

New Developments in Fluid Resuscitation

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Hemorrhage control and resuscitation are the top priorities in trauma care. Exsanguination is the leading cause of possibly preventable death in civilian [1,2] and military trauma [3]. The optimal resuscitative strategy, however, remains controversial: who, when, and how are questions that have yet to be answered fully in regards to fluid resuscitation.

Evolution of fluid use in trauma

During the Vietnam War era, aggressive crystalloid resuscitation became popular because of seminal research by Shires, Moyer, Moss, and others [4–7]. Their work suggested that infusion of large-volume isotonic crystalloids improved survival, and resuscitation fluids were needed not only to replace the intravascular volume loss, but also to replenish interstitial deficits. These investigators recommended fluid replacement equal to three times the volume of blood loss (and as high as 8:1 for severe shock). Reflecting the technology and knowledge available at that time, the focus of research was on physiology, and investigators concentrated primarily on the restoration of intravascular and interstitial fluid deficits. As a result emphasis was placed on establishing intravenous access in all trauma patients to initiate early resuscitation. The Advanced Trauma Life Support course, which has been instrumental in standardizing trauma care, recommends that for patients in shock, 2 L of crystalloids be infused followed by packed red blood cell transfusions. This recommendation has been

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extrapolated and it is now common that all trauma patients (not just patients in shock) are infused with two or more liters of lactated Ringer's (LR) solution.

In addition, Shoemaker and coworkers [8] suggested that there was an oxygen debt that needed to be repaid, and popularized aggressive resuscitation in the intensive care setting. This oxygen debt to the tissues was repaid by "maximizing or supernormalizing" cardiac output [9] with volume loading, blood transfusion, and inotropic drugs. This was continued until cardiac output no longer improved, or when oxygen consumption became independent of oxygen delivery. Numerous subsequent studies have shown, however, that this approach does not improve outcome [10–15]. On the other hand, aggressive fluid resuscitation may contribute to such conditions as abdominal compartment syndrome [16–18].

If early use of fluids is beneficial, there should be some data to support this practice. Isotonic fluids were used widely during the Vietnam conflict as the fluid of choice in massive resuscitations, but the mortality rates failed to improve compared with previous conflicts (Table 1). The only real change in outcome was noted between the first and second World Wars, and this was attributed to the widespread use of antibiotics. Coincidentally, "shock lung" or "Da Nang lung," which is now commonly referred to as acute respiratory distress syndrome [19], was first described during this period. The Navy Field Hospital in Da Nang, Vietnam, described this as a common finding in severely injured patients who were aggressively resuscitated. Current research suggests that it is caused by aberrant immune activation and immune-mediated organ injury. This condition is thought to be a part of a spectrum that can progress to multiple organ dysfunction syndrome. Since the 1990s these conditions have become main causes of death in trauma patients [1,20,21], and have been extensively investigated.

Prehospital fluids

Although it was once widely believed that early aggressive fluid resuscitation is beneficial, many are questioning this approach because clinical and

Table 1
Mortality rates of military conflicts

	KIA%	DOW%
US Civil War	16	13
Russo-Japanese War	20	9
WW I	19.6	8.1
WW II	19.8	3
Korean War	19.5	2.4
Vietnam War	20.2	3.5

Abbreviations: DOW, died of wounds refers to casualties that died after reaching a facility with a physician; KIA, killed in action refers to casualties that died before arriving at a medical facility with a physician.

