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NEW TRENDS IN RESUSCITATION

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1. INTRODUCTION

Overall, injuries are the third leading cause of death in the United States, but they affect the younger and most productive segment of our society disproportionately. According to the National Center for Health Statistics, injuries are the number one cause of death and disability under age 44, and more Americans between the ages of 1–34 years are killed by injuries than by all other diseases combined¹. The financial impact of injuries is staggering—50 million injuries that required medical treatment in 2000 will ultimately cost the US society \$406 billion, including \$80.2 billion in medical care costs and \$326 billion in lost productivity².

Analysis of epidemiological data from large trauma centers reveals consistent patterns of death^{3–7}. Up to half of the deaths occur prior to arrival in a hospital as a result of massive blood loss or central nervous system (CNS) damage. Compared to severe CNS damage, death resulting from bleeding is potentially preventable, and life saving efforts focus on early control of bleeding and adequate resuscitation. Unfortunately, conventional resuscitation methods often exacerbate the underlying cellular injury⁸. Of the patients that are transported to the hospital, the majority (70–80%) dies within the first 24–48 hours, with a much smaller percentage (<10%) succumbing to late death as a result of sepsis and organ failure. As hemorrhage-related deaths primarily occur in the first six hours after injury⁵, early delivery of high quality care is of critical importance. Despite hemorrhage being a common problem, the optimal resuscitative strategy remains controversial, with vigorous debates about the type of fluid, volume, rate, route of administration, and end points of resuscitation. This review highlights recent advances in resuscitation strategies as our understanding of the body's response to hemorrhage and resuscitation has evolved.

2. EVOLUTION OF FLUID RESUSCITATION

- a. **THE EARLY EVIDENCE:** Although it is widely believed that early aggressive fluid resuscitation is beneficial, clinical and basic science literature fails to provide supporting evidence^{9–13}. As a matter of fact, the rationale for administering intravenous fluids in patients with ongoing bleeding has been challenged repeatedly for almost a century¹⁴. Historically, the concept of large volume crystalloids resuscitation originated from the seminal work by Shires, Moyer, Moss and others

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during the 1960s^{15–18}, and it became common practice during the Vietnam conflict. Their research suggested that infusion of large-volume isotonic crystalloids improved survival, and resuscitation fluids were needed not only to replace the intra-vascular volume, but also to replenish interstitial deficits. Therefore, these investigators recommended fluid replacement equal to three times the volume of lost blood (and as high as 8:1 for severe shock). At that time emphasis was primarily on restoration of intra-vascular and interstitial fluid deficits, without much importance attached to the cytotoxic effects of the fluids. Isotonic fluids were used widely in Vietnam and it was during this period that the appearance of “shock lung/ Da Nang lung” (later termed acute respiratory distress syndrome or ARDS) was first described in soldiers that received massive crystalloid resuscitation. Today, ARDS and Multiple Organ Dysfunction Syndrome are major causes of delayed mortality in trauma patients. Crystalloid resuscitation was also incorporated into the Advanced Trauma Life Support (ATLS) course, which has been instrumental in standardizing trauma care. For patients in shock, ATLS guidelines recommend infusion of two liters of crystalloids followed by packed red blood cell transfusions. Although this recommendation was only for patients in advanced stages shock (and based upon the logistical limitations of small hospitals without trauma center capabilities), it was enthusiastically adopted and applied widely. It became common for all trauma patients (not just the patients in shock) to be infused with two or more liters of crystalloids during the pre-hospital and early hospital phases of care.

- b. FROM TOO LITTLE TO TOO MUCH:** More than 2 decades ago, Shoemaker et al. reported that shock results in a tissue oxygen debt and proposed aggressive resuscitation to correct this problem in critically ill patients¹⁹. They suggested that this oxygen debt must be repaid by “maximizing or supra-normalizing” cardiac output²⁰ with volume loading, blood transfusion, and inotropic drugs. According to this widely adopted protocol, aggressive resuscitation was continued until tissue oxygen consumption became independent of oxygen delivery. However, numerous subsequent studies have shown that aggressive resuscitation does not improve outcomes^{21–26} and often leads to volume overload complications^{27–29}. Furthermore, this concept was often erroneously extrapolated to bleeding patients, where fluid resuscitation can potentially lead to disruption of early soft thrombus, coagulopathy, and hemodilution^{30–33}.

A systematic review of 52 pre-clinical trials has concluded that, although fluid-resuscitation tends to decrease the risk of death in models of severe hemorrhage (RR = 0.48), it increases the risk in those with less severe hemorrhage (RR = 1.86)³⁴. Furthermore, hypotensive resuscitation (targeting a lower blood pressure), whenever tested, reduced the risk of death (RR=0.37). Similarly, a critical review of the literature failed to find any evidence that pre-hospital advanced life support improves outcomes in trauma patients³⁵. In a study that has generated vigorous debate since its publication in 1994³⁶, hypotensive patients with penetrating torso injury were randomized to routine fluid resuscitation, or resuscitation 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%, $p = 0.04$). Despite all the controversy related to the study design, the most impressive finding remains that withholding fluid resuscitation until hemorrhage control 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 Reviews³⁷. 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. Based upon all this information, it is reasonable to conclude that fluid resuscitation is *not* a substitute for early hemorrhage control. Low-volume resuscitation is reasonable, especially while trying to rush a dying patient to definitive care.

