Published in final edited form as:
Int J Surg. 2011 ; 9(1): 5–12. doi:10.1016/j.ijsu.2010.09.001.

ADVANCES IN RESUSCITATION STRATEGIES

Hasan B. Alam, MD, FACS
Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA

Abstract

Shock, regardless of etiology is characterized by decreased delivery of oxygen and nutrients to the tissues and our interventions are directed towards reversing the cellular ischemia and preventing its consequences. The treatment strategies that are most effective in achieving this goal obviously depend upon the different types of shock (hemorrhagic, septic, neurogenic and cardiogenic). This brief review focuses on the two leading etiologies of shock in the surgical patients: bleeding and sepsis, and addresses a number of new developments that have profoundly altered the treatment paradigms. The emphasis here is on new research that has dramatically altered our treatment strategies rather than the basic pathophysiology of shock.

2. Hemorrhagic shock

Exsanguination is one of the leading causes of death following trauma[1, 2] and prompt hemorrhage control along with adequate fluid resuscitation are the key components of early trauma care. Similarly, hemorrhage is often encountered in non-trauma patients as a complication following major surgeries. Despite hemorrhage being a common problem, the optimal resuscitative strategy remains controversial, with vigorous ongoing debates about issues such as the type of fluid, volume, rate, route of administration, and end points of resuscitation.

a. Futility of current methods/adverse effects of aggressive resuscitation

Although it is widely believed that early aggressive fluid resuscitation is beneficial, clinical and basic science literature fails to provide conclusive supporting evidence [3, 4, 5, 6, 7]. As a matter of fact, the basic rationale for administering intravenous fluids in patients with ongoing bleeding has been challenged repeatedly for almost a century[8]. Theoretically, fluid resuscitation in the absence of (or prior to) hemorrhage control can exacerbate bleeding due to the disruption of early soft thrombus, coagulopathy, and hemodilution[9, 10, 11, 12]. A systematic review of 52 animal trials concluded that fluid resuscitation appeared to decrease the risk of death in models of severe hemorrhage (RR=0.48), but increased the risk of death in those with less severe hemorrhage (RR=1.86)[13]. 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 improved outcomes in trauma patients[14]. In a study that has generated vigorous debate since its publication in 1994[15], hypotensive patients with penetrating torso injury were randomized to routine fluid resuscitation, or resuscitation was delayed until

Contact information: Hasan B. Alam, MD, Director of Research, Division of Trauma, Emergency Medicine and Surgical Critical Care, 165 Cambridge Street, Suite 810, Boston, MA 02114, Ph : 617-643-2433, hbalam@partners.org.

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, the most impressive finding remains that withholding fluid resuscitation until hemorrhage control did not increase the mortality. The issue of timing and volume of fluid resuscitation in bleeding patients has also been addressed by The Cochrane Database of Systematic Reviews[16]. 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, careful resuscitation is reasonable, especially when trying to get a dying patient to definitive care. However, early aggressive fluid resuscitation, in the absence to hemorrhage control, can't be justified.

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 completely innocuous, and they may actually potentate the cellular injury caused by hemorrhagic shock[17]. 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 efforts[18]. Historically, the concept of large volume crystalloids resuscitation was a product of seminal work by Shires, Moyer, Moss and others during the 1960s[19, 20, 21, 22], and it became common practice during the Vietnam conflict. Their work suggested that infusion of large-volume isotonic crystalloids improved survival, and resuscitation fluids were needed not only to replace the intra-vascular volume loss, but also to replenish interstitial deficits. Therefore, these investigators recommended fluid replacement equal to three times the volume of blood loss (and as high as 8:1 for severe shock). At that time the emphasis was on restoration of intra-vascular and interstitial fluid deficits, without much importance attached to the cytotoxic effects of crystalloid 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. 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 cellular 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 activation[23]. 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 kept in mind[24]. Excessive fluid resuscitation increases the chances of developing abdominal compartment syndrome in critically ill surgical/trauma, burn, and medical patients[25, 26, 27]. 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)[28].