basic science literature fails to provide conclusive evidence supporting this theory [22–29]. It is interesting that as early as 1918, Cannon and coworkers [30] stated “inaccessible or uncontrolled sources of blood loss should not be treated with intravenous fluids until the time of surgical control.” The most controversial study proving this in humans was published in the *New England Journal of Medicine* in 1994 [24]. In that study, hypotensive patients with penetrating injury to the torso were randomized to routine fluid resuscitation, or resuscitation that was delayed until bleeding had been surgically controlled. The results of this study demonstrated a survival advantage in the delayed resuscitation group (70% versus 62%, $P = .04$). This study has generated a vigorous debate, and its findings have been extensively scrutinized for faults. Despite all the controversy, the most impressive finding remains the fact that delaying fluid resuscitation did not increase mortality in these patients. The issue of timing and volume of fluid resuscitation in bleeding patients has also been addressed by The Cochrane Database of Systematic Reviews. Only six randomized clinical trials met the inclusion criteria, and a careful review failed to provide any evidence in support of (or against) early or large-volume intravenous fluid administration in uncontrolled hemorrhage [30a]. Theoretically, fluid resuscitation in uncontrolled hemorrhage exacerbates bleeding because of the disruption of early soft thrombus, coagulopathy, and hemodilution [31–34]. A systematic review of 52 animal trials concluded that fluid resuscitation seemed to decrease the risk of death in models of severe hemorrhage (relative risk [RR] = 0.48), but increased the risk of death in those with less severe hemorrhage (RR = 1.86) [35]. Furthermore, hypotensive resuscitation, whenever tested, reduced the risk of death (RR = 0.37).

Trauma as an immune disease

Experts in the field tend to agree that serious traumatic and thermal injuries lead to immune dysfunction and subsequent cellular damage [20]. According to this concept, trauma patients who survive the early postinjury period may develop a spectrum of conditions, such as systemic inflammatory response syndrome, acute lung injury, acute respiratory distress syndrome, and multiple organ dysfunction syndrome. Most seriously injured patients survive the initial systemic inflammatory response syndrome response (without developing early multiple organ dysfunction syndrome), however, and manifest a compensatory anti-inflammatory response syndrome with suppressed immunity and significant risk of developing an infection. The resultant infection can then lead to late multiple organ dysfunction syndrome and death. A number of approaches have been tried, albeit unsuccessfully, to correct this posttraumatic immune dysfunction [36–38].

Fluids causing inflammation: changing paradigm

It is now recognized that resuscitation fluids are not completely innocuous, and they may actually potentate the cellular injury caused by

hemorrhagic shock. This concept of “resuscitation injury” has steadily gained attention in recent years. A report by the Institute of Medicine (IOM) in 1999 described in detail the wide spectrum of adverse consequences that can follow resuscitative efforts [39]. Most of the adverse findings were cytotoxic effects of various fluids. The IOM report acknowledged that the D-isomer found in LR solution as a racemic mixture along with the L-isomer was not optimal and recommended that efforts be made to eliminate the D-isomer of lactate. Since that report, a number of studies have provided evidence to support the new paradigm that cellular injury is influenced not only by shock, but also by resuscitation strategies. The IOM report also recommended the replacement of lactate with other substances, such as ketone bodies. Today, with the availability of advanced cellular research techniques, one can study the effect of resuscitation fluids on the biologic systems in much greater detail. These findings now have practical implications. Although some of the modified Ringer’s solutions (ketone and pyruvate based) remain experimental, LR is commercially available in the conventional racemic formulation or as a pure L-isomer solution, with markedly different properties. It is not clearly known whether the attenuation of cellular injury markers seen in the preclinical studies will translate into a measurable improvement in clinical outcome in trauma patients. Once activated, neutrophils bind to complimentary adhesion molecules (selectins, β_2 integrins) on the endothelium before transmigration into the tissues. It has been demonstrated that these adhesion molecules are up-regulated following resuscitation with racemic LR in a rodent model of hemorrhagic shock [40,41]. Furthermore, in these studies LR resuscitation was associated with histologic evidence of acute lung injury, whereas none of these adverse findings were noted following resuscitation with fresh whole blood.

