

# Fluid Choice for Resuscitation in Trauma

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**Learning Objectives:** To determine: 1) What is the risk of hypovolemia in trauma patients? 2) What strategies of fluid resuscitation are available? 3) What are the risks of the different fluids for correcting hypovolemia? 4) How do we identify hypovolemia and how do we guide fluid resuscitation? 5) Are meta-analyses and recommendations from the literature a help to us?

## Abstract

The “ideal” fluid replacement regimen in trauma patients is still discussed controversially. Aside from blood, several nonblood alternatives—including crystalloids, hypertonic solutions, albumin, and nonprotein (synthetic) colloids—are available to correct hypovolemia in the trauma patient. Interpretation of the literature is difficult because of variations in study design, patient population, target for volume replacement, end points, and type of fluids. Meta-analyses are not very helpful because patients of all types, not just trauma patients, and very old studies are included. Reviewing the meager literature on this issue, the choice of fluid therapy in trauma patients engenders the most controversy. Recommendations for fluid resuscitation in trauma patients are more likely based on “personal guidelines” than on research results. It is imperative to continue the search for substances that are effective in avoiding development of posttrauma multiorgan dysfunction syndrome and that are without detrimental side effects.

Trauma is the fourth leading cause of death in the United States.<sup>1</sup> Volume deficits are often present in trauma patients (Fig. 1) and may result in the development of posttrauma multiple organ failure in the intensive care unit (ICU). In addition to apparent blood loss, fluid deficits may also occur secondary to generalized alterations of the endothelial barrier, resulting in diffuse capillary leakage and fluid shift from the intravascular to the interstitial compartment.

Adequate volume therapy appears to be fundamental in the management of the trauma patient. In a prospective review of 111 consecutive patients who died in hospital after admission for treatment of injuries, the most common defect in patients’ care was related to inadequate fluid resuscitation.<sup>2</sup> Trauma patients are definitely different from cardiac surgery patients, patients with malignancies undergoing surgery, or septic patients; thus, volume-

replacement strategies should be considered separately for these patients.

Besides (hypo-, iso-, and hypertonic) crystalloids, human albumin (HA), and various synthetic colloids (e.g., dextrans, gelatins, hydroxyethyl starch [HES] preparations) are available to treat trauma-related volume deficits. In recent years, the crystalloid/colloid dispute has been enlarged to a colloid/colloid debate because, aside from the natural colloid albumin, several synthetic colloids are increasingly used as plasma substitutes in the trauma patient.

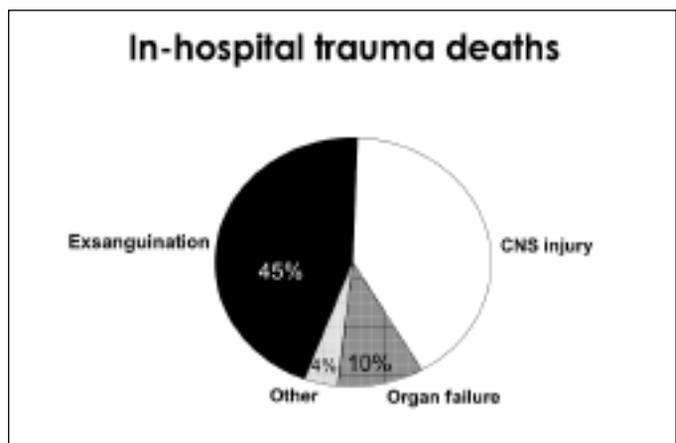
Aggressive prehospital fluid administration (“in the field”) has been common practice for more than 25 years in trauma patients. Some recent studies, however, have shown that early volume restoration in certain types of trauma before definite hemostasis has been performed may result in accelerated blood loss, hypothermia, and dilutional coagulopathy.<sup>3</sup> It has been recommended that volume replacement should not be started early (concept of “permissive hypotension,” “scoop and run” principle).<sup>4</sup> This review is not designed to intensify the controversy between delayed fluid resuscitation and early (field) volume replacement because different emergency care systems make a comparison between countries almost impossible; subsequently, no clear general recommendation can be given. Instead, this review is aimed to recall the options for volume replacement in trauma patients.

## Pathophysiology of Shock in the Trauma Patient

Hemorrhage-related hypovolemia after trauma can be divided into three phases<sup>5</sup>:

- Phase I is the period from injury to operation for control of bleeding (predefinite care),
- Phase II is the period immediately during and after surgery, and
- Phase III is the period of the trauma patient in the ICU (postdefinite care).

Trauma-related hypovolemia may be associated with flow alterations that are inadequate to fulfill the nutritive role of the circulation. Many of the manifestations of organ failure after successful primary resuscitation after trauma may result from peripheral, microcirculatory derangements. In spite of achieving “normal” systemic hemodynamics, it is not guaranteed that perfusion in all organs and tissues is maintained as well. During low output



**Figure 1. Reasons of in-hospital trauma death. CNS, central nervous system. (Data derived from Sauaia et al.)**

syndrome, the organism tries to compensate perfusion deficits by redistribution of flow to vital organs (e.g., heart, brain) resulting in an underperfusion of other organs (e.g., splanchnic bed, kidney). Inflammatory mediators and vasopressors are released in this situation and are of particular importance for development of impaired perfusion.

