitably leads to hyperchloremic metabolic acidosis.\(^2^4^,^2^5\) Supraphysiological chloride concentrations in the distal tubule of the nephron produce afferent arteriolar concentration and a decline in glomerular filtration rate in conjunction with other postulated mechanisms.\(^2^6^–^2^8\) Questions linger, however, about the extent to which these perturbations are clinically relevant or effect outcomes.\(^2^9^,^3^0\) One common scenario in the authors’ experience is that of investigation into the cause of acid/base disturbance following saline infusion. One large retrospective study demonstrated that patients who received 0.9% saline were approximately 60% more likely to undergo ABG testing and 3 times more likely to undergo lactate measurement compared with those who received other crystalloid solutions.\(^3^1\)

**Lactated Ringers (LR)**

Lactate is metabolized primarily by gluconeogenesis and to a lesser extent by oxidation, both of which consume H\(^+\) ions, thus producing a relative alkalinizing effect through the combination of excess OH\(^-\) ions with CO\(_2\) to form HCO\(_3^-\). The buffering effects of lactate appear to be poorly understood by clinicians, and complications related to LR infusion in patients with hepatic dysfunction are rare but have been described.\(^3^2^,^3^3\) Lactate is, however, a physiological substance with which human metabolism can contend. In contrast to 0.9% saline, LR is mildly hypotonic but contains a chloride concentration close to that of typical plasma levels. This is of hypothetical concern in patients with traumatic
brain injury (TBI) as cerebral edema could contribute to worsened outcomes. LR infusion has led to increased intracranial pressure in nonhuman mammals, and retrospective data have demonstrated an association between prehospital resuscitation of trauma patients with LR and increased mortality compared with 0.9% saline.34,35

**Other Multielectrolyte Solutions**

Numerous buffered multielectrolyte solutions are commercially available, such as variants of Plasma-Lyte (Baxter Healthcare), Isolyte (B. Braun Medical), and Normosol (Hospira). These solutions share in common relative isotonicity and buffering with some combination of sodium acetate and/or sodium gluconate. The most widely studied multielectrolyte solution is Plasma-Lyte 148, which is buffered with both acetate and gluconate and has a pH of 5.5 adjusted with hydrochloric acid (Plasma-Lyte A is an equivalent solution with a pH adjusted to 7.4 using sodium hydroxide). Acetate is widely and rapidly metabolized even in shock states and appears to be an effective buffer.36 However, its use in conjunction with continuous renal replacement therapy has been associated with vasodilation and negative inotropy.37,38 Conversely, little is understood about the efficacy of gluconate as a buffer in humans. Animal studies have suggested it has a minimal buffer effect owing to incomplete metabolism and predominant excretion via urine.39–41

**Which Isotonic Crystalloid is Best?**

At present there is no compelling prospective evidence to help guide the selection of an isotonic crystalloid. Large meta-analyses based largely on retrospective observational studies have suggested that high-chloride fluids (ie, 0.9% saline) are associated with acute kidney injury and mortality in a broad swath of critically ill patients when compared with buffered crystalloids.42,43 However, there has been no large randomized controlled trial comparing 0.9% saline versus LR.44 The best prospective evidence in this domain came from the 0.9% Saline versus Plasma-Lyte 148 for Intensive Care Unit Therapy (SPLIT) trial.45 The SPLIT investigators randomized 2278 intensive care unit (ICU) patients to receive either saline or Plasma-Lyte. About half of patients were admitted to the ICU postoperatively, illness severity was modest (average APACHE II = 14.1), and average fluid volumes were 2 liters after enrollment over the entire ICU stay. No difference in any studied outcome was demonstrated. The Plasma-Lyte 148 versus saline (PLUS) trial (ClinicalTrials.gov ID NCT02721654), sponsored by the Australian and New Zealand Intensive Care Society Clinical Trials Group, will hopefully bring clarity to this issue with a targeted enrollment of 8800 patients with a primary end point of 90-day mortality. Results of a small
pilot study were recently published, which did not demonstrate a convincing benefit to Plasma-Lyte 148.46