- c. **CELLULAR INJURY AND DELAYED COMPLICATIONS:** In addition to the impact of resuscitation on bleeding, resuscitation fluids have profound cellular effects. It is now widely recognized that resuscitation fluids are not innocuous and may actually potentiate the cellular injury caused by hemorrhagic shock³⁸. This concept of “resuscitation injury” has steadily gained attention since a report by the Institute of Medicine (1999) described in detail the wide spectrum of adverse consequences that can follow resuscitative efforts³⁹. An ever-increasing basic science literature supports the new paradigm that cellular injury is influenced not only by shock, but also by our resuscitation strategies. Today, with the easy availability of advanced research techniques, we can study the effect of resuscitation fluids on the biological systems in much greater detail. Review of the literature suggests that commonly used resuscitation fluids (especially racemic lactated Ringer’s solution) can exaggerate the post trauma immune activation⁴⁰. Therefore, in addition to the immediate side effects (worsening of hemorrhage), delayed complications of fluid resuscitation such as systemic inflammatory response, fluid overload (leading to compartment syndromes, pulmonary edema etc), anemia, thrombocytopenia, electrolyte/acid-base abnormalities, and cardiac and pulmonary complications must also be considered⁴¹. Excessive fluid resuscitation increases the chances of developing abdominal compartment syndrome in critically ill surgical/trauma, burn, and medical patients^{42–44}. Similarly, in a multicenter study of burn patients, administration of excessive fluids (in excess of 25% of predicted) increased the odds of ARDS (OR 1.7), pneumonia (OR 5.7), multiple organ failure (OR 1.6), blood stream infections (OR 2.9), and death (OR 5.3)⁴⁵.
- d. **SPECIAL GROUPS:** The concept of hypotensive resuscitation or delayed resuscitation applies well to young patients, especially following penetrating trauma. However, blunt trauma patients often have traumatic brain injury which may be exacerbated by hypotension. Similarly, elderly patients with coronary or carotid arterial disease may not be able to safely tolerate hypotension. However, even in these patients excessive volume loading can stress the cardiopulmonary reserve (e.g. congestive heart failure, pulmonary edema), worsen pulmonary contusions, and increase the chances of developing other complications such as compartment syndrome.
- e. **CRYSTALLOID USE IN CONTEMPORARY TRAUMA PRACTICE:** It is now clear that resuscitation fluids, like other drugs, have indication for appropriate use, safe therapeutic doses, potential side effects and complications. Despite a paucity of good randomized controlled trials (RCT) in this arena, clinical practices are rapidly changing. In general, large-volume, aggressive fluid resuscitation is becoming increasingly rare, and low-volume, carefully guided resuscitation is more common. In appropriate patients (e.g. in young victims of penetrating trauma) limiting the rate and volume of fluid resuscitation prior to hemorrhage control is rapidly becoming standard practice in large trauma centers. Blunt trauma patients with associated head injury are still resuscitated to a higher blood pressure in an attempt to maintain adequate cerebral perfusion, but early use of blood products and vasopressors is replacing large volume crystalloid infusion. Supported by recommendations from important consensus conferences^{46–49}, and influenced by the unique logistical challenges of the battlefield, US military has dramatically

revised its resuscitation protocols: resuscitation is selective and low volume, uses practical endpoints, and fluids with logistical advantages (e.g. hetastarch) are preferred. The endpoint of early resuscitation is not a normal blood pressure, but simply a palpable radial pulse and normal mental status (in the absence of head injury). Thus, IV fluids are given only selectively, and in much less volumes. Also, early hemorrhage control is prioritized over aggressive fluid resuscitation. It is difficult to determine the direct impact of these new strategies on combat casualty outcomes, but it is very encouraging to note that for the first time since the Crimean War, the killed in action rate has markedly dropped below the historic 20% to around 10%⁵⁰.

Pre-clinical data shows that resuscitation to target mean arterial pressure (MAP) of 40mmHg, as opposed to 80mmHg or higher, results not only in decreased blood loss but also in better splanchnic perfusion and tissue oxygenation⁵¹, less acidemia, hemodilution, thrombocytopenia, and coagulopathy⁵², decreased apoptotic cell death and tissue injury^{52, 53}, and improved survival^{52,53}. In contrast others have shown in large animal models that prolonged duration (8 hours) of hypotension increases metabolic stress, tissue hypoxia, and mortality⁵⁴⁻⁵⁵. The majority of the pre-clinical data favors keeping the MAPs between 40 and 60 mmHg or systolic blood pressure (SBP) between 80 and 90 mmHg. Consequently, the best approach for urban trauma services (short transport times) appears to be “scoop and run”⁵⁶, where unnecessary field interventions and aggressive fluid resuscitation are avoided in favor of fast and efficient transport to the hospital. Once in the hospital, hemorrhage control is prioritized while keeping crystalloid resuscitation to a minimum. This approach, coupled with early use of blood products, is often called “damage control resuscitation”.

3. NEW DEVELOPMENTS

- a. **VASOPRESSORS AND INOTROPES:** The use of inotropic agents and vasopressors for the treatment of non-hemorrhagic shock (i.e. cardiogenic, septic, and neurogenic) is well-established and logically sound (as these drugs address the underlying etiologies). The same rationale applies to patients that survive acute blood loss and develop Systemic Inflammatory Response Syndrome (SIRS) which is physiologically indistinguishable from septic shock. Because the shock is due to an exaggerated inflammatory response (and not due to active bleeding), they can be treated like septic shock patients where early goal-directed resuscitation clearly improves survival⁵⁷. Normally, tissue perfusion remains stable over a fairly wide range of blood pressure. However, septic shock/SIRS disrupt this autoregulation, and tissue perfusion becomes linearly dependent on blood pressure. There is also an inadequate pre-load due to venous dilation and increased capillary leak, and these patients commonly require fluid resuscitation to maintain adequate cardiac output. In addition to fluid resuscitation, these patients often require vasopressors to maintain the mean arterial pressure >65 mmHg to maintain adequate tissue perfusion^{58, 59}. There is no compelling, high quality evidence that shows one agent to be superior to another⁶⁰, and vasopressors should be started after providing adequate initial fluid resuscitation. However, the Surviving Sepsis Campaign recommends “norepinephrine or dopamine as the first choice vasopressor agent to correct hypotension in septic shock (Grade IC)”⁶¹. Norepinephrine has some attractive features as it increases MAP (due to vasoconstriction) with little change in heart rate and some increase in stroke volume. Dopamine is another appropriate choice, which increases MAP and stroke volume. However, it also increases heart rate, which is not desirable. Other choices have some unattractive features. For example, epinephrine can cause tachycardia, decreased splanchnic circulation, and

hyperlactemia. Phenylephrine is a pure vasopressor and is least likely to cause tachycardia, but it decreases stroke volume. Vasopressin has recently gained popularity for treating refractory hypotension in septic shock patients, as there is a relative deficiency of this hormone in septic shock⁶². However, a recent study, the Vasopressin and Septic Shock Trial (VASST), which enrolled 778 patients, failed to show a survival advantage of vasopressin over norepinephrine or a reduction in overall rate of serious adverse events⁶³. In addition, patients with documented or suspected decrease in cardiac function (elevated filling pressures and low cardiac output) should be given dobutamine as the inotropic agent of choice⁶¹. Administration of these agents should be guided by serial measurements of markers of tissue oxygenation, filling pressures, and cardiac output, without making an attempt to achieve supra-normal values⁶¹.

In contrast, use of vasopressors during the early management of hemorrhagic shock is much more controversial. Vasopressors are logistically attractive in austere environments (e.g. battlefield) due to their small volume/weight. Also, a number of pre-clinical studies has shown that drugs such as vasopressin can improve outcomes from irreversible hemorrhagic shock⁶⁴, traumatic brain injury complicated by hemorrhage⁶⁵, and uncontrolled bleeding from solid organ injuries⁶⁶. This has prompted many to consider it as a rescue medication for life-threatening hemorrhage⁶⁷, but a recent multicenter prospective cohort study has shown that early vasopressor use after injury is independently associated with an increase in mortality (hazard ratios for use within 12 and 24 hours were 1.81, $p = 0.013$; and 2.15, $p = 0.001$, respectively), regardless of the type of vasopressor used⁶⁸. Therefore, we recommend that unless proven to be effective by newer studies, vasopressors should be avoided during the acute stages of hemorrhagic shock, and their use limited to patients where shock is due to SIRS.