Recent evidence suggests that the endothelium is not only a passive barrier between the circulating blood and the tissue, but may also be markedly involved in the regulation of microcirculatory blood flow by producing important regulators of the vascular tone (e.g., prostaglandins, nitric oxide, endothelins, angiotensin II).<sup>6</sup> The regional regulation of blood flow is likely due to a balance between systemic mechanisms (e.g., the autonomous nervous system) and other more locally active blood flow regulators. One important approach to improve perfusion in this situation appears to be the use of adequate volume. Our pathophysiologic knowledge of the importance of the endothelium in modulating microcirculation and inflammation has increased; however, the influence of different volume-replacement strategies on endothelial function has still to be elucidated.

### Goals of Volume Replacement in the Trauma Patient

The primary goal of volume administration is to guarantee stable systemic hemodynamics and microcirculation by rapidly restoring circulating plasma volume (Table 1). Excessive fluid accumulation, particularly in the interstitial tissue, should be avoided. The infused fluid may stay in the intravascular compartment or equilibrate with the interstitial/intracellular fluid compartments. Different mechanisms are involved in the control of volume and composition of each compartment including the antidiuretic hormone and the renin-angiotensin systems. The principal action of these systems is to retain water to restore water or intravascular volume deficits, to retain sodium to restore intravascular volume, and to increase hydrostatic perfusion pressure by vasoconstriction. Increased activity of these systems is known to occur in stress situations, such as trauma. If water or intravascular volume deficits and the stress-related stimuli are additive, volume therapy may inhibit this process through counterregulatory mechanisms. Antidiuretic hormone production depends on sufficient extracellular volume, in particular of the intravascular compartment. Administration of a restricted amount of crystalloid could replace a water deficit, but the replacement of an intravascular volume deficit would require much more volume to inhibit the activation of this system. Thus, it can be expected that replacement of only water (crystalloids) will not inhibit the normal response of antidiuretic hormone and renin-angiotensin, whereas administering a combination of crystalloids and colloids (replacement of water deficit and simultaneous maintenance of a sufficient intravascular volume) may achieve this goal.

**Table 1. Goals for Fluid Resuscitation**

- Achievement of normovolemia and hemodynamic stability
- Correction of major acid-base disturbances
- Compensation of fluxes from the interstitial/intracellular compartments
- Improvements of microvascular blood flow
- Prevention of activation of inflammatory cascade system
- Normalization of oxygen delivery to tissue cells and cell metabolism
- Prevention of reperfusion injury

One important aspect of fluid therapy in the traumatized patient is the risk of inducing interstitial edema. Tissue edema is related to an imbalance in the sum of the Starling forces across capillary membranes or an increase in protein permeability, by which an increase in fluid flux to the interstitial space is promoted. A decrease in membrane integrity, an increase in hydrostatic pressure, and a decrease in intravascular colloid oncotic pressure (COP) will induce fluid movement across the microvascular membrane and may produce interstitial fluid accumulation (e.g., pulmonary edema). Moreover, endothelial swelling may also occur by which organ perfusion is further disturbed. Thus, the choice of fluid for correcting hypovolemia in trauma patients should take this regulatory issue into account.

### Fluid Choice in Trauma Resuscitation

The choice of fluid therapy engenders the most controversy, and an examination of the body of literature on this subject results in confusion. Volume replacement in the trauma patient should not only aim at increasing the circulating intravascular volume, adverse effects, effects on inflammation, perfusion and tissue oxygenation should be considered as well. The different fluids show varying effects on the volume compartments (Table 2).

#### Homologous Blood

The increasing awareness of the risk of transmitting viral diseases and the negative effects on the immune system result in more aggressive use of nonsanguinous volume replacement instead of homologous blood.<sup>7-9</sup> Reduction in hematocrit and in arterial oxygen content is not deleterious even in “high-risk” patients because compensating mechanisms are able to guarantee tissue oxygenation and systemic oxygen transport.<sup>7</sup> Careful attention is necessary to evaluate the patient’s oxygen-carrying capacity. Although extensive information is available on this issue, the “safe” hemoglobin level is still not definitely known. In the elderly and the critically ill surgical patient, it has to be taken into account that limitations of cardiac and pulmonary function will influence the components of oxygen delivery. Nevertheless, blood/blood component therapy should be restricted to those cases presenting severe anemia or coagulation disorders.

#### Crystalloids

Hypotonic (e.g., dextrose in water), isotonic (e.g., Ringer’s lactate), and hypertonic crystalloids (e.g., 7.5% saline solution) have to be distinguished when using crystalloids for volume replacement. Crystalloids are freely permeable to the vascular membrane and are therefore distributed mainly in the interstitial and/or intercellular compartment. Only 25% of the infused crystalloid solution remains in the intravascular space, whereas 75% extravasates into the

**Table 2. Changes of the Different Fluid Compartments When Using Different Fluid-Replacement Strategies**

Compartment	Glucose 5%	Crystalloid	Colloids
Intravascular	↑	↑	↑↑↑
Interstitial	↑↑	↑↑	—
Intracellular	↑↑↑	—	—

interstitium.<sup>10</sup> Dilution of plasma protein concentration may also be accompanied by a reduction in plasma COP, subsequently leading to tissue edema. It has been shown in animal experiments that even a massive crystalloid resuscitation is less likely to achieve adequate restoration of microcirculatory blood flow compared with a colloidal-based volume-replacement strategy.<sup>11</sup> In a near-fatal model of hemorrhagic shock, early colloid infusion using a modern HES preparation resulted in prompt recovery of tissue perfusion when compared with infusion with an equal volume of crystalloid (Ringer's lactate).<sup>12</sup> In an animal shock experiment, the main clinical effect of 0.9% saline solution was the undesired expansion of the peripheral compartment.<sup>13</sup>

### Colloids

**Human albumin (HA).** Albumin is a naturally occurring plasma protein. The molecular weight of HA is approximately 69 kD. Albumin is derived from pooled human plasma, heated and sterilized by ultrafiltration. Albumin is generally accepted to be safe in terms of transmission of infectious diseases. Albumin may have some additional specific effects aside from its volume-replacement properties such as transport function for various drugs and endogenous substances (e.g., bilirubin, free fatty acids)<sup>14</sup> or beneficial effects on membrane permeability secondary to free radical scavenging.<sup>15</sup> These effects were shown only experimentally, and no clinical study has demonstrated any of these effects in comparison with other plasma substitutes.