Effect of resuscitation fluids on cellular regulation and functions

There is now accumulating evidence that most cellular functions are influenced by infusion of resuscitation fluids. There are a number of key variables that govern the response: (1) fluid composition, (2) fluid tonicity, (3) duration of exposure, (4) type of cells that are exposed, (5) presence or absence of infection or inflammation, (6) presence or absence of second hit, and (7) timing of fluid administration. Although cellular responses during the postresuscitation period involve almost all cell types through multiple interconnected cascades, for ease of presentation, findings from selected studies have been summarized under discrete categories.

Effects of resuscitation strategies on neutrophil excitation and immune activation in vivo

Neutrophil-mediated tissue injury has been identified as a key mechanism of postresuscitation organ damage [42]. In a swine model of hemorrhagic

shock, it has been shown that resuscitation with racemic LR solution (equal amounts of D and L isomers of lactate) or mere infusion of racemic LR (without hemorrhage) caused an increase in neutrophil oxidative burst [43]. In a similar model, neutrophil excitation was influenced by the dose and rate of racemic LR administration, and resuscitation with artificial colloids (dextran and Hespan) had an even more pronounced effect on neutrophil excitation [44]. No significant neutrophil excitation was seen, however, in animals that were resuscitated with hypertonic saline (HTS) or fresh whole blood.

Impact of resuscitation fluids on human white blood cells (ex vivo)

Similar to the animal data, exposure of human blood to isotonic crystalloids and artificial colloids has been shown to cause an increase in oxidative burst, and the expression of adhesion molecules on the neutrophils in a dose-dependent fashion [45]. Interestingly, in that study natural colloids (albumin) did not excite the neutrophils, and exposure to HTS actually suppressed neutrophil functions. This suppressive effect of HTS on neutrophil functions may be through the modulation of chemoattractant receptor signaling pathways [46]. When HTS is combined with dextran, the suppressive properties of HTS overcome the stimulatory properties of dextran [47]. Response of cells to LR solution depends on its composition. Although conventional LR containing racemic lactate (D- and L-isomer) is proinflammatory, substitution of racemic lactate with L-isomer of lactate, or ketone bodies (β -hydroxybutyrate), can attenuate neutrophil activation and alter the expression of leukocyte genes known to be involved in inflammation, cell migration, and apoptosis [48]. Using customized cDNA microarrays, it has been shown that isotonic and hypertonic fluids do not differ in their effect on the cytokine genes in human leukocytes [49], but hypertonicity decreases the expression of immune activation associated genes [50]. Furthermore, the composition and tonicity of the resuscitation fluids can also have a dramatic influence on the life span of circulating cells [51].

Differential effects of resuscitation fluids on markers of cellular injury in various organs

Injured cells undergo death by two distinct mechanisms: apoptosis and necrosis. Apoptosis, although more controlled, requires energy. In the absence of energy the cells may undergo death by the poorly controlled process of necrosis. Although balanced apoptosis is essential for homeostasis and in the recovery from certain disease processes [52–55], a marked increase in apoptosis can be a marker of cellular injury and organ dysfunction [56,57]. Using apoptosis as a marker of diffuse cellular injury, it has been shown that resuscitation with racemic LR results in increased apoptosis in intestinal mucosa, smooth muscle, liver [58], and lung [59] in

rodents. Pulmonary and hepatic apoptosis is markedly reduced if lactate in the solution is substituted with β -hydroxybutyrate (ketone Ringer's) or sodium pyruvate (pyruvate Ringer's) [60–62]. Designer fluids containing other formulations of pyruvate (eg, ethylpyruvate) are also superior to conventional solutions [63]. In a recent study Shires and coworkers [64] have confirmed that fluids differ dramatically in their capacity to induce tissue apoptosis, and that modified Ringer's solutions (ketone and bicarbonate Ringer's) cause significantly less apoptosis compared with the racemic LR. These findings, noted in small animal models (rodents), have also been validated in a clinically relevant model of hemorrhage in swine, where resuscitation with conventional LR solution increased apoptotic cell death in liver and lung [65]. This was easily prevented by simple elimination of D-lactate from the Ringer's solution. The modified Ringer's solutions exert their protective effects through posttranslational modifications of key regulatory proteins [66], and by selective acetylation of histones (with subsequent alterations in gene transcription) [67]. The impact of resuscitation strategies can also be seen in well-protected sites, such as the brain, where the physiologic state of the central nervous system cells can be altered by changing the composition of resuscitation fluids (across the blood-brain barrier) [68]. Furthermore, resuscitation influences not only the regulation and functions of cells but also the integrity of the surrounding extracellular matrix [69].