b. New developments

It is now being appreciated 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. A few of these issues are discussed in more detail below:

i. Controlled hypotensive resuscitation—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 routine 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. Prompted by the recommendations of some consensus conferences[29, 30, 31, 32], and due to the unique logistical challenges of the battlefield, the resuscitation strategies being utilized by the US military have changed dramatically: resuscitation is selective, emphasizing low volume and practical endpoints, and the use of fluids with logistical advantages (e.g. hetastarch) is preferred. The endpoint of resuscitation is not a normal BP, 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 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 10–14%[33]. Hypotensive resuscitation can be performed by infusing fluids to achieve a desired goal (e.g. target blood pressure), or at a predetermined fixed rate. Pre-clinical data shows that resuscitation to target mean arterial pressure (MAP) of 40mmHg, as opposed to 80mmHg or higher not only results in decreased blood loss but also in better splanchnic perfusion and tissue oxygenation[34], less acidemia, hemodilution, thrombocytopenia, and coagulopathy[35], decreased apoptotic cell death and tissue injury[35, 36], and improved survival[35, 36]. However, others have shown in large animal models that prolonged duration (8 hours) of hypotension increases metabolic stress, tissue hypoxia, and mortality[37, 38]. Still the majority of the pre-clinical data favors MAPs between 40–60mmHg or systolic blood pressure (SBP) between 80–90mmHg. Furthermore, in each of these studies, hypotensive resuscitation with crystalloids was beneficial compared to non-resuscitated controls. An alternative means of hypotensive resuscitation, particularly useful in pre-hospital or austere environments where accurate blood pressure measurement may not be feasible, is by fluid infusion at a pre-determined rate (carefully selected to avoid over resuscitation). In animal studies, empiric rates of infusion have shown promise. Slow infusion rates with crystalloid have been shown to reduce organ injury[39], causes faster recovery of hemorrhage suppressed cell mediated immune function[40, 41] and reduce mortality. Overall, the data suggest that hypotensive resuscitation at a fixed rate of 60–80cc/kg/hour generally maintains controlled hypotension to a SBP of 80–90mmHg (MAP of 40–60mmHg) and that this empiric control of infusion rates is beneficial in hemorrhagic shock. Regardless of which approach is selected (goal directed vs. fixed volume), these pre-clinical data combined with the clinical evidence [15, 16] argues strongly against routine large volume crystalloid resuscitation. The best approach for an urban trauma services (short transport times) appears to be “scoop and run”, where unnecessary field interventions are avoided and the focus is on fast and efficient transport of the patient to the hospital[42].

ii. Hypertonic Saline—Another new development is the renewed interest in hypertonic saline (HTS), not just as a volume expander but also as an immune modulator. The use of HTS for resuscitation from hemorrhage was first described in 1980, when Velesco et. al[43], and DeFelippe et. al[44], 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 to resuscitation with 2–3 liters of 0.9% saline. Since the original reports, HTS or