- b. “DAMAGE CONTROL” RESUSCITATION: An idea that is gaining momentum due to the ongoing war (Iraq and Afghanistan) is the concept of hemostatic/damage control resuscitation⁶⁹. The basic tenants of damage control resuscitation are to: 1) avoid crystalloid resuscitation; 2) aim for permissive hypotension whenever possible; 3) prevent coagulopathy through early use of blood products; 4) aggressively break the vicious cycle of acidosis, coagulopathy, and hypothermia. Clearly, a key component of this damage control approach is early hemorrhage control. Another core concept is that resuscitation fluids should resemble what the trauma patient lose- *warm fresh whole blood*. In civilian setting, fresh whole blood is not available for transfusion, and we must use cold-stored blood components in appropriate ratios to achieve the desired goal. This topic is discussed in more detail later in this paper.
- c. BLOOD AND BLOOD PRODUCTS: Trauma patients are often coagulopathic due to shock and tissue injury, and this coagulopathy can be worsened by resuscitation with crystalloids and packed red blood cells (PRBC), as both are deficient in clotting factors. The best method for early and effective reversal of coagulopathy remains controversial. We know that transfusion of blood components [fresh frozen plasma (FFP), platelets, and packed red blood cells (PRBC)] corrects coagulopathy by restoring normal physiologic milieu⁷⁰, and this continues to be the mainstay of treatment⁷¹. However, debate is still ongoing about the optimal rate of transfusion, as well as the precise volumes and ratios of various products. Observational data from civilian trauma centers and the battlefield seem to suggest that early administration of component therapy containing fresh frozen plasma (FFP) and platelets may be beneficial^{72, 73}. A recent retrospective analysis of mixed trauma patients, requiring surgery and massive transfusion, compared FFP:PRBC ratios of

1:1 and 1:4, and showed that only 26% of patients treated with the former ratio died while 87.5% of patients treated with the latter ratio died ($p < 0.0001$). In this high risk group with an overall mortality of 55.5%, a 1:4 ratio of FFP:PRBC increased the relative risk of dying by 18.9 ($p < 0.001$) when controlling for all other patient variables⁷⁴. Holcomb et al's study of trauma patients at 16 trauma centers who required massive transfusion found that an FFP:PRBC ratio of 1:2 or higher ($n = 252$) compared to lower ratios ($n = 214$) was associated with improved 30-day survival (59.6% with high ratio vs. 40.4% with low ratio, $p < 0.01$)⁷⁵. A similar pattern has been reported with platelet transfusion. Higher ratios of platelets:PRBC were associated with improved survival in retrospective studies⁷⁶. These conclusions have been questioned by others that suggest that the observed survival differences may simply be due to the fact that survivors live long enough to receive component therapy (survivor bias)⁷⁷. Also, FFP transfusion is not without risks, and the risk-benefit profile is especially unfavorable in patients who do not suffer from large volume blood loss. In a recent retrospective study, Inaba et al reported that for non-massively transfused trauma patients a high ratio of FFP:PRBC administration was associated with a substantial increase in complications, in particular ARDS, with no improvement in survival⁷⁸. Also, an increase in multiple organ dysfunction, pneumonia, and sepsis was seen as increasing volumes of FFP were transfused. Compatibility of plasma is also an important variable, as exposure to ABO-compatible (compared to ABO-identical) plasma results in an increase in overall complications, in particular ARDS and sepsis⁷⁹.

Based on the battlefield experience, the US Army has instituted a policy of using a 1:1:1 ratio of PRBC:FFP:platelets in the battlefield for those that are expected to receive >10 units PRBC (massive transfusion). However, no well-designed randomized clinical trial has conclusively identified the optimal ratios of blood components. Our own institutional policy is to start FFP infusion as early as possible in massively bleeding patients, by activating a Massive Transfusion Protocols (MTP) which delivers PRBC:FFP in a ratio of 2:1, and administers 6 units of platelets for every 10 units of PRBC (Appendix). Despite an ongoing debate about the precise ratios, there is a general agreement that the blood products should be administered in the form of a MTP to optimize the processes of care and to improve outcomes. Despite these obvious attractive features, in a recent review Malone et al found only 10 such published protocols worldwide⁸⁰. The utility of MTP has already been verified in some case-controlled studies. Cotton et al tested the effectiveness of a Trauma Exsanguination Protocol (1:2:4 ratio of platelets:FFP:PRBC) by comparing patients treated with the protocol ($n = 94$ over 18 months) to a cohort of similar patients admitted during the prior 18 months ($n = 117$). The study found that implementation of the protocol reduced 30-day mortality (51% vs. 66%, $p < 0.03$), decreased intra-operative crystalloid administration (4.9 liters vs. 6.7 liters, $p = 0.002$), and reduced post-operative blood product use (2.8 units PRBCs vs. 8.7 units, $p < 0.001$; 1.7 units FFP vs. 7.9 units, $p < 0.001$; 0.9 units platelets vs. 5.7 units, $p < 0.001$)⁸¹. Dente et al conducted a similar study of a MTP (1:1:1 ratio of platelets:FFP:PRBC) by comparing matched patients during one year period before and after implementation of protocol (73 protocol and 84 matched controls). Implementation of the protocol was found to reduce mortality in the first 24 hours (17% with MTP vs. 36% pre-MTP, $p = 0.008$) and at 30 days (34% vs. 55%, $p = 0.04$), with a more pronounced impact in the blunt trauma patients⁸². This study also showed that MTP patients required fewer overall transfusions of PRBC and FFP after the first 24 hours (2.7 vs. 9.3 PRBC units, $p < 0.0001$; 3 vs. 7.5 FFP units, $p < 0.05$). While further prospective research is needed to specify the exact ratios, there is convincing evidence that

implementation of standardized protocols for blood component transfusion improves processes of care, reduces overall use of blood components, and improves outcomes.

Although not commonly thought of as a blood product, albumin-based solutions contain protein derived from human blood. The SAFE study⁸³ has shown that albumin and crystalloids are equally safe and effective for septic shock resuscitation, except for patients with traumatic brain injury in which albumin was found to be associated with a significant increase in mortality⁸⁴. In our opinion, albumin based solutions have no role in trauma resuscitation.