Effect on gene regulation: integrated approach to data analysis

Similar to the circulating cells, regulation of gene expression in the tissues is also influenced by resuscitation strategies. The authors have discovered that approximately 7% of genes in rats are altered following shock and resuscitation. In each organ studied, the gene expression profile was dependent on the fluid used for resuscitation [70]. Although transcriptional profiling is now a well-established technique, its application to systematic studying of various biologic phenomena is still limited because of problems with high-volume data analysis and interpretation. Interpretation of these large datasets in the context of accumulated knowledge on human functional networks could yield biologically meaningful information. Using this integrated approach to data analysis, a comprehensive database has now been published, which further confirms that cellular mechanisms at the level of gene regulation are profoundly influenced by shock, and by the choice of resuscitation strategy [71].

Pharmacologic resuscitation

Although resuscitation restores tissue perfusion, it does not have any specific anti-inflammatory or prosurvival properties. To improve the outcome, investigators have added various protective agents to the

resuscitation regimen with good results [72–75]. An even more exciting approach is to improve survival through specific pharmacologic agents without any fluid resuscitation, that can alter gene transcription (epigenetic code) to create a prosurvival phenotype. A brief description of the underlying mechanisms may help to clarify this concept. The key regulatory site of gene transcription (and subsequent downstream pathways) is located at the level of chromatin, a 1:1 complex of DNA and proteins, predominantly composed of histone proteins. Various regulatory signals can affect gene transcription by influencing the activity of histones, most notably through acetylation. The two enzymes that govern the process of acetylation are histone acetyl transferase [76], and histone deacetylase [77,78]. Modulation of the histone code is one of the most upstream cellular events, which simultaneously regulates a subset of genes that are coordinately expressed to produce specific downstream effects. The authors have previously shown that hemorrhagic shock is associated with an imbalance in histone acetyl transferase/histone deacetylase ratio, an altered acetylation pattern of histones, and a decrease in gene transcription potential [67]. In that experiment, resuscitation reversed the shock-induced suppression of gene transcription in a fluid-specific fashion (ie, each resuscitation fluid had a distinctive pattern of histone acetylation [histone code]). Interestingly, brief administration of histone deacetylase inhibitors in this model, during 45 minutes of resuscitation, was even more effective in reversing the shock-induced imbalance, and increasing acetylation of histones. The follow-up experiments have now established that directly targeting the histones with histone deacetylase inhibitors, such as valproic acid (300 mg/kg) and suberoylanilide hydroxamic acid, can rapidly correct shock-induced alterations and improve survival in preclinical models of hemorrhage [79]. Impressively, this survival advantage was achieved without administration of any resuscitation fluids. The effect of hemorrhage and resuscitation on histone acetylation is almost identical in rodents and swine [80], and theoretically administration of histone deacetylase inhibitors should improve survival in large animal models in a similar fashion (under investigation). This raises the possibility that cell survival, and ultimately organism survival, can be improved through direct modulation of gene transcription in the setting of lethal hemorrhage. This exciting approach is currently being tested and refined under the Defense Advanced Research Programs Agency “Surviving Blood Loss” program.