hypertonic saline combined with dextran (HSD) have been tested in a number of RCTs, without showing a clear survival advantage[45]. A meta-analysis evaluated HSD as the initial treatment for hypovolemic shock by reviewing the original records from six trials (and 604 subjects)[46]. Overall discharge survival rates were better with HSD resuscitation as compared to conventional resuscitation. HSD resuscitation was particularly effective for the sub-group of patients that had sustained head injury with a discharge survival rate of 38%, as compared to a rate of 27% for the control group receiving saline. All of these 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 pre-clinical studies have demonstrated that HTS has the potential to modulate the immune response, with an overall attenuation of immune mediated cellular injury[47, 48, 49, 50, 51, 52, 53, 54, 55, 56]. A small RCT has also shown that initial treatment of trauma patients with HSD inhibits neutrophil adhesion molecule expression and favorably modulates the inflammatory response[57]. The recently established Resuscitation Outcome Consortium (ROC)[58], funded by the National Institutes of Health and the US Department of Defense initiated two multicenter trials of hypertonic resuscitation in blunt or penetrating trauma patients in hypovolemic shock, and severe traumatic brain injury. Both studies were designed to have three randomized groups comparing hypertonic saline/dextran (7.5% saline/6% dextran 70, HSD), hypertonic saline alone (7.5% saline, HTS), and normal saline (NS) as the initial resuscitation fluid for the pre-hospital setting. In addition to the primary endpoints, comprehensive data about the immunologic consequences of hypertonic resuscitation would also be collected. Unfortunately, the interim analysis of the data was not favorable, HTD treated patients experienced higher early mortality and no overall benefit compared to the control arm (the full analysis remain unpublished at the time of this writing)[59]. Despite the much lauded laboratory effects of hypertonic saline, this fluid has not been the magic bullet hoped for by many researchers. Based upon these clinical data, HTS cannot be recommended for resuscitating trauma patients outside an approved trial. Another fluid that remains controversial is albumin. A recent report [post hoc analysis of patients from the Saline versus Albumin Fluid Evaluation (SAFE) study] suggests that albumin should be avoided in patients with traumatic brain injury, as it was associated with a significant increase in mortality[60].

iii. Damage Control Resuscitation—An idea that is gaining momentum due to the ongoing war (Iraq and Afghanistan) is the concept of hemostatic/damage control resuscitation[61]. 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. 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[62, 63]. 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 variables[64]. Holcomb'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, $p<0.01$)[65]. These conclusions have recently been questioned by a study that suggests that the observed survival differences between patients receiving high and low ratios in the first 24 hours may simply be due to the fact that survivors live long enough to receive component therapy (survivor bias)[66]. 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 meet the criteria for massive resuscitation (expected to receive >10 units PRBC). 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 10 units PRBC. Despite an ongoing debate about the precise ratios, there is 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. The often disorganized process of blood component transfusion in the face of massive hemorrhage benefits from an organized and standardized approach that delivers the needed blood products while avoiding their misuse. Despite these obvious attractive features, in a recent review Malone found only 10 such protocols published worldwide[67]. The utility of MTP (using different ratios of blood components) has already been verified in some case controlled studies. Cotton 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 intraoperative 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, $p<0.001$)[68]. Dente conducted a similar study of an 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 patients[69]. This study also showed that MTP patients required fewer overall transfusions of PRBCs and FFP after the first 24 hours (2.7 units PRBCS vs. 9.3 units, $p<0.0001$; 3 units FFP vs. 7.5 units, $p<0.05$). While further prospective research is needed to specify the exact ratios, there is convincing evdence that implementation of standardized protocols for blood component transfusion improves processes of care, reduces overall use of blood components, and improves outcomes.

iv. Red Blood Cell Substitutes—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 Systemic Inflammatory Response Syndrome (SIRS), and a delayed immune suppression which predisposes the patients to infections[70]. As a matter of fact, transfusion of PRBC remains an independent risk factor for increased infections, multiple organ failure, length of hospital stay, and mortality[71, 72, 73, 74]. This has prompted many researchers to focus their attention on testing alternative oxygen carrying solutions[75]. 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 the 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 storage and length of shelf-life. Of the HBOCs 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 diaspirin cross-linked human hemoglobin)

have fallen out of favor due to negative phase III clinical trials. In Sloan's multicenter randomized clinical trial (RCT) trauma patients in severe hemorrhagic shock reveived either 500ml 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)[76]. 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 mortality[77]. 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 no mortality benefit in the treatment arm, and a higher rate of adverse events (93% for Polyheme versus 88% for controls, p=0.041)[78]. A 2008 meta-analysis of 16 HBOC trials, including four trials of trauma patients receiving HemAssist or Polyheme, raised alarm as patients receiving HBOCs 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)[79]. 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 rested in a trauma patient population in South African study but the final results of this trial remain unpublished[80]. HOC 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 use of HBOC-201 resulted in less need for PRBC transfusion but a significant increase in serious adverse events[81]. 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 HBOCs can't be endorsed at this time outside of well-designed, thoroughly vetted clinical trials.