### Synthetic Colloids

The term *synthetic colloids* is somewhat misleading because all of them are from biologic origin. Thus, nonprotein colloids does not sound as negative as synthetic colloids.

**Dextrans.** Dextran is a glucose polymer that is available in two preparations of different molecular weights and concentrations (3% dextran with an average molecular weight of 60; 6% dextran with an average molecular weight of 70 kD; 10% dextran with an average molecular weight 40 kD). The increase of plasma volume after infusion of 1,000 mL of dextran 70 ranged from 600 to 800 mL. Some negative side effects of dextrans have been well described, including coagulation abnormalities resulting in increased bleeding tendency and severe life-threatening hypersensitivity reactions.

**Gelatins.** Gelatins are modified beef collagens. Because of their average low molecular weight (approximately 35 kD), the intravascular half-life of gelatin infusion is short (approximately 2 hours) and gelatins are supposed to be the least effective colloids.<sup>16</sup> This disadvantage is balanced by the absence of a dose-limitation with gelatins. Gelatins were abandoned in the United States in 1978

because of the high incidence of hypersensitivity reactions.<sup>17-19</sup> Although the raw product is from beef, gelatins are generally agreed to be free of risk of prion transmission.<sup>20</sup>

**Hydroxyethyl Starch (HES).** HES is a high-polymeric glucose compound that is manufactured through hydrolysis and hydroxyethylation from the highly branched starch amylopectin. Polymerized D-glucose units are joined primarily by 1-4 linkages with occasional 1-6 branching linkages. The degree of branching is approximately 1:20, which means that there is one 1-6 branch for every 20 glucose monomer units. Natural starches cannot be used as plasma substitutes because they are unstable and rapidly hydrolyzed by circulating amylase. Substituting hydroxyethyl for hydroxyl groups results in a highly increased solubility and retards hydrolysis of the compound by amylase, thereby delaying its breakdown and elimination from the blood. The hydroxyethyl groups are introduced mainly at carbon position C<sub>2</sub>, C<sub>3</sub>, and C<sub>6</sub> of the anhydroglucose residues.

The pharmacokinetics of HES preparations are characterized by the pattern of hydroxyethylation, in particular by the molar substitution and by the degree of substitution. The molar substitution (MS) is computed by counting the total number of hydroxyethyl groups present and dividing the number by the quantity of glucose molecules. The available HES preparations are characterized by (Table 3):

- Concentration (low, 3%; medium, 6%; high, 10%),
- MS (low, 0.4 and 0.42; medium, 0.5; high, 0.62 and 0.7),
- Mean molecular weight (low molecular weight [LMW] HES, 70 kD; medium-molecular-weight [MMW] HES, from 130 to 260 kD; high-molecular-weight [HMW] HES, >450 kD),
- Ratio of the C<sub>2</sub>:C<sub>6</sub> hydroxyethylation, and
- The solvent (nonbalanced HES are solved in saline solution; balanced HES are solved in a plasma adapted solution).

Several HES preparations are available in Europe, whereas in the United States only the first-generation HMW HES with a high MS (Hetastarch; concentration, 6%; molecular weight, 450 kD; MS, 0.7) is approved for volume replacement. In Canada only an MMW HES (10% HES 270/0.45; pentastarch) is available for treating hypovolemia in trauma patients.

**Hypertonic Solutions.** Enthusiasm has been expressed for hypertonic solutions or hypertonic/hyperoncotic solutions in the treatment of hypovolemic shock in trauma patients. The concentration of sodium ranged from 3% to 7.5%. Hypertonic solutions and hypertonic/hyperoncotic solutions may improve cardiovascular function on multiple levels: displacement of tissue fluid into the blood compartment (Fig. 2), direct vasodilatory effects in the systemic and pulmonary circulation, reduction in venous

**Table 3. Physicochemical Properties of the Different Hydroxyethyl Starch (HES) Preparations**

	HES 70/0.5	HES 130/0.4	HES 130/0.42	HES 200/0.5	HES 200/0.5	HES 200/0.62	HES 450/0.7
Concentration (%)	6	6	6	6	10	6	6
Volume efficacy (approx. 1%)	100	100	100	100	130	100	100
Volume effect (hours)	1-2	2-3	2-3	3-4	3-4	5-6	5-6
Mean molecular weight (kD)	70	130	130	200	200	200	450
Molar substitution	0.5	0.4	0.4	0.5	0.5	0.62	0.7
C <sub>2</sub> /C <sub>6</sub> ratio	4:1	9:1	6:1	6:1	6:1	9:1	4.6:1

kD, kilodalton.

capacitance, and positive inotropic effects through direct actions on myocardial cells.