Hypertonic saline and the clinical experience

The use of HTS for resuscitation from hemorrhage was first described in 1980, when Velasco and coworkers [81] and DeFelippe and coworkers [82] reported in separate studies that hypersomotic sodium chloride rapidly expands plasma volume after major blood loss. Because of its ability to

mobilize interstitial fluids into the vascular space, 250 mL of 7.5% saline can achieve results comparable with resuscitation with 2 to 3 L of 0.9% saline. Since the original reports, HTS has been used in a variety of circumstances and thousands of papers have appeared in the literature, including eight double-blinded randomized trials evaluating HTS or HTS with dextran for prehospital or emergency department treatment of traumatic hypotension. Improved rates of survival with HTS were reported with HTS in seven of eight trials, although statistically significant improvement in overall survival was seen in only one trial. A meta-analysis for the evaluation of HTS with dextran as the initial treatment for hypovolemic shock reviewed the original records from six trials (and 604 subjects) [83]. Overall survival rates were better with HTS with dextran resuscitation as compared with conventional resuscitation. HTS with dextran resuscitation was particularly effective for the subgroup of patients that had sustained head injury with a discharge survival rate of 38%, as compared with a rate of 27% for the control group receiving saline. In the clinical literature, there has been a remarkable absence of deleterious effects with HTS administration in more than 1000 trauma and surgical patients. No increase in the incidence of hypernatremic seizure, increased bleeding or blood transfusion requirement, coagulopathies, renal failure, cardiac arrhythmias, or central pontine myelinolysis has been attributed to hypertonic resuscitation in trauma patients. These clinical trials had used HTS as a volume expander, but a more advantageous effect of HTS administration may be the attenuation of immune-mediated cellular injury. A number of preclinical studies have demonstrated that HTS has the potential to modulate the posttrauma immune response, with an overall attenuation of immune-mediated cellular injury [84,85]. The salutary properties of HTS are primarily exerted through its effects on neutrophil-endothelial interactions. For example, in addition to decreasing neutrophil excitation [43–45], HTS resuscitation decreases inflammation [86], neutrophil-endothelial binding [87], lung damage [88], and bowel injury [89]. A number of elegant studies have further elucidated the subcellular pathways that are influenced by exposure to HTS [90–93]. The recently established Resuscitation Outcome Consortium [94], funded by the National Institutes of Health and the US Department of Defense, has started two multicenter trials of hypertonic resuscitation in two populations of trauma patients to be conducted simultaneously. Study 1 determines the impact of hypertonic resuscitation on survival for blunt or penetrating trauma patients in hypovolemic shock, whereas study 2 evaluates its impact on long-term (6 month) neurologic outcome after severe traumatic brain injury. Both studies are three-arm, randomized, blinded intervention trials comparing HTS with dextran (7.5% saline, 6% dextran 70), HTS alone (7.5% saline), and normal saline as the initial resuscitation fluid administered to these patients in the prehospital setting. In addition to the primary end points, comprehensive data about the immunologic consequences of hypertonic resuscitation are also being collected. It is hoped that these studies

would provide the conclusive evidence that is needed to get Food and Drug Administration (FDA) approval for the routine use of HTS in the treatment of trauma patients.