**Hypertonic Saline (HTS)**

The use of HTS preparations has previously been explored in the context of hemorrhagic shock following trauma.47 The primary rationale for the use of hypertonic resuscitation fluids is that fluid can be mobilized intravascularly from the interstitium. HTS has been explored in a number of experimental and animal physiological models of hemorrhagic shock that have been reviewed at length elsewhere.48 To summarize, HTS has been variably associated with immunomodulatory effects and microcirculatory augmentation.49,50 Despite these theoretical benefits, no definitive benefit with regard to clinical outcomes compared with isotonic fluids has been demonstrated.51,52 One trial examining the use of HTS early in the course of resuscitation following traumatic hypovolemic shock was stopped early owing to futility, which has served to dampen enthusiasm for subsequent investigation.53 Further complicating matters, many trials examining HTS have used solutions of varying sodium content and containing various colloids, thus making comparisons challenging. At present, only 3% and 5% HTS have been approved by the United States Food and Drug Administration (FDA). 3% HTS solutions are familiar to many practitioners, given the role of HTS in the treatment of intracranial hypertension.54 Practical experience with 5% HTS suggests that it is safe and well tolerated.48,55

**Colloids**

Debate about the optimal choice and role, if any, of colloids in fluid resuscitation dates back to the inception of colloid resuscitation fluids in 1915.56 Since then, a dizzying array of colloids have been developed and subjected to both experimental and clinical use. Broadly, they can be classified into 2 categories: natural and synthetic. Synthetic colloids include starch derivatives, gelatin, and dextran, although the latter 2 have not seen widespread adoption in the United States.

**Human Albumin and the Saline versus Albumin Fluid Evaluation (SAFE) Study**

Albumin is the primary protein constituent of human plasma. As a modern resuscitation fluid, human albumin is most commonly available worldwide as a 4% to 5% solution in saline. Following an unfavorable Cochrane meta-analysis that was published in 1998, a large multicenter prospective randomized controlled trial was designed to more definitively evaluate the effects of albumin resuscitation in critically ill patients,
the SAFE study.\textsuperscript{57,58} The SAFE investigators recruited a diverse group of critically ill patients deemed to be in need of fluid resuscitation by their treating clinician and randomized them to receive either 4\% albumin or 0.9\% saline for the duration of the patient’s ICU stay. Nearly 7000 patients were enrolled, and no difference was found in the primary outcome of 28-day mortality or any of the study’s secondary outcomes. Subgroup analysis and a later post hoc study has suggested that albumin administration is deleterious in patients with TBI.\textsuperscript{59} The size of the SAFE study has heavily influenced all subsequent meta-analyses such that no definitive benefit to the use of albumin for fluid resuscitation has been shown.\textsuperscript{60} The relevance of the SAFE study to the resuscitation of patients in the rescue phase of severe shock (in the ROS-D framework) is uncertain, as many patients were in the optimization stage of fluid management.\textsuperscript{9} However, it remains our best evidence that the use of albumin in critically ill patients without TBI is likely safe, although without clear outcome benefits.

\textbf{Hydroxyethyl Starch (HES)}

Modern starch-based resuscitation fluids are derived from plant matter and coupled with a crystalloid carrier fluid. Four HES solutions are currently approved by the FDA, and pharmaceutical development efforts over the years have focused on the development of lower molecular weight preparations with greater molar substitution to avoid issues with incomplete clearance.\textsuperscript{61} A single large trial has examined the role of HES in the early resuscitation of traumatic hypovolemic shock, the FIRST study.\textsuperscript{62} Notably, it involved fluid management in the rescue phase of the ROS-D framework among sick, severely injured patients as was evidenced by the frequency of hypotension and volumes of fluid administered.\textsuperscript{9} Patients who sustained blunt or penetrating trauma were randomized to receive low molecular weight HES (HES, 130/0.4) or 0.9\% saline. No difference in mortality was demonstrated among the 109 patients who were analyzed of 115 randomized, although ultimately the study was underpowered for this end point. FIRST was manufacturer-sponsored and sufficiently flawed to preclude the development of any definitive conclusions.