- d. **HEMOGLOBIN-BASED SOLUTIONS:** Although advances in viral screening have markedly decreased the risks of infectious transmissions, blood transfusion continues to be associated with numerous serious side effects. In trauma patients, transfusion of red blood cells (especially after prolonged storage) has been shown to disturb the immune system with an early immune activation, resulting in SIRS and a delayed immune suppression which predisposes the patients to infections⁸⁵. As a matter of fact, transfusion of PRBC remains an independent risk factor for increased infections, multiple organ failure, length of hospital stay, and mortality⁸⁶⁻⁸⁹. This has prompted many researchers to focus their attention on testing alternative oxygen-carrying solutions⁹⁰. A detailed discussion about the history and the development of these products is beyond the scope of this article. However, all of these solutions contain some form of polymerized hemoglobin molecule and are thus labeled as hemoglobin-based oxygen carriers (HBOC). A common problem with HBOC relates to the scavenging of nitric oxide by the free hemoglobin molecule, which results in severe vasoconstriction, a pro-inflammatory response, and end-organ injury. Different formulations differ in the mammalian source of the hemoglobin and how it is cross-linked, as well as in the storage and length of shelf-life. Of the HBOC tested thus far only Hemopure or HBOC-201 (13g/dL glutaraldehyde polymerized bovine hemoglobin) has remained in contention for possible human use, while other formulations such as Polyheme (10g/dL glutaraldehyde polymerized human hemoglobin) and HemAssist (10g/dL dapsirin cross-linked human hemoglobin) have fallen out of favor due to negative phase III clinical trials. In Sloan et al's multicenter RCT trauma patients in severe hemorrhagic shock received either 500 ml of saline (n = 53) or HemAssist (n = 58) within 60 minutes of presentation. The study found a higher 28-day mortality in the treatment arm (47% for HemAssist versus 25% for saline, p=0.015)⁹¹. In another multicenter RCT, trauma patients with severe hypovolemic shock were randomized to standard of care (n= 62) or HemAssist (n= 53) without any difference in 5- or 28-day mortality⁹². Similar findings were reported with Polyheme in a subsequent RCT, where trauma patients in severe hemorrhagic shock were given either standard of care (crystalloid and allogenic blood transfusion, n=365) or up to 6 units of Polyheme (n = 349). Even after accounting for numerous protocol violations (17%), there was similar mortality and a higher rate of adverse events in the treatment arm (93% for Polyheme versus 88% for controls, p=0.041)⁹³. A 2008 meta-analysis of 16 HBOC trials, including four trials of trauma patients receiving HemAssist or Polyheme, raised alarm as patients receiving HBOC were noted to have a significant risk of myocardial infarction (RR, 2.71; 95% CI, 1.67–4.40), and mortality (RR, 1.30; 95% CI, 1.05–1.61)⁹⁴. This meta-analysis also included a single study data from a 2005 presentation to the U.S. Food and Drug Administration (FDA) on HBOC-201 use in surgical patients. HBOC-201 (Hemopure) has also been tested in a South African trauma patient population but the final results of this trial remain unpublished⁹⁵. HBOC 201 has been extensively tested with good results in animal models and is approved for veterinary use. It has

also been tested in a large phase III clinical trial (n-688) in elective orthopedic surgical patients, where the use of HBOC-201 resulted in a lower need for PRBC transfusion but a significant increase in serious adverse events⁹⁶. A phase II multicenter trial in trauma patients entitled Restore Effective Survival in Shock (RESUS) was first submitted to the FDA for approval in 2005. However, after an initial positive response the FDA has repeatedly refused to allow the clinical trial to proceed due to concerns about patient safety despite multiple revisions in the study protocol. Thus, based upon these current data, the use of any HBOC can not be endorsed at this time outside of well-designed, thoroughly vetted clinical trials.

- e. **CLOTTING FACTORS:** While FFP infusion delivers the full spectrum of clotting factors, it is also possible now to administer individual recombinant clotting factors for the treatment of coagulopathy. The one that has generated a lot of attention recently is factor VII. In 1999, the FDA approved the use of recombinant human coagulation factor VIIa (rFVIIa) for the treatment of bleeding in hemophiliacs and in patients with inhibitors to factor VIII or factor IX. Recombinant FVIIa promotes clotting by activating factors IX and X in the presence of tissue factor. Once activated, factor X along with factor V, calcium, and phospholipids, converts prothrombin to thrombin, which in turn converts fibrinogen to fibrin. rFVIIa also promotes thrombin generation on the surface of activated platelets. The end result of this process is formation of a fibrin-platelet plug at the site of vascular damage/injury. Trauma patients are inherently different from hemophiliacs due to a global deficiency of all clotting factors along with hemoglobin and platelets. Although never approved for use in trauma patients, rVIIa was used off-label in this patient population resulting in a number of very promising early case reports. However, it failed to improve outcomes when tested in a RCT of trauma patients⁹⁷. A follow up phase III randomized trial was stopped ahead of schedule (573 out of 1502 patients enrolled) for futility⁹⁸. A meta-analysis of the published literature yielded the same conclusions⁹⁹. Although costly, this drug has logistical appeal for the military and was therefore, used by the US troops fairly aggressively. Despite anecdotal success stories, when 506 patients treated with rVIIa were critically analyzed and compared to matched controls (n=266 per group), the drug was not found to be associated with an improvement in survival or a decrease in need for massive transfusion¹⁰⁰. One application that still held promise regarded the treatment of traumatic brain injury, as the use of rVIIa had been shown to decrease the expansion of intracerebral hemorrhage in stroke patients¹⁰¹. However, the effect was modest (3.8 ml decrease in volume of hemorrhage) and not associated with an improvement in survival or functional outcomes. Traumatic hemorrhage is very different from stroke, and it was unclear whether the drug was actually effective (despite being used by many) for traumatic intra-cranial bleeding. There was also mounting concern about the risks of thrombotic complications following the unlabelled use of rVIIa¹⁰². When tested for traumatic intracranial hemorrhage, the first prospective study showed no clear benefit¹⁰³. A subsequent Cochrane Systematic Review also found no reliable evidence supporting the use of rFVIIa to reduce mortality or disability in patients with TBI¹⁰⁴. It should also be pointed out that in the early case series, the use of rFVIIa was often reported in situations where “damage control” resuscitation is now recommended. We believe that early and aggressive blood component therapy delivers the clotting factors, fibrinogen, platelets, and red cells that are required for generation of a clot, making it unnecessary to use individual recombinant factors. We have, therefore, abandoned the use of rFVIIa except in highly selected trauma patients.

One situation where there is still need for a low-volume, rapid, and effective treatment for coagulopathy is in elderly trauma patients on warfarin, especially after TBI. Rapid infusion

of required plasma volume (15–20 ml/kg) is often not possible due to multiple comorbid problems (e.g. congestive heart failure, pulmonary edema, renal failure) in these patients. Prothrombin complex concentrates (PCC) provide a rapid and effective method for delivering vitamin K dependent clotting factors to correct the coagulopathy. A variety of PCC products has been around for nearly 30 years, and they all contain factors II, IX, and X with variable amounts of VII and anti-coagulant proteins C and S¹⁰⁵. Early studies have shown PCC to be effective in rapidly reversing anticoagulation (n=50), to allow surgical procedures or control post-operative bleeding without complications¹⁰⁶. RCTs are ongoing in patients that require correction of coagulopathy for surgery or for TBI, where PCC are being compared to standard treatment (FFP of vitamin K). Currently, no data exists to support their use in massively bleeding poly-trauma patients without a history of warfarin use.