Fluid resuscitation for combat casualties: consensus conferences

Control of hemorrhage and judicious resuscitation are critical elements of early battlefield care. The optimal strategy for both of these goals is highly controversial, because of a general lack of category I-II clinical evidence. In addition to clinical benefits, the military must also take into account the logistical aspects of the approach (weight, volume, storage requirements, and so forth). The Office of Naval Research and the United States Army Medical Research and Materiel Command have supported the basic research in this field for many years. Primarily as a result of leadership and funding by the Office of Naval Research, three significant consensus conferences were held where data on fluid resuscitation were analyzed by experts, and recommendations made to improve clinical practice and to guide future research. The first meeting was under the supervision of the IOM in 1998. The IOM report concluded that the current resuscitation strategies were inadequate, potentially harmful, and needed radical changes. It identified numerous areas of future research, and recommended that combat casualties should be resuscitated with 250 mL bolus of 7.5% saline [39]. Unfortunately, the FDA has not yet approved this fluid for clinical use. In the follow-up meeting (June 2001, Uniformed Services University) a number of clinical recommendations were made including who should (and should not) be resuscitated; end point of resuscitation; and the optimal fluid [95]. Because the choice was deliberately limited to FDA-approved agents (available in the United States), hetastarch (hydroxy ethyl starch, 500 mL) was narrowly recommended as the fluid of choice for use in the battlefield. In the third meeting (October 2001, Toronto, Canada) the scope was widened to include fluids that were available in other NATO countries (even if not available in the United States) [96]. At this meeting a combination fluid (7.5% saline and 6% dextran [HTS with dextran]) was recommended as the initial fluid of choice [97]. At all of these meetings experts agreed that aggressive resuscitation is deleterious, an ideal fluid is yet not available, and low-volume resuscitation (hypertonic, colloid, or combination) is the most suitable choice for military needs. Proceedings of the last two meetings have been published as a special supplement of the *Journal of Trauma* (May 2003), including the recommendations for the initial fluid resuscitation of combat casualties [98].

The glaring absence of good clinical evidence has prompted collaboration between the National Institutes of Health and the United States Department of Defense to establish a consortium of clinical centers for conducting resuscitation research. It is hoped that this consortium will provide the much-needed clinical data to validate and confirm the promising basic science findings.

Changes in the military practice

The consensus conferences described here systematically evaluated all the available data and made strong recommendations that have catalyzed a noticeable paradigm shift. For example, the United States Army and Navy have authorized the use of low-volume resuscitation for combat casualty care and other NATO forces have developed similar protocols. The US Military's Committee on Tactical Combat Casualty Care is a standing committee comprised of members from the Army, Air Force, Navy, and Marines. This committee currently advocates the use of "permissive hypotension," which is to administer low-volume resuscitation to keep the casualty alive with a palpable pulse or consciousness but not to restore the blood pressure to normal until definitive control of hemorrhage. Early aggressive fluid resuscitation, in the absence of hemorrhage control, is no longer recommended. As a result, resuscitation in the combat zones is more selective (fluids given only when needed); is low volume; and aims for practical end points (eg, palpable pulse). Colloid fluids (eg, Hespan and Hextend) are replacing conventional crystalloids for early resuscitation, minimizing the logistical burden. Also, early hemorrhage control is being prioritized over aggressive fluid resuscitation. The resuscitation strategies that are being used by the US military in Iraq and Afghanistan already reflect the changing trends. It is too early to determine the direct impact of these new hemorrhage control and resuscitation strategies on combat casualty outcomes. It is very encouraging to note, however, that for the first time since the Crimean war the killed in action rate has markedly dropped below the historic 20% to around 10% to 14% [99,100].

Summary on current and future resuscitation fluids

Isotonic crystalloids

Significant immune activation and induction of cellular injury are seen with these fluids, especially racemic LR solution. It is known that a very large number of trauma patients receive LR and do well clinically. The patients who develop late complications of increased inflammatory response, however, are usually the ones who also have undergone severe hemorrhagic shock and massive fluid resuscitation. LR may be safe in small doses that the body can obviously tolerate, but not in larger amounts given over short periods following hemorrhagic shock and trauma. Modifications of LR, such as elimination of D-lactate, can decrease these adverse effects, and complete substitution of lactate with other monocarboxylates (eg, ketone bodies or pyruvate) seems to be beneficial.

Hypertonic crystalloids

As compared with LR, HTS causes suppression of neutrophil oxidative burst activity, decreases neutrophil-endothelial adhesions, and attenuates

immune-mediated cellular injury. Because of its logistic advantages (smaller volume) and immunologic benefits, HTS with or without a colloid seems to be the ideal fluid today for military application. A manufacturer has to obtain FDA approval, however, for its use as a volume expander in the United States. Although addition of dextran to HTS tends to prolong the volume expansion response, the authors believe that it might be easier to obtain FDA approval for a simple solution (HTS) than a combination solution (HTS and dextran). Studies scheduled to be performed under the National Institutes of Health-sponsored Resuscitation Outcome Consortium are expected to provide the conclusive evidence.