In the absence of high-quality evidence about the use of HES in hemorrhagic shock, we have previously argued that findings from trials among critically ill patients should be considered, the majority of which centered around the safety of HES in patients with sepsis.\textsuperscript{63} Sepsis remains a leading cause of death among survivors of major trauma.\textsuperscript{64} A series of studies in critically ill patients resulted in serious doubts about the safety of HES with regard to renal failure and coagulopathy.\textsuperscript{65–69} As a consequence, HES garnered warnings about its use from both the FDA
and the European Medicines Agency. Despite these concerns, some continue to envision a role for HES in specific patient populations.\(^{70,71}\)

### Crystalloids or Colloids for Resuscitation?

The best prospective evidence about the general use of colloids versus crystalloids specifically in the rescue phase of resuscitation comes from the CRISTAL trial.\(^{69}\) The investigators randomized nearly 2857 patients across 57 ICUs to receive either crystalloid or colloid at the discretion of the investigators for acute resuscitation in an open-label fashion. The CRISTAL trial was notable in that patients were acutely ill with an average systolic blood pressure of 92 mm Hg, lactate of 2.3 mmol/L, and SOFA score of 8. No difference in 28-day mortality was demonstrated.

A recent systematic review and metaregression demonstrated that colloids confer a smaller volume-sparing effect than has been traditionally espoused with an average crystalloid to colloid ratio of 1.3:1, spanning recent investigations.\(^{72}\) The balance of existing evidence has failed to demonstrate any benefit of colloids over crystalloids in either traumatic hypovolemic shock or mixed shock states in critically ill patients.\(^{60,73}\) Given the higher cost of colloids and evidence of harm in certain patient populations, crystalloids continue to be the resuscitation fluid of choice.\(^{74,75}\)

### Contemporary Principles in the Management of Traumatic Hemorrhage

Traumatic hemorrhage remains the leading preventable cause of death after injury, despite continual advances, and improvements in care.\(^{76,77}\) As such, acute care after trauma is focused toward early interventions to reverse shock while avoiding overresuscitation, preventing coagulopathy, temporizing hemorrhage, and then rendering definitive care.\(^{78}\)

#### Pathophysiology of Acute Traumatic Coagulopathy

Traditional teaching has held that failure of hemostasis after trauma results from 3 primary factors: dilution or depletion of clotting factors secondary to resuscitation, and enzymatic dysfunction. The latter entity has been termed the lethal triad or vicious bloody cycle whereby hypothermia, acidosis, and coagulopathy lead to a gross failure of hemostasis.\(^{79}\) The conduct of resuscitation can serve to either worsen or alleviate these traditional mechanisms of coagulopathy, which some have called resuscitation-associated coagulopathy.\(^{80}\) Coagulopathy after trauma is more complex than was originally conceived.\(^{81,82}\) Approximately 30% of civilian trauma patients manifest evidence of coagulopathy very early after injury and before appreciable resuscitation.\(^{83-85}\) This
phenomenon has been termed acute traumatic coagulopathy (ATC) or trauma-induced coagulopathy. ATC is thought to involve multiple pathophysiological derangements of the clotting system, including the endogenous anticoagulant activated protein C, platelet dysfunction, and fibrinolysis. ATC typically develops in proportion to injury severity; however, ATC itself appears to be an independent risk factor for early mortality.

Damage Control Resuscitation (DCR)

Damage control derives its name from the maritime practice of rendering immediate, but usually temporary, interventions to correct issues that would otherwise result in loss of the ship. DCR refers to a multifaceted strategy that aims to avoid the negative sequelae of resuscitation following hemorrhage (Table 2). The current civilian DCR practice evolved from military experience in Iraq and Afghanistan. The primary goals of DCR are to prevent coagulopathy during resuscitation and promote early hemostasis until definitive control of hemorrhage can be rendered through surgical or procedural intervention.