4. FUTURE DIRECTIONS

- a. **FLUIDLESS RESUSCITATION:** Resuscitation fluids simply replace the lost intravascular volume, but have no inherent pro-survival properties. It seems logical that we should design therapies promoting a pro-survival phenotype. Among patients resuscitated from hemorrhagic shock, a wide spectrum of responses is observed. While some patients recover without any complications, other develop multiple organ failure. This is true even for patients who are identical in terms of gender, age, risk factors, and injury severity. This unpredictable response is not caused by a widespread variation in the human genome. Since the decoding of the human genome, it has become obvious that only 20,000–35,000 protein-coding genes are responsible for millions of different phenotypes. The DNA sequence of base pairs is fixed for life and identical in every cell type of the entire body. Thus, the markedly different phenotypes expressed by different people, as well as various tissues/cells within the same person (with identical DNA), support the presence of very precise systems that regulate gene transcription. The rapidly expanding field of “epigenetics” focuses on mechanisms and phenomena that affect the phenotype of a cell or an organism without affecting the genotype^{107, 108}.

Over the years, a number of pharmacologic agents have been tested as possible adjuncts (or substitutes) to conventional fluid resuscitation. These drugs cover a wide spectrum including neuroendocrine agents, calcium-channel blockers, ATP-pathway modifiers, prostaglandins, sex steroids, anti-oxidants, anti-inflammatory agents, and immune-modulators. Although there is strong laboratory evidence of their beneficial effects on tissue perfusion, myocardial contractility, reticulo-endothelial function, cell survival, oxidative injury, and immune activation, the majority of these agents are not yet in clinical use as resuscitative agents. A thorough discussion of the research in this area is beyond the scope of this article. However, a number of agents aimed at correcting the circulatory and immunologic derangements of hemorrhage are worth mentioning as promising pharmacologic adjuncts to resuscitation. Dr. Chaudry’s group has extensively studied the role of sex steroids in cytokine responses and neutrophil adhesion after hemorrhage; they have proposed estrogen and its analogs as possible beneficial treatments¹⁰⁹. Dr. Coimbra’s group has studied the phosphodiesterase inhibitor, pentoxifylline, already widely used for vascular disease due to its rheologic properties, as a treatment for hemorrhage because it reduces neutrophil activation and adhesion¹¹⁰. Opiate antagonist Naloxone has been studied based on the finding that central Mu, Epsilon, Kappa, and Delta receptors are activated during hemorrhagic shock and inhibit Ca⁺⁺ channels. However, a Cochrane review recently analyzed data on this topic and concluded that further clinical trials are needed to determine if the

beneficial effects on blood pressure by administration of Naloxone result in any durable improvements in survival¹¹¹. A common thread across all of these potential agents is that they are already in wide clinical use for other disorders. Thus, there is great hope that with more clinical evidence, these agents, whose safety profile has already been tested for various non-trauma indications, can be rapidly implemented as adjuncts to fluid resuscitation. Our group has been studying another group of drugs, also in widespread clinical use for non-trauma indications, in animal models of shock. Following hemorrhage, the stress of shock and resuscitation causes an immediate modulation of genes and proteins involved in a variety of cellular defense pathways through an alteration in their acetylation status^{112, 113}. We hypothesized that histone deacetylase (HDAC) inhibitors such as valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA) may be useful in the treatment of shock through restoration of normal cellular acetylation. We subsequently have shown that HDAC inhibitors rapidly reverse shock induced alterations, restore normal histone acetylation, and improve survival in different models of otherwise fatal hemorrhagic shock and poly-trauma^{114–116}. Impressively, this survival improvement was achieved without conventional fluid resuscitation or blood transfusion, which makes this approach very appealing for the logistically constrained pre-hospital and battlefield environments. It appears that HDAC inhibitors rapidly activate nuclear histones as well as numerous cellular proteins to create a “pro-survival” phenotype in hemorrhagic and septic shock^{117–121}. Unpublished data also demonstrate that this approach is very promising for the treatment of traumatic brain injury. A number of these HDAC inhibitors are currently being tested in phase I and II clinical trials (non-traumatic situations). We believe that additional research in this arena could ultimately lead to a potent pharmacologic adjunct to the treatment of hemorrhagic shock that works by promoting cell survival during periods of lethal stress¹²².

- b. PROTECTIVE HYPOTHERMIA (EMERGENCY PRESERVATION AND DELAYED RESUSCITATION):** Even when the source of massive blood loss can be controlled and circulation restored, cerebral ischemia lasting 5 minutes or longer invariably results in severe brain damage. Often the underlying injuries are reparable but the patient dies of irreversible shock or severe brain damage. In this setting, strategies to maintain cerebral and cardiac viability long enough to gain control of hemorrhage and restore intra-vascular volume could be life saving. This requires an entirely new approach to the problem, with emphasis on rapid total body preservation, repair of injuries during metabolic arrest, and controlled resuscitation: *Emergency Preservation and Resuscitation* (EPR). Currently, hypothermia is the most effective method for preserving cellular viability during prolonged periods of ischemia. Although, no clinical studies have been conducted to test the therapeutic benefits of hypothermia in trauma patients, numerous well-designed pre-clinical studies clearly support this concept. It should be emphasized upfront that *induced hypothermia* and *hypothermia secondary to shock* are very different entities (table 1). Induced hypothermia is therapeutic in nature whereas hypothermia, seen in severely traumatized patients, is a sign of tissue ischemia and failure of homeostatic mechanisms to maintain normal body temperature. It is clear from the literature that rapid induction of deep/ profound hypothermia (<15°C) can improve otherwise dismal outcome after exsanguinating cardiac arrest^{123–125}. Depending on the degree of hypothermia, good outcomes have been achieved with cardiac arrests of 15, 20, 30 and even 90 minutes in canine models^{126, 127}. Furthermore, the period of hypothermia can be safely extended to 180 minutes if blood is replaced with organ preservation fluids and low flow cardiopulmonary bypass is continued (as opposed to no flow) during the arrest period¹²⁸. Although