The main mechanism of action of hypertonic solutions is the rapid mobilization of endogenous fluid and subsequent plasma volume expansion. Because of the hypertonicity of the solutions, only a small volume of fluid (approximately 4 mL/kg) is necessary to effectively restore cardiovascular function (“small-volume resuscitation”). The initial improvement in cardiovascular function (e.g., increase in cardiac output) seems to be mediated by the hypertonicity of the solution, whereas the solute composition does not seem to be important. Beneficial effects of hypertonic saline solutions were reported to be rather transient. Consequently, hypertonic solutions were often mixed with colloids (dextran or HES), and these solutions showed a prolonged efficacy. Improved microcirculation/organ perfusion, inflammatory response, endothelial integrity, and reduction in tissue edema have been demonstrated with hypertonic solutions or hypertonic/colloid solutions in experimental and some human studies. Although the ideal concentration of hypertonic solutions has not been clearly elucidated, 7.5% or 7.2% hypertonic solutions have been used most often.

### Risks of Fluid Replacement Strategies in the Trauma Patient

All fluids used for correcting hypovolemia in the trauma patient have merits and demerits. The most alarming problems are anaphylactoid reactions, increased bleeding tendency, development of tissue edema, renal dysfunction, and alterations of the immune function.

#### Allergic Reactions

The use of crystalloids is not associated with anaphylactic reactions. Severe dextran-associated anaphylactic reaction are widely known for their frequency and severity.<sup>18</sup> As shown in a large trial including approximately 20,000 patients, gelatins are at risk to produce a larger number of anaphylactic reactions compared with starch preparations.<sup>19</sup> Gelatins were shown to be associated more often with severe anaphylactic reactions, whereas this is very rare after the infusion of HES.<sup>19</sup>

#### Influence on Coagulation and Increased Bleeding Tendency

Coagulopathy is a common complication of hemorrhagic shock. Additionally, resuscitation-associated hemodilution may alter hemostasis by lowering the concentration of clotting proteins. Use of *crystalloids* has been thought to be without negative influence on coagulation except for that attributable to hemodilution, although

recent studies have demonstrated an increased coagulability during hemodilution with saline.<sup>21</sup> *Albumin* is considered to be the colloid with the least negative influence on coagulation, but some procoagulatory or anticoagulatory effects (e.g., inhibiting platelet aggregation, enhancing the inhibition of factor Xa by antithrombin III) have been described with albumin.<sup>22</sup> *Dextrans* are the plasma substitutes with the most pronounced negative effects on hemostasis, that is, increasing bleeding tendency. Using dextran, both factor VIII ristocitin antigen (VIII:Rst) and factor VIII ristocitin cofactor (VIII:Rco) levels decrease significantly.<sup>23</sup> With reduced VIII:Rco there is a reduced binding to platelet membrane receptor proteins GPIIb and GPIIb/IIIa that results in decreased platelet adhesion.<sup>23</sup> *Gelatins* have been thought to possess no negative effect on coagulation. However, in a study in which healthy humans received either 1,000 mL of gelatin or saline solution, de Jonge et al<sup>24</sup> found that the infusion of gelatin resulted in a significant impairment of primary hemostasis and thrombin generation.

Changes in coagulation have most often been reported with the use of *hydroxyethylstarch*.<sup>25</sup> The different HES preparations have to be distinguished regarding their influence on the hemostatic process.<sup>26,27</sup> HMW HES (hetastarch) diminishes concentrations of VIII:Rst and VIII:Rco more than HES with a lower molecular weight.<sup>23</sup> Platelet aggregation abnormalities have also been observed after the infusion of HMW HES, whereas infusion of HES with a lower molecular weight did not change platelet aggregation induced by adenosine diphosphate.<sup>28</sup> A substantial body of evidence supports the concept that HES with medium molecular weight (MMW HES, 130 kD, 200 kD) and a low MS (0.4 or 0.42) have significantly fewer negative effects on coagulation and can be safely used with regard to hemostasis.<sup>27,28</sup>

#### Tissue Edema

Factors contributing to tissue edema formation are venous congestion, reduced COP, arteriolar vasodilation/venous vasoconstriction, disorganization of the interstitial matrix, increased endothelial permeability, and lymphatic dysfunction. COP is an important aspect in determining fluid shifts between the intravascular and interstitial compartments. Manipulation of COP appears to be promising to ensure adequate intravascular volume. Controversy still exists whether the choice of fluid for restoration of circulating volume is able to limit development of tissue edema. Dilution of serum proteins by the massive administration of *crystalloids* lowers COP with the risk of progressive expansion of the interstitial space. In a nontrauma experimental peritonitis model, crystalloid infusion resulted in more pronounced endothelial cell swelling and decreased systemic capillary cross-sectional area compared with volume therapy with colloids.<sup>29</sup>

Maintenance of COP by the administration of *albumin* has been postulated to be a desirable goal. The oncotic force of concentrated albumin (e.g., HA 20%) has been shown to reduce tissue edema (e.g., pulmonary edema).<sup>30</sup> In patients with impaired vascular endothelial integrity (e.g., trauma patients), albumin may pass into the interstitial compartment and fluid will subsequently shift from the intravascular to the interstitial space. A rapid and profound increase in the transcapillary escape rate of radiolabeled albumin has been described within 6 hours of surgery.<sup>31</sup> The endothelium may also swell and, subsequently, microcirculatory perfusion is altered. In severely ill patients, the addition of albumin resulted in more signs of respiratory failure compared with patients who did not receive albumin. This appears to be most likely due to increased leakage into the interstitial space.<sup>32</sup>

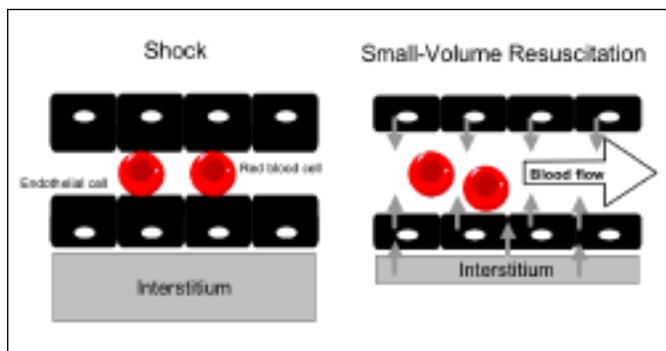


Figure 2. Improved microperfusion resulting from infusion of hypertonic solutions (small-volume resuscitation).