Massive Transfusion in the Damage Control Paradigm

Until recently, aggressive resuscitative efforts in civilian trauma centers often began with the early administration of appreciable crystalloid volumes, massive transfusion with a preponderance of packed red blood cells (PRBC) in relation to fresh frozen plasma (FFP), and resuscitation to normotension. Although a body of literature was beginning to suggest that these practices were counterproductive, it was ultimately military experience with massive transfusion that served to inform and change civilian resuscitation practices. One element was the suggestion that early administration of plasma with higher FFP:PRBC ratios improved hemostasis and outcomes, which served to reinforce the practices of some civilian trauma centers. By essentially reconstituting whole blood, the goal was to provision clotting factors (and platelets) early in the course of resuscitation to support coagulation during the hectic course of resuscitation during which traditional laboratory assays of coagulation were either too slow or insensitive to

<table>
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<tr>
<th>Table 2. Elements of Damage Control Resuscitation</th>
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<tr>
<td>Intervene to temporize and control hemorrhage</td>
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<tr>
<td>Minimize crystalloids</td>
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<tr>
<td>Treat and avoid hypothermia</td>
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<tr>
<td>Permissive hypotension when appropriate</td>
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<tr>
<td>Optimize hemostasis with fixed transfusion ratios or viscoelastic coagulation testing</td>
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<td>Administer antifibrinolytics early after injury</td>
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be practical. These criticisms ultimately led to the design of the Pragmatic, Randomized Optimal Platelets and Plasma Ratios (PROPPR) trial. The PROPPR investigators randomized 680 patients to receive blood products in either a 1:1:1 or 1:1:2 ratio of FFP:platelets:PRBC. No statistically significant differences were found among the 2 primary outcomes of 24-hour mortality (12.7% vs. 17%) and 30-day mortality (22.4% vs. 26.1%). Similarly, no significant differences were found between any secondary outcomes. A post hoc analysis suggests that deaths from bleeding and early hemostasis were both superior in the 1:1:1 group, although these differences did not translate into a mortality benefit at the 2 predefined mortality endpoints. PROPPR was ultimately underpowered in that the investigators had expected a 10% mortality difference at 24 hours and 12% at 30 days. Confounding secondary to delayed death from TBI may also have obscured a detectable difference in mortality. Additionally, it did not investigate less aggressive FFP infusion schema. Regardless, the practical effect of PROPPR has been to reinforce the already established practice of 1:1 or 1:2 FFP:PRBC transfusion at many centers.

Hemodynamic Goals in the Damage Control Paradigm

Intuitively, resuscitation to normotension before the cause of hemorrhage has been corrected exposes patients to the risks of further transfusion while furthering the development of resuscitation-associated coagulopathy. As such, interest has grown in the practice of delayed resuscitation wherein a minimally tolerable blood pressure is maintained until hemorrhage can be controlled. The practice was originally suggested as a result of battlefield experience in World War I, and likewise military experience has been responsible for its renewed attention. Apart from the initial trial by Bickell et al that garnered significant interest, subsequent trials have failed to demonstrate a convincing improvement in outcomes when delayed resuscitation is undertaken either prehospital or in-hospital. However, delayed resuscitation has been advocated in both American and European guidelines. The optimal blood pressure target, if any, is yet to be defined. Patients with TBI and the elderly are likely at higher risk for harm.

Pharmacologic Coagulation Support

Hyperfibrinolysis has been implicated as one consequence of ATC via the effect of activated protein C on thrombomodulin. As such,
antifibrinolytics have been investigated as procoagulant adjuncts in trauma. Tranexamic acid (TXA) is a synthetic lysine analog that inhibits the conversion of plasminogen to plasmin, thus blocking one mechanism of fibrinolysis. Support for the use of TXA comes from one large prospective randomized control trial (CRASH-2), one smaller prospective study, and 2 military retrospective investigations (MATTERs and MATTERs II).109–112 Of these, CRASH-2 is perhaps the most compelling. Over 20,000 patients with, or at risk for, hemorrhagic shock across 40 countries were enrolled and randomized to either placebo or 1 g of TXA given over 10 minutes followed by 1 g infused over 8 hours. A small but statistically significant decline in 28-day mortality in the TXA arm was observed (14.5% vs. 16%, 95% confidence interval, 0.85-0.87; \( P = 0.0035 \)). Of note, a subsequent subgroup analysis revealed that maximum benefit was seen from administration within 1 hour of injury, and administration 3 hours after injury was associated with an increased risk of mortality.113