ground breaking, these original studies were limited by the reliance on pressure-controlled models of hemorrhagic shock (or no hemorrhage), an absence of major injuries, and lack of surgical interventions. To fill these gaps, our team has utilized clinically realistic large animal models of lethal vascular injuries and soft tissue trauma to demonstrate that profound hypothermia can be induced through an emergency thoracotomy approach for total body protection, with excellent long-term survival and no neurological damage or significant organ dysfunction¹²⁹. In a follow up study, it was established that lethal vascular injuries, above and below the diaphragm, can be repaired under hypothermic arrest with >75% long term survival¹³⁰. More importantly, it was shown that hypothermia could be used successfully even after 60 minutes of normothermic shock (transport time), and that the surviving animals were neurologically intact and had normal cognitive functions. Subsequent studies have determined that to achieve the best results, profound hypothermia must be induced rapidly (2°C/minutes) and reversed at a slower rate (0.5°C/minutes)^{131, 132}. Induction of hypothermia has been shown to preserve various cell types in the central nervous system, while providing some immunological advantages and modulating cell survival pathways^{133–135}. The optimal depth of hypothermia is 10°C, and decreasing the temperature to ultra-profound levels (5°C) may actually worsen the outcome¹³⁶. If done appropriately, the safe duration of total body preservation in poly-trauma is about 60 minutes¹³⁷, and it does not increase post-operative bleeding or septic complications¹³⁸. Technically, it is now feasible to induce hypothermia using small, battery-operated, portable equipment (suitable for austere settings and pre-hospital environment)¹³⁹. This is associated with excellent “total body preservation” which may have significant implications not only for treatment of traumatic injuries but also for preserving organs for transplant¹⁴⁰. Induction of hypothermia not only modulates metabolism but also influences a wide variety of cellular and sub-cellular mechanisms¹⁴¹, including alteration in transcription of numerous beneficial genes¹⁴², the downstream effects of which persists long after the period of hypothermia. There is also some data from small animal models to suggest that similar metabolic arrest (and tissue preservation) can be achieved with other methods, such as inhaled hydrogen sulfide¹⁴³. It may sound futuristic, but the expertise to preserve the viability of key organs during repair of otherwise lethal injuries is now available¹⁴⁴, and a prospective multi-institutional clinical trial is scheduled to start later this year¹⁴⁵.

- c. **PRESERVED BLOOD PRODUCTS:** When component therapy is not available, military hospitals often resort to using fresh whole blood (FWB) for this purpose. According to a report, thirteen percent of all transfused patients in the Operation Iraqi Freedom (OIF) received FWB¹⁴⁶. The use of FWB, PRBC, FFP and platelets for the treatment of trauma-associated coagulopathy has some logistic limitations, especially in austere environments such as a battlefield. These include: need for refrigerated storage and transportation, limited shelf life, type and screen, dependence on available donors, and long thaw times¹⁴⁷. As most of the trauma deaths take place before reaching a medical facility, there is a clear need for the development of innovative and effective strategies for the early (pre-hospital) treatment of coagulopathy. One solution is to convert blood components into shelf-stable, lyophilized freeze dried products. Such product would have a number of potential advantages including storage at ambient temperature, longer shelf life, quicker preparation time, ABO universality, and reliable viral inactivation methods. Freeze drying technology has been used to preserve different components of the blood with variable success. As plasma is acellular (contains proteins but no cells), it is much more suitable for freeze drying and subsequent rehydration. Although

protein function is impaired to some degree by this process, this is much less pronounced compared to the impact on inherently more complex functions of the cells such as RBC and platelets.

1. **Freeze-Dried Plasma (FDP):** Currently, plasma for clinical use is stored in a frozen form (FFP) at -18°C for a maximum of one year. It requires refrigerated transportation, 30 minutes to thaw, and used ideally within 6 hours of thawing. These features make it impractical for pre-hospital use. Lyophilized plasma was developed to overcome some of these logistical limitations, and it has been used for bleeding control since World War II with the first clinical reports appearing in the literature in the 1950's. Oktavec *et al* assessed the reliability and longevity of lyophilized plasma, which was used as a control for clotting studies, and showed a high degree of correlation to fresh plasma from healthy volunteers¹⁴⁸. It has also been used to treat bleeding episodes in hemophiliac patients^{149, 150}. Lyophilization (freeze drying) clearly improves the stability of proteins, and after a year of storage at -25°C , lyophilized plasma has been shown to have the same clotting factor stability as its fresh counterpart¹⁵¹. Plasma proteins are heat labile, hence the need to store FFP at such low temperatures (-18°C). Lyophilization also makes the proteins more heat-stable. In a very important study, Ramsey *et al* studied the effects of heat treatment, as part of viral inactivation methods, on lyophilized plasma¹⁵². Samples of lyophilized plasma were heated in a water bath at 60°C for 1, 4, 8, 24, and 72 hours before reconstitution. Heating fresh plasma or lyophilized plasma after reconstitution significantly prolonged prothrombin time (PT) in these samples. However, non-reconstituted lyophilized plasma showed no change in PT after as long as 24 hours of heating, with only a mild increase after 48 and 72 hours. Factor V activity decreased after heating (60% after 8 hours and 48% after 24 hours), but the activities of Factor VII, VIII and IX exhibited minimum deviations from their unheated levels. The preservation process is remarkably effective and storage of lyophilized plasma for as long as 30 years fails to alter its components, including hormones, enzymes and other proteins¹⁵³.

Despite these attractive features, use of freeze-dried lyophilized plasma fell out of favor during the 1960's and 1970's due to concerns about the inability of the lyophilization process to inactivate viruses present in pooled plasma¹⁵⁴. Viral inactivation methods have evolved since then and the risk of Human Immunodeficiency Virus (HIV) or Hepatitis C Virus (HCV) transmission in blood component therapy has dropped to one in two million units¹⁵⁵. The modified solvent/detergent treatment for human plasma inactivates $>10^6$ chimpanzee-infectious doses (CID_{50}) of Hepatitis B Virus (HBV) and $>10^5$ CID_{50} of HCV¹⁵⁶. The same techniques are now used for viral inactivation during the production of the FDP. Two recent pre-clinical trials have shown that FDP is extremely effective in reversing coagulopathy in clinically relevant poly-trauma models^{157, 158}.

Preservation techniques that are even better than freeze-drying are now available. There is some evidence that freeze-drying adversely affects protein viability¹⁵⁹, and that drying of proteins using the process of distillation (spray drying with controlled heat) results in an even better product. Furthermore, the spray-drying process yield fine powder (compared to a lyophilization protein "cake") that is much easier to reconstitute. It can be quickly dissolved in a small volume of water to produce a hyperoncotic, hyperosmotic plasma¹⁶⁰, which is logistically a

very attractive option for austere environments, such as the battlefield. Currently, none of these products have been approved by the FDA for use in the US, but a similar product developed by the German Red Cross has been used clinically in Europe¹⁶¹. Aggressive efforts, mostly funded by the US Department of Defense, are currently underway to refine and produce a preserved plasma product for clinical use in the near future.