In inflammatory-related capillary leak, *HES* has been reported to have “occlusive” effects on damaged capillaries, subsequently limiting the extravasation of fluid. LMW *HES* may exert beneficial effects on endothelial function by stabilization of fragile cell membranes or by avoiding endothelial swelling.<sup>33</sup> This may be of benefit in those trauma patients suffering from severe endothelial leakage.<sup>34</sup>

### Renal Function

Renal dysfunction in trauma patients may develop for several reasons, including insufficiently treated hypovolemia. *Crystalloids* have no specific adverse effects on renal function except that they may not restore blood volume adequately. The effects of the different *colloids* on renal function are controversial. In patients with excessive fluid deficits, glomerular filtration of hyperoncotic colloids (dextrans, 10% *HES*, 20% or 25% albumin) may cause a hyperviscous urine and stasis of the tubular flow, resulting in obstruction of tubular lumen.<sup>35</sup> Some commercially available albumins contain remarkable quantities of ions from the preparation process, resulting in toxic concentrations of aluminium in patients with acute renal failure.<sup>36</sup> *HES* molecules and gelatin molecules are eliminated by glomerular filtration. *Gelatins* appear to be almost without significant damaging effects on the kidneys. In a retrospective analysis of patients undergoing kidney transplantation and in whom *HES* with a high MS (0.62) was infused, “osmotic-nephrosis-like lesions” were documented.<sup>37</sup> However, this phenomenon did not have negative effects on graft function 3 and 6 months after transplantation.

Use of 6% *HES* 200/0.62 (2,100 ± 660 mL) in brain-dead donors resulted in impaired renal function in kidney transplant recipients.<sup>38</sup> Patients treated with this *HES* preparation with a high MS showed higher serum creatinine concentrations and a more frequent need for hemodialysis compared with a gelatin-treated group of patients. In a multicenter study in intensive care patients, *HES* (200/0.62) resulted in a significantly higher incidence of renal failure compared with a comparable group of patients who received a gelatin preparation.<sup>39</sup> Fortunately, the authors distinguished between different types of starches, and state that the results of the study may not be applicable to more rapidly degradable *HES* preparations (e.g., *HES* 130/0.4). Use of *HES* 200/0.5 over 5 days in a study of critically ill ICU patients was without negative effects on renal function compared with a control group in whom albumin was administered.<sup>40</sup> In a study in elderly patients (>75 years), administration of 6% *HES* 200/0.5 for major abdominal surgery was not associated with relevant changes of kidney-specific proteins that are sensitive markers of renal injury.<sup>41</sup>

### Accumulation and Dose Limitations

Storing, accumulation, and dose limitations have to be considered only when using nonprotein (“synthetic”) colloids. Gelatin and dextrans are naturally occurring substances and both are fully metabolized in man. Dose limitation exists for dextrans (approximately 2,500 mL/day) most likely because higher doses are associated with severe bleeding complications, but not for gelatins. All available *HES* preparations are stored and may accumulate, depending on the preparation. The smaller molecules are rapidly eliminated by glomerular filtration. A varying proportion of the *HES* administered leaves the vascular space and is taken up by the reticuloendothelial system. However, reticuloendothelial system storage appears to be without detrimental consequences.<sup>42</sup> A dose limitation exists for all *HES* preparations ranging from 20 mL/kg (10% *HES* 200/0.5) to 50 mL/kg (6% *HES* 130/0.4).

### Immune Modulation

Traumatic injury is known to induce intense alterations in circulatory homeostasis and cell-mediated or humoral immunity.<sup>43</sup> These sequelae of trauma predispose to the development of posttrauma sepsis or systemic inflammatory response syndrome. The mediators of immunosuppression secondary to trauma are not definitely elucidated. Endotoxin, tissue metabolic products resulting from cellular hypoxia, shock proteins, and hormonal mediators (e.g., catecholamines) are suspected to take part in this process. Polymorphonuclear cells are supposed to be key mediators of tissue injury and organ failure. Although neutrophils are essential for bacterial killing, they paradoxically have the capacity to injure host tissue. The interactions of neutrophils with endothelial cells are regulated by complementary adhesion molecules, which are present on these cells (e.g., the immunoglobulin superfamily, such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1); the integrin family, such as lymphocyte function-associated antigen [= CD11a/CD18]; and the selectins [E-selectin = endothelial leukocyte adhesion molecule, L-selectin = e.g., leukocyte endothelial cell adhesion molecule; P-selectin = granule membrane protein 140]). Soluble forms of some of these adhesion molecules appear to be excellent markers of inflammation and endothelial activation or damage.<sup>44</sup> The influence of *HES* on endothelial cell activation was studied experimentally by Collis et al<sup>45</sup> using endothelial cell cultures (human umbilical vein endothelial cells). E-selectin expression on lipopolysaccharide-stimulated endothelial cells was not influenced by *HES*. The authors suggested a possible beneficial role of *HES* by inhibiting endothelial activation: thrombin-stimulated vWF release was significantly more reduced in the presence of *HES* than in the presence of HA. The authors concluded from their data that *HES* may be able to inhibit endothelial activation with subsequent damage of endothelial integrity and that, by this mechanism, *HES* may be able to ameliorate capillary leak secondary to inflammation. The effects of 10% *HES* 200/0.5 or 20% albumin given over 5 days to guarantee normovolemia in severely (nonseptic) traumatized patients on plasma levels of circulating adhesion molecules were assessed in a prospective randomized study.<sup>46</sup> Soluble endothelial leukocyte adhesion molecule-1, soluble intercellular adhesion molecule-1, and soluble vascular cell adhesion molecule-1 plasma levels did not differ between *HES*- and HA-treated patients, indicating no negative effect of the synthetic colloid *HES* on endothelial function.