### Should Traumatic and Nontraumatic Hemorrhage be Treated Similarly?

As with the discussion regarding fluid resuscitation, we must rely on some degree of data extrapolation when considering nontraumatic hemorrhage, as there is a dearth of clinical evidence to guide practice in the management of hemorrhage not associated with trauma.114,115 As experience with massive transfusion in fixed ratios for trauma has grown, the application of massive transfusion protocols (MTPs) has spread from trauma resuscitation to the operating room and intensive care unit.116 It is conceivable that plasma-rich resuscitation and use of antifibrinolytics may be inappropriate in the resuscitation of nontraumatic hemorrhage as changes similar to those of ATC have not been convincingly demonstrated.117 The ideal ratio, if any, of FFP:RBC in nontraumatic hemorrhage associated with major surgery is not currently clear.118–122 Plasma-rich resuscitation is common in scenarios typically associated with coagulopathy, such as liver transplantation and postpartum hemorrhage.123 Overall, clinicians are left with little evidence to help guide clinical decisions in this domain, and many decisions will rely on clinical judgment regarding the severity of bleeding, the likelihood of needing massive transfusion, and the likelihood of developing a coagulopathy.

### Conduct of Massive Transfusion and MTPs

Given the rise of transfusion with fixed blood product ratios, MTPs have been developed to speed the delivery of blood products, reduce workload for both bedside clinicians and blood bank personnel, and help standardize the practice of massive transfusion.124,125
the MTP is typically based on clinician judgment and/or a set of objective activation criteria based on markers of injury severity, hemodynamics, or blood product need. After activation, the blood bank will give priority to the designated patient and work to speed product delivery in predefined batches. Bedside clinicians should likewise prioritize delivery of a blood sample to the blood bank to facilitate typing, an antibody screen, and an eventual crossmatch. Most MTPs facilitate delivery of FFP:platelets:PRBC in either a 1:1:1 or 1:1:2 ratio in keeping with the discussions above. Although MTPs are typically associated only with blood product delivery, coordination between the pharmacy and blood bank can likewise standardize the timely delivery of TXA. Cognitive aids can not only serve as a reminder to activate the MTP but also help facilitate appropriate preparation for the equipment and personnel-intensive process of massive resuscitation.

### Blood Product Maintenance and Delivery

Blood banks have been challenged to adapt to the growing demand for both PRBCs and plasma. In response to the growing demand for O—blood despite a relatively fixed supply, O+ blood is being increasingly substituted for women not of childbearing potential and men wherein the consequences of alloimmunization are lessened.

Plasma management represents a greater challenge for blood banks as group AB—donors represent only about 4% of individuals. Type A plasma is being substituted for type AB plasma in some centers to help preserve the stock of type AB. Type AB plasma has weaker anti-B antibodies than the corresponding anti-A antibodies in types O and B plasma; furthermore, only about 15% of the North American population has type B or AB blood.

Traditional frozen storage of plasma poses a barrier to rapid delivery as thawing takes about 45 minutes. Likewise, thawed plasma can be stored refrigerated for only about 24 hours until factor activity levels begin to diminish. However, practical experience with thawed plasma kept up to 5 days after initial thawing suggests clinical equivalency to FFP. Similarly, liquid plasma is making a comeback under pressure to maintain ready stores of plasma backed by both experimental and clinical evidence as to its efficacy. These and other solutions are being increasingly used by blood banks at major hospitals to help meet the growing need for timely delivery of blood products.

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The authors declare that they have nothing to disclose.
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