2. Platelets: Clinically, the most widely used preparation today is a pooled platelet concentrate stored as a liquid at 22°C. In most countries, such liquid-stored platelets have a mandated shelf life of only 5 days, due to increased risk of septic complications, which increase in frequency with increasing length of storage at this temperature. Numerous platelet products have been developed to improve this storage limitation including frozen platelets, cold storage (4°C) platelets, lyophilized intact platelets, as well as platelet derived particles¹⁶². Frozen platelets are cryopreserved in 6% dimethylsulfoxide and can be stored for up to 10 years at -80°C, representing the gold standard for the long term preservation of platelets. However, requirement for sophisticated refrigeration makes them impractical for pre-hospital use. Lyophilized, or freeze-dried human platelets have been under development for nearly 50 years¹⁶³, but initial efforts yielded products that were functionally impaired and lacked any meaningful hemostatic properties. Results with the more recent human platelet preparations (treated with 1.8% paraformaldehyde, frozen in 5% albumin, and then lyophilized) have been more encouraging¹⁶⁴. Once rehydrated, these platelets appeared structurally similar to fresh platelets, contained most of the glycoproteins (at decreased concentration), and were capable of supporting thrombin generation and fibrin deposition¹⁶⁵. However, in-vivo testing shows that the duration of hemostatic activity is rather brief (~4–6h)¹⁶⁶, and sometimes limited to only 15 minutes¹⁶⁷. Despite short life span in circulation, infusion of these lyophilized platelets has been shown to correct coagulopathy and improve bleeding times in large animal models of cardiopulmonary bypass¹⁶⁸, and dilutional thrombocytopenia¹⁶⁹. Recent studies of human lyophilized platelets in a swine liver injury model have demonstrated improved survival and reduced blood loss, but 13% of the surviving animals were found to have thrombotic complications¹⁷⁰. One of the key challenges remains the development of a product that has robust hemostatic properties without any thrombotic complications¹⁷¹.
3. Red Blood Cells: Goodrich was awarded a patent for lyophilization of red blood cells in 1989¹⁷², but the development of this product for clinical use faces numerous challenges due to the complex functions that are carried out by the normal RBC. The process of freeze-drying and rehydration is stressful for the RBC, resulting in either cell death or severe functional impairment. Although lyophilized red blood cells have acceptable visco-elastic deformability properties¹⁷³, and storage times can be increased to around 1 week by adding a sugar molecule (trehalose)^{174, 175}, this product is still in the very early stages of development¹⁷⁶.

5. SUMMARY

Hemorrhage is the leading cause of potentially preventable deaths in the battlefield and in civilian trauma. Prompt control of hemorrhage and adequate resuscitation are considered critical in the management of these patients. With a better understanding of shock, it is not

surprising that our treatment strategies have also evolved¹⁷⁷. This transformation has been especially dramatic over the last decade- large volume crystalloids resuscitation is out, whereas low-volume resuscitation has become the new norm. Drugs that can augment tissue perfusion or selectively create a “pro-survival phenotypes” are being aggressively investigated. Custom designed protocols are preferred over generic resuscitation efforts, and permissive hypotension is the new buzz word.

Emerging data, basic science and clinical, have challenged the dogma of large volume crystalloid resuscitation, and our clinical paradigms are in a state of flux (table 2). Resuscitation strategies being utilized by the US military in Iraq and Afghanistan have already changed: resuscitation is selective, low volume, aims for practical endpoints (e.g. pulse and mental status), and fluids with logistical advantages (e.g. hetastarch) are preferred. Also, early hemorrhage control is prioritized over aggressive fluid resuscitation. Although civilian trauma centers don’t face the same logistical limitations as the military hospitals, they have also adopted a similar approach. It is difficult to determine the direct impact of these new strategies on outcomes, but it is very interesting to note that post-resuscitation complications such as ARDS are becoming increasingly rare in this new era of judicious resuscitation (4 fold decrease over 5 years)¹⁷⁸.

The concept of “damage control resuscitation” with early use of blood components in appropriate patients has been widely adopted over the last few years. Trauma surgeons are avoiding crystalloids and using blood products early during the resuscitation of severely injured patients, not only to avoid the complications of crystalloids but also to maintain better oxygen delivery and normal coagulation status. We still don’t know the optimal ratio of component therapy, but ongoing studies should provide the answer in the near future. Along the same lines, efforts to preserve blood products for pre-hospital use are being heavily funded, and shelf-stable plasma is now ready for clinical trial. Finally, novel resuscitation techniques, such as therapeutic hypothermia and cyto-protective drugs, may soon become part of our armamentarium. These are exciting times, with battlefield challenges along with robust funding by the Department of Defense fueling rapid advances. It can be argued that the only winner in any war is the field of trauma care itself, and the current conflict is no exception¹⁷⁹. We may not have all the right answers yet, but the ongoing research has the potential to revolutionize the care of the critically injured patients.

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Appendix: MASSACHUSETTS GENERAL HOSPITAL – TRAUMA SERVICE

MASSIVE TRANSFUSION POLICY/PROTOCOL

Policy

To provide a mechanism to facilitate replacement of massive blood loss with appropriate blood and blood products within a clinically significant timeframe.

Protocol

Application of the Massive Transfusion Protocol requires a multidiscipline/multiservice practice based on clinical judgment and decision-making, clear communication patterns and strong cooperative efforts.

1. The decision to utilize the Protocol will be determined by one of the following appropriate trauma team members:
 - a. Trauma/CC anesthesiologist
 - b. Trauma staff attending
 - c. EM staff attending
 - d. Senior Trauma Resident
 - e. EM 4 resident
 - f. PGY 3 ED surgical resident

The protocol can be initiated at any time during the trauma patient's hospitalization, including prior to arrival to the MGH ED.

2. Appropriate candidates for this Protocol include:

- a. any patient with an initial blood loss of at least 40% of blood volume, or in whom it is judged that at least 10 units of blood replacement is immediately required;
 - b. any patient with a continuing hemorrhage of at least 250cc/hour;
 - c. any patient, when clinical judgment is made such that blood loss as identified in “A” and “B” is imminent.
3. if the protocol is initiated prior to the patient’s arrival at the MGH, an ‘Trauma Pack’ should be utilized.
4. Once the decision is made to initiate the Massive Transfusion Policy, the appropriate physician needs to:
 - a. Notify the Blood Bank (red phone in ED) communicating the age and gender of the incoming patient, and the initiation of the protocol
 - b. Sign the ‘Emergency Release Form’
 - c. Ensure that a properly labeled, dated and signed blood bank sample is obtained and sent by a runner to the Blood Bank
5. Once the protocol has been initiated, the Blood Bank technologist will:
 - a. Alert personnel in the dispensing area to anticipate an “Emergency Release Form” initially and a blood specimen, when it is available from the patient; so that they may begin the selection of appropriate units
 - b. Notify the Blood Bank Fellow if a problem is encountered in providing the appropriate components or if deviation from the protocol is required.
6. The clinical team and the Blood Bank team maintain joint responsibility for the success of the Massive Transfusion Protocol.