### Fluid Replacement in Trauma Patients in the Mirror of the Literature

In the *Advanced Trauma Life Support* guidelines, Ringer’s lactate is recommended as part of the emergency resuscitation of the trauma patient, proceeding to blood products as required.<sup>47</sup> The *American College of Surgeons Classes of Acute Hemorrhages* specify four classes of acute hemorrhage using a blood loss ranging from up to 750 mL to >2,000 mL.<sup>48</sup> Fluid replacement should be performed with crystalloids exclusively (3:1 rule): there is no place for infusing (synthetic) colloids in their recommendations (Fig. 3).

### Fluid Resuscitation in Trauma Patients and Meta-Analyses

We are living in times of meta-analyses and evidence-based medicine (EBM). Meta-analyses bring together information from randomized controlled trials of the same intervention, and today the choice of therapy is often related to results from meta-analyses.

### American College of Surgeons Classes of Acute Hemorrhage

Factors	I	II	III	IV
Blood loss (mL)	<750	750-1500	1500-2000	>2000
Blood loss (%BV)	<15	15-30	30-40	>40
Pulse (beats per minute)	>100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal/increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respiration per minute	14-20	20-30	30-40	>35
Urine output (mL/hr)	30 or more	20-30	5-10	Negligible
CNS (mental status)	Slightly anxious	Mildly anxious	Anxious-confused	Confused-lethargic
Fluid replacement	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood (3:1 rule)

**Figure 3. Fluid resuscitation in patients with acute hemorrhage according to American College of Surgeons Classes of Acute Hemorrhage. %BV, percent of blood volume replaced; CNS, central nervous system. (Data derived from Bell et al.<sup>47</sup>)**

#### Meta-Analyses: Crystalloids versus Colloids.

- In a meta-analysis from 1989, a possible reduction in mortality was documented when crystalloids were used in traumatized patients.<sup>49</sup> In this analysis, five trauma studies were included, two were from 1981, one from 1979, one from 1978, and one from 1977.
- In a meta-analysis by Schierhout and Robertson<sup>50</sup> in 1998, the use of colloids was associated with an increased incidence of death. Seven trauma studies were included in this meta-analysis: three studies used hypertonic/colloidal solutions, two used albumin, one used them dextran, and another one used gelatin. Summarizing all 37 analyzed studies, resuscitation with colloids was associated with an increased absolute risk of mortality of 4% (or four extra deaths for every 100 patients resuscitated).
- In the Cochrane EBM analysis on volume replacement in 1998, four trauma studies were included, one was from 1977, two were from 1978, and one was from 1983.<sup>51</sup> The message of this EBM analysis was that albumin “kills our patients” (for every 17 patients treated with albumin, there was 1 additional death).
- Only one meta-analysis distinguished between trauma patients and other kind of patients (e.g., cardiac surgery, critical care patients).<sup>52</sup> In this analysis from 1999, four trauma studies were included. All of them were more than 17 years old. A mixture of all kinds of colloids were compared with crystalloid-based resuscitation. There were no differences between the two volume-replacement strategies.
- The influence of an albumin-based volume therapy on mortality compared with other volume-replacement strategies was compared in a meta-analysis of randomized controlled trials from 2001.<sup>53</sup> No study was included that was more recent than 2000. In one subgroup, studies involving surgery and trauma (27 studies total) were included. None of the analyzed factors (e.g., outcome, mortality) were significantly influenced by either volume-replacement regimen. There was, overall, no beneficial effect of albumin on mortality in comparison with other (cheaper) plasma substitutes.

Meta-analyses have some fundamental problems<sup>54</sup>: there may be a selection bias of included trials and the results of the analyses may be similar, but they are interpreted quite differently. Specific objections to all meta-analyses on fluid therapy are:

- The mixing of patients with different diseases (trauma, surgical, and septic patients are different!!).
- The physicochemical properties of the different colloids have been neglected in all meta-analyses. Because of the important differences between individual colloids, it is not appropriate to summarize all colloids in a “colloid group.”
- Most meta-analyses include studies more than 15 years old. Important innovative strategies have been developed in managing trauma patients during the last 15 years, including improved monitoring techniques, ventilation strategies, feeding, and others that may also influence outcome.
- Mortality was used as the major end point for volume replacement in all meta-analyses. However, mortality was not the end point of most of the volume-replacement studies. None of the studies found a statistically significant effect that favored “colloids.” It is still unclear whether mortality is helpful to determine the ideal volume-resuscitation strategy.<sup>55</sup>

#### Volume Replacement Using Hypertonic Solutions

Treatment of trauma-related hypovolemia using hypertonic (and hyperoncotic) solutions should be assessed separately from the “classic” colloid/crystalloid or colloid/colloid debate because this represents a special issue. This strategy is mostly used in the early (field) resuscitation of severe hypovolemia.