Artificial colloids

Dextran and Hespan cause significant neutrophil activation. Combination of dextran with HTS, however, blunts this response. When given in combination, colloids add the theoretical advantage of prolonging the hemodynamic response of HTS resuscitation.

Plasma

Plasma has a favorable effect, because it does not seem to activate neutrophils and numerous other pathways of cellular injury. Plasma is also a very effective volume expander. It has all the well-recognized problems, however, that are associated with storage, transport, and infusion of blood products. Autologous freeze-dried plasma is a promising alternative that can be reconstituted in a hyperoncotic, hypertonic fashion when needed. This is currently a focus of active investigations under the Department of Defense funded research programs.

Fresh whole blood

Fresh whole blood is by far the best and most effective fluid for resuscitation of hemorrhagic shock in animal models. Fresh whole blood is, however, not clinically available. Even if available, logistics of storage and transport make it an unrealistic option. One exception is the use of the “walking blood bank” by the military, where fresh whole blood is used in emergency situations. There is currently tremendous interest in investigating whether early use of whole blood (or components combined to create whole blood) benefits the severely traumatized [101].

Artificial blood

All the artificial blood products tested to date have failed to live up to expectations. There are now reasons, however, for developing and testing fluids that actually mimic the constituents of what humans bleed, which is whole blood. This starts with the recognition that currently available fluids are

not optimal. There is currently an ongoing multi-institutional phase III trial testing a human hemoglobin-based solution. If this type of product is deemed to be safe and beneficial, perhaps a combination product that combines freeze dried plasma along with oxygen-carrying hemoglobin may be of benefit.

Pharmacologic resuscitation

Administering specific agents to protect against ischemia-reperfusion injury and therapies that can induce a prosurvival phenotype (through up-regulation of selected genes) are attractive concepts. These are likely to be the next frontier in resuscitation research. In the future, severely traumatized patients may be treated with “designer fluids” supplemented with a cocktail of agents specifically chosen to augment the intrinsic survival pathways.

Who, when, and how?

The answers are simple but these questions are often never asked. In trauma, fluid resuscitation is only needed in patients who have lost blood. It is clear that not all the trauma patients need fluid resuscitation. For bleeding patients intravenous access is critical but should not be synonymous with fluid infusion. In the absence of traumatic brain injury, “permissive hypotension” with systolic pressures greater than 80 mm Hg, consciousness, or palpable pulse are reasonable goals until hemorrhage has been controlled. Rather than resuscitating the patient before definitive hemorrhage control, emphasis should be on controlling hemorrhage and using fluids only to keep the patient alive during the process. It can be argued that the initial fluid of choice among commercially available fluids in the United States should be 5% HTS because it is commercially available. Two 250-mL boluses are safe and offer many potential advantages. This should be followed by infusion of L-isomer LR (Baxter, Deerfield, Illinois) if further volume expansion is needed. For the hypotensive bleeding patient, initiation of blood transfusion should be early, and blood component therapy should be initiated immediately without waiting for the development of coagulopathy. Thawed fresh frozen plasma should be given in a 1:1 ratio to packed red blood cells. For the military, fresh whole blood from the walking blood bank should be obtained immediately for early use.