The Blood Bank Fellow is available to both the Blood Bank proper and the clinical team to assist in decision-making and recommendations. Transfusion recommendations include:

7. RBC Selection :
 - a. At least 4 units of Emergency –release, uncrossmatched Group O Negative RBC’s will be released for all Rh negative or Rh unknown patients.
 - b. All patients will receive Rh negative cells as long as inventory is adequate. An effort will be made to provide Rh negative cells to females under 50 as long as inventory is adequate. The laboratory will decide to switch the patient to Rh-positive RBCs based on the available inventory and the anticipated RBC requirement.
 - c. Group O RBCs will be used until the patient’s blood group is known after which the patient will be switched to group-specific RBCs.
8. Blood Component Requests:

After the initial assessment, the clinical team should request more blood as follows:

- if hemorrhage appears controllable and if < 10 TOTAL units are anticipated, the clinical team should order RBCs (in addition to the emergency-release 4 units); and send a properly labeled “Pick-up slip” for these units.

- if > 10 TOTAL units are expected to be needed, the clinical team should request (in addition to the initial 4 emergency RBCs):

1. 10 RBCs
2. 10 FFP
3. 1 dose of platelets

d. Upon receipt of a properly labeled “Pick Up Slip” indicating the location (ED, OR, ICU, etc) the request will be filled and units issued ASAP. The blood bank will fill partial orders so as not to delay the entire order. For example, 6 RBCs and 4 FFP and 1 dose of platelets may be issued immediately and then followed by 4 RBCs and 6 FFP.

9. Movement of the patient from the ED to the OR or to Radiology:

It is ESSENTIAL that the clinical team communicate to the blood bank when the patient is being moved from the ED to the OR or to Radiology so that additional blood units, as available, will be directed to the proper location. Failure to communicate the movement of the patient will lead to delays in administration of blood components. The blood bank staff is instructed NOT to issue blood to two locations for one patient simultaneously.

10. Laboratory monitoring and Targets for on-going blood support in cases requiring > 10 units of RBCs:

- a. Transfusion support should be individualized for each patient.
- b. The following “general guidelines” apply:
 1. Check H/H, Platelet count, INR, and Fibrinogen after each blood volume lost/infused.
 2. Include the number of “cell saver” units in the tally of packed RBCs.
 3. Target a ratio of 2 RBCs to 1 FFP during the course of acute bleeding.
 4. Anticipate fibrinolysis and treat with anti-fibrinolytics if there is ongoing diffuse bleeding.
 5. Verify that the INR is < 2 and fibrinogen >100. Values outside these ranges may indicate systemic fibrinolysis, DIC, or failure to avoid hemodilution.
 6. In the absence of platelet infusion, anticipate a halving of the platelet count with each blood volume resuscitation. Transfuse platelets to maintain an anticipated platelet count >50,000/uL.
 7. A stat AST or ALT can be used to document shock liver (values > 800) which is an independent indication for anti-fibrinolytic therapy.
- c. Monitor and treat abnormalities of ionized Ca⁺⁺, K⁺, pH and temperature.

11. Not all massive injured patients can be saved.

The decision to withdraw support for the massively injured patient should be made by consensus of the treating team and with approval of the trauma attending

responsible for the case. Considerations include likelihood of survival, nature of injuries, and impact of blood requirements on other patients in the hospital in need of blood support. Consultations with the senior blood bank physician on duty is welcome.

Table 1

Physiologic differences between spontaneous and therapeutic hypothermia

	Hemorrhagic Shock	Hemorrhagic Shock Complicated by Spontaneous Hypothermia	Emergency Preservation Resuscitation (EPR) in Hemorrhagic Shock
Cardiac	Hypotension, tachycardia, hypovolemic shock	Cardiac depression, Bradycardia, Arrhythmias with worsening hypothermia – J waves	Induced cardiac arrest, and maintenance of low flow state with CPB
Respiratory	Variable response	Central respiratory depression	Patient intubated and maintained on mechanical ventilation
Metabolic	Increase oxygen requirements. Switch from aerobic to anaerobic metabolism	Energy (ATP) depletion Supply/ demand mismatch	ATP reserved with reduced metabolism. Minimal to no oxygen/ substrates requirements
Coagulopathy	Trauma-induced consumptive coagulopathy. Reperfusion dilutional coagulopathy	Decrease platelets and coagulation factors activity	Irrelevant. Cellular viability is independent of blood supply. Ongoing blood loss can be recycled through the CPB
Mental Status	Variable, but often depressed	Progressive depression in mental status and eventually coma with flat EEG	Patient deliberately sedated and paralyzed
Immune system	Initiation of inflammatory response with multiple organ damage	Blunted cytokine production and neutrophil migration with increased risk of infections	Antibiotics coverage and sepsis precaution during induced hypothermia
Shivering	Not observed early in hemorrhage	Increased attempt to produce heat increases energy demand and over-utilizes ATP	Neuro-muscular blockade or deep sedation to control shivering
Hyperglycemia	Variable response	Decreased insulin production and increased tissue resistance leads to hyperglycemia	Controlled and reversible

ATP= Adenosine Tri-Phosphate. EEG= Electroencephalogram. CPB= cardiopulmonary bypass

Table 2

Historical trends in resuscitation strategies

Era	Resuscitation approaches and other related issues	Outcomes
WWI	None	Early death
WWII/Korean war	Albumin, plasma and blood use	Better early survival but organ failure resulting in late deaths (especially acute renal failure)
Vietnam War	Crystalloids and banked blood use. Improved rapid evacuation methods	Better early survival. Organ failure resulting in late deaths still a problem, with less acute renal failure and more ARDS
1970s-early 1980s	Goal directed aggressive resuscitation, use of pulmonary artery catheters and oxygen delivery calculations to deliver "supra-normal" resuscitation	Further improvement in early survival, increased MOF and late deaths
Mid 1980s- 1990s	Rapid field triage, maturation of civilian trauma systems, introduction of "damage control surgery", improved ICU care	Improved early survival in severely injured. More MOF but better survival in MOF patients due to improved ICU care
Afghanistan and Iraq Wars	Dramatic improvement in triage and long distance transfers. Excellent in-transit ICU care. "Damage Control Resuscitation", permissive hypotension, limited use of crystalloids, early use of blood products, higher ratio of FFP and platelets, and fresh whole blood use. In field use of recombinant factor VII. Development and use of advanced hemostatic dressings. Significant improvements in injury prevention with better body armor, and protective gear. Adoption of battlefield strategies by civilian trauma centers	Lowest KIA rate in any major conflict. Decreased incidence of ARDS, MOF, and coagulopathy. Significant improvement in early and late survival and long term outcomes compared to historical controls.

ARDS= Acute Respiratory Distress Syndrome. MOF= Multiple Organ Failure. ICU= Intensive Care Unit. FFP= Fresh Frozen Plasma. KIA = Killed in Action