**Meta-Analyses: Hypertonic Volume Replacement.** The efficacy of hypertonic 7.5% saline/6% dextran solution in trauma patients was reviewed in a meta-analysis from 1997, including nine (original) studies.<sup>56</sup> The analysis revealed no significant improvement in outcome after the infusion of hypertonic saline solution, whereas the use of hypertonic saline plus dextran “may” be superior compared with isotonic fluid resuscitation.

In a systematic review from the Cochrane Group from 2002, hypertonic-based volume-replacement regimen was compared with

crystalloid-based volume replacement in critically ill patients.<sup>57</sup> Although many studies have been published on this topic, only 12 studies were included into the analysis. The authors concluded that there is no evidence that one strategy of volume therapy is superior to another when comparing patients with trauma (five studies included), burns (three studies included), or those undergoing surgery (four studies included). No beneficial influence of hypertonic solutions on outcome was found.

One major factor with studies on hypertonic volume replacement is that in most of the studies, a fixed volume of either fluid was given (e.g., 250 mL) and no “goal-directed therapy” has been used. It is doubtful that 250 mL of an isotonic crystalloid (such as normal saline) was adequate to treat a hypovolemic trauma patient. Systemic hemodynamics after hypertonic volume replacement were either improved or without differences compared with crystalloids. No negative influence on hemostasis, bleeding, or use of packed red cells was documented. Nevertheless, hypertonic solutions appear to be very effective for rapidly treating severe hypovolemia; as it is only a very short effect, this approach must be considered as a “bridging” until volume deficit is corrected with more long-lasting substances, such as with synthetic colloids (or blood when necessary).

## How To Guide Fluid Therapy in Trauma Patients

Detection of volume deficits and guiding adequate volume therapy remain a challenge. The aim of an appropriate monitoring is to avoid insufficient fluid infusion as well as fluid overload. Standard hemodynamic monitoring such as measuring blood pressure and heart rate are often inaccurate to detect volume deficits or to guide volume therapy. Cardiac filling pressures (e.g., central venous pressure and pulmonary artery occlusion pressure) are often misleading surrogates for assessing optimal left ventricular loading conditions. Cardiac filling pressures are influenced by several factors other than blood volume, including alterations in vascular or ventricular compliance and intrathoracic pressure. In spite of some negative data on the value of pulmonary artery catheters (PACs), they are still widely used for hemodynamic monitoring in critically ill patients. One recent retrospective database analysis including a total of 53,312 patients has demonstrated an improved survival in trauma patients when using a PAC<sup>58</sup>: Trauma patients managed with a PAC are more severely injured and have a higher mortality. Severely injured patients (Injury Severity Score, 25-75) who arrive in severe shock, and older patients, have an associated survival benefit when managed with a PAC.

Measurement of intrathoracic blood volume has been reported to be a more reliable method to monitor volume therapy in this situation.<sup>59</sup> A reduction in ICU and hospital stay was shown and even mortality was reduced when using intrathoracic blood volume monitoring.<sup>59</sup> However, there are no convincing data available with this monitoring instrument in trauma patients.

Echocardiography, especially transesophageal echocardiography, appears to be the most specific instrument to evaluate cardiac filling. Because of its high costs, it is not available in every ICU patient. Moreover, transesophageal echocardiography is an intermittent diagnostic tool rather than a continuous monitoring device, and thus appears to be unreliable to guide volume therapy.

Perturbation of organ perfusion is thought to be of fundamental importance in the pathogenesis of developing organ dysfunction in the posttrauma period.<sup>60</sup> Even occult hypovolemia may be associated with the development of organ perfusion deficits and subsequently with organ dysfunction.<sup>61,62</sup> There still does not exist a reliable, easy-to-use monitoring tool to detect perfusion deficits. Cardiac output,  $VO_2$ , and

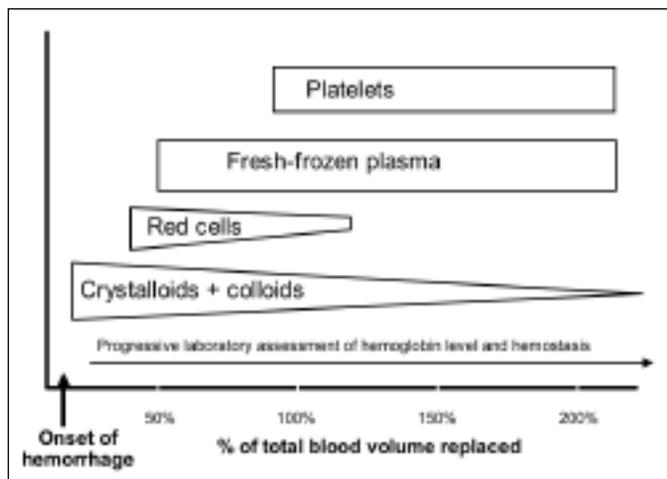
$DO_2$  are not regarded as ideal measures for assessing the adequacy of regional or microcirculatory perfusion.<sup>63</sup> The hypovolemic patient is at risk of experiencing splanchnic hypoperfusion with subsequent development of translocation and systemic inflammatory response syndrome.<sup>64</sup> Abnormalities of splanchnic perfusion may coexist with normal systemic hemodynamic and metabolic parameters. Noninvasive, continuous tonometry measuring gastric mucosal partial pressure of carbon dioxide may be an attractive option for diagnosis and monitoring of splanchnic hypoperfusion. This monitoring instrument has produced some promising results, but it is far from being the new “gold standard” for guiding volume therapy.<sup>65</sup>