This aggressive approach is already being practiced at some centers with excellent results. For example, at the Los Angeles County Medical Center, six units of thawed fresh frozen plasma and platelets are given when six units of packed red blood cells are transfused (Fig. 1). For patients with thoracic hemorrhage, strong emphasis is placed on auto transfusion of blood collected from the chest tube. In the intensive care unit, blood pressure, urine output, and clinical judgment are used to guide the fluid resuscitation. As long as the serum lactate or base excess are trending toward normal, gentle resuscitation is preferred with an aim to correct acidosis over approximately

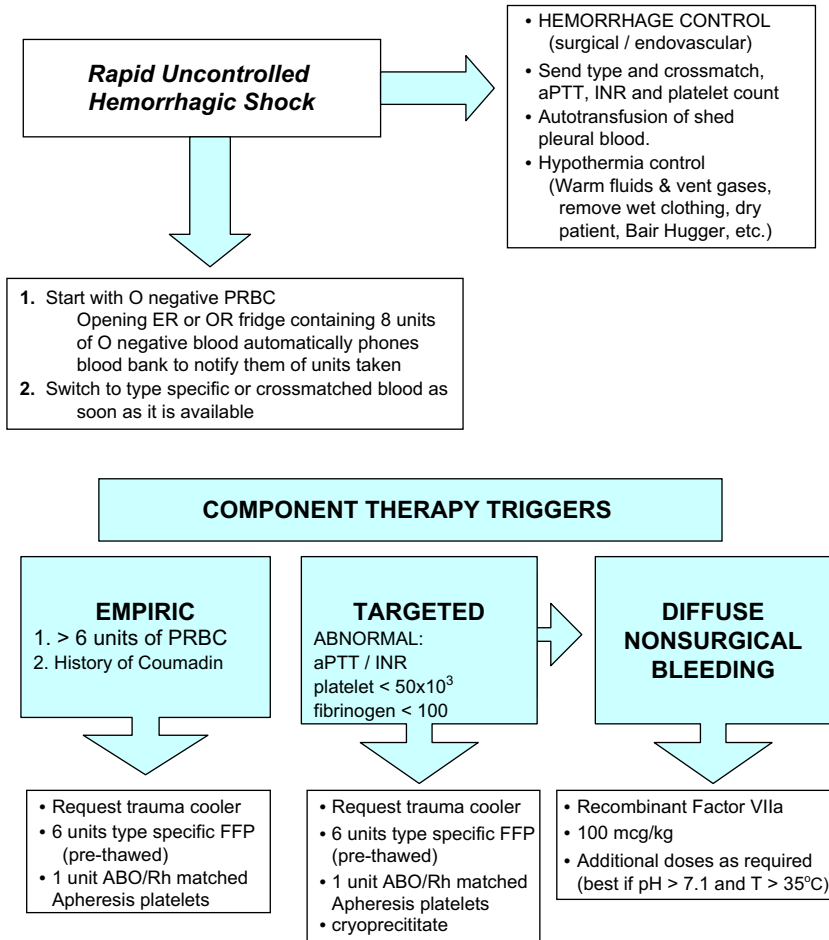


Fig. 1. LAC-USC trauma transfusion protocol. aPTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalized ratio; PRBC, packed red blood cells.

24 hours. The rate of acute respiratory distress syndrome in the authors' intensive care unit has decreased from the national average of 24% to 9% in severely injured trauma patients requiring intensive care admission [102]. Although the exact causes for this dramatic reduction cannot be specifically pinpointed, it coincides with a documented reduction in the volume of fluids used for resuscitation.

Summary

An ideal fluid for the resuscitation of trauma victims should be safe; efficacious; cheap; easy to store and transport (especially important for the military); have the capacity to carry oxygen and nutrients to the cells; and

protect the cells from resuscitation injury. Unfortunately, such a fluid is not available today. Because of the emerging data on fluid cytotoxicity, clinicians should consider resuscitation fluids as drugs, with well-defined indications and contraindication, safe dosages, and side effects. A logical approach is to prevent the onset of immune dysfunction, rather than try to control multiple interconnected cascades once they have been activated. Patient's response to trauma is influenced by a number of variables (comorbid problems, severity of injuries, degree of shock, delay in definitive care, and so forth). As compared with most of the other variables that cannot be altered, resuscitative strategy is entirely under clinicians' control. They choose the nature of the fluids, rate of administration, timing, and the end points of resuscitation. They also may decide not to resuscitate in selected patients.

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