## Conclusions

In the hypovolemic trauma patient, adequate volume restoration appears to be fundamental to prevent noncompensatory, irreversible shock. Lengthy uncorrected hypovolemia will jeopardize survival by the continuous stimulation of various vasopressive and immune cascades. Prolonged underresuscitation of the hypovolemic trauma patient may have fatal consequences for organ function. Thus, vigorous optimization of the circulation, at least when surgical hemostasis has been achieved, is a prerequisite to avoid development of multiple-organ dysfunction syndrome in the posttrauma period. This maneuver is aimed at guaranteeing stable macro- and microhemodynamics while avoiding excessive fluid accumulation in the interstitial tissue.

There is still no consensus regarding the optimal treatment of hypovolemia in trauma patients. Continued controversy exists with regard to the most appropriate fluid during trauma resuscitation. What did we learn from the recent years?

- Allogenic blood should be avoided as far as possible; it cannot, however, be completely eliminated from our strategy to manage the hemorrhagic shock patient (Fig. 4).
- Human albumin is the most expensive plasma substitute. Nononcotic, additional effects of albumin (e.g., radical scavenging properties) have been shown in some experimental/animal studies but are lacking in trauma patients. No beneficial effects on perfusion, inflammation, tissue edema, or organ function have been demonstrated in humans to justify the use of this expensive plasma substitute. In a large multicenter, randomized double-blind trial, the safety (not the efficacy!) of 4% albumin was compared with normal saline solution in approximately 7,000 critically ill, ICU patients, including a subgroup of trauma patients (Sedation and Airway Support for Everyone [SAFE] study<sup>66</sup>). Albumin has been shown to be a safe plasma substitute; however, no beneficial effects on mortality, morbidity, or length of ICU stay has been shown with the use of albumin compared with crystalloid-based fluid resuscitation.
- Although there is convincing evidence that blood volume is restored more rapidly with colloids than with crystalloids and colloids are also more efficient to improve microcirculation, crystalloids are still often recommended as the first choice to treat hemorrhage.<sup>67</sup> *The American College of Surgeons Classes of Acute Hemorrhage* specified four classes of acute hemorrhage using a blood loss ranging from up to 750 to >2,000 mL<sup>47</sup> (Fig. 3). Fluid replacement should be performed with crystalloids exclusively (3:1 rule). There is no place for infusing colloids.
- Using high doses of crystalloids is associated with the risk of fluid overload, and using saline solution is associated with the risk of hyperchloremic acidosis. Crystalloids are often recommended for treating hypovolemia because they are



**Figure 4. Management of the bleeding patient with fluids and blood/blood products.**

cheap and are suggested to have only few side effects. Delayed and inadequate restoration of intravascular circulating volume by crystalloids, however, have been shown to worsen microvascular flow, endothelial integrity, and tissue oxygenation. Experimental, animal, and human studies have documented negative effects of crystalloids on inflammation, endothelial activation, and capillary leakage. Consequently, the Institute of Medicine raised concern with a Ringer's lactate-based volume-replacement strategy because it aggravated the inflammatory process following resuscitation.<sup>68</sup>

- Certain colloids (such as HES) are associated with beneficial effects beyond their volume-replacement properties (e.g., improving microperfusion, capillary integrity, inflammatory response, and endothelial activation/integrity).
- Great enthusiasm has been expressed for hypertonic saline or hypertonic/colloid solutions in the treatment of hypovolemic shock in the trauma patient. Hypertonic solutions and hypertonic/colloid solutions may improve hemodynamics on multiple levels. Although shock-associated microvascular failure is often unresolved after standard resuscitation, hypertonic solutions and hypertonic/colloid solutions appear to reduce microvascular collapse, restoring vital nutritional blood flow. Hypertonic solutions tends to blunt the up-regulation of leukocyte and endothelial adhesion molecules that occurs with isotonic resuscitation of shock. Most problems with hypertonic solutions arise because convincing data on outcome in trauma patients are still lacking
- The determination of which end points should be chosen when volume is administered remains unsolved. Although often used, “clinical signs” of hypovolemia are nonspecific and insensitive. Most studies of volume replacement in trauma patients were not focused on outcome. It remains unclear if mortality is an appropriate end point when comparing different volume-replacement strategies. New concepts such as the development of systemic inflammatory response syndrome and posttrauma organ dysfunction (e.g., renal or pulmonary insufficiency) should change this point of view.
- Few studies are available comparing different volume-replacement protocols exclusively in trauma patients. Based on these limited data, strict recommendations on the “best” volume-replacement strategy in the hypovolemic trauma

patient are surprising.<sup>67,69</sup> Further studies are necessary to distinguish different types of trauma (e.g., with/without head injury, blunt trauma, penetrating trauma) and severity of trauma. Moreover, we should not only consider young, strong male victims but also—especially in highly industrialized countries—the >70 years old trauma patient who presents with several comorbidities.

Therapeutic decisions should be made on the basis of solid scientific evidence. Unfortunately, the debate on the choice of the fluid-replacement strategy in the trauma patient is widely influenced by personal choices, availability, cost, and emotions. In spite of many years of intensive research on this topic, we should remember “Not everything that counts can be counted and not everything that can be counted counts” (Albert Einstein).

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