3. Septic shock

a. Initial resuscitation

As opposed to hemorrhagic shock, early goal directed resuscitation has been shown to improve 28-day mortality in a single center, prospective, RCT[82]. Although the exact parameters used to guide resuscitation in that study have been challenged, the basic concept is clearly sound, as has been validated by a number of subsequent studies[83, 84, 85, 86, 87]. For optimal results, the resuscitation protocol must be initiated as soon as shock is diagnosed and should not be delayed until admission to the intensive care unit (ICU). Due to venous dilation, and increased capillary leak, most of these patients require aggressive fluid resuscitation over the first 24 hours. During this period, in addition to ensuring adequate cardiac pre-load (e.g. central venous pressure, pulmonary artery occlusion pressure), parameters of tissue perfusion and oxygen delivery (e.g. serum lactate, base deficit, urine output, central/mixed venous oxygen saturation, cardiac output) should be carefully monitored. The SAFE study[88] has shown that albumin and crystalloids are equally safe and effective (except for patients with traumatic head injury). Surviving Sepsis Campaign has recently reviewed the literature and published updated and comprehensive guidelines to guide the resuscitation in adult and pediatric patients[89]. These guidelines also provide evidence-based recommendations regarding a wide spectrum of supportive/adjunctive therapies (e.g. glycemic control, steroids, vasoactive agents, activated protein C etc).

b. Vasopressors and inotropes

Within reasonable limits, blood flow through the tissue beds is more important than blood pressure. However, during septic shock autoregulation is not normal and perfusion can become linearly dependent on blood pressure. Thus, after the initial fluid resuscitation (or concomitantly) hypotensive patients may require administration of vasopressors to keep the mean arterial pressure >65 mmHg (which has been shown to preserve tissue perfusion)[90, 91]. Whenever possible, vasopressors should be started after providing adequate initial fluid resuscitation. There is no compelling, high quality evidence that shows one agent to be superior to another[92]. However, Surviving Sepsis Campaign recommends “norepinephrine or dopamine as the first choice vasopressor agent to correct hypotension in septic shock (Grade IC)”[89]. According to them, norephephrine 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 good choice, which increases MAP and stroke volume. However, it also increases heart rate, which may not be 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 shock[93]. However, a recent RCT-Vasopressin and Septic Shock Trial (VASST), which enrolled 778 patients failed to show a survival advantage of vasopressin (0.03 units/min) over norepinephrine, or a reduction in overall rate of serious adverse events[94]. In addition to agents that restore the vascular tone, patients with documented or suspected decrease in cardiac function (elevated filling pressures and low cardiac output) should be given dobutamine as an inotropic agent[89]. 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 levels[89].

c. Blood products

The optimal hemoglobin level has not been determined for severely septic patients. Rivers and associates in the early goal directed therapy trial[82] used a target hematocrit of 30% in patients who continued to show low central venous oxygen saturation. In a more recent multi-institutional trail of mixed ICU patients (not necessarily septic shock patients) hemoglobin levels of 7–9 gm/dL and 10–12 gm/dL were associated with identical outcomes[95]. Thus, it is reasonable to aim for target hemoglobin between 7–9 gm/dL if parameters of tissue oxygenation are adequate. But in cases of depressed tissue oxygenation or in patients with other co-morbid issues (e.g. coronary artery disease, stroke, etc), hemoglobin levels can be pushed up to 10–12 gm/dL to optimize the tissue oxygen delivery. However, this area remains controversial and evidence based guidelines have been proposed by experts in the field to steer the transfusion practices in these critically ill patients[96].

4. Future Directions

A number of new and exciting developments in the arena of resuscitation research have the potential of radically transforming clinical care in the near future. Two such areas of research are discussed here:

a. Pharmacologic therapy

Over the years, a number of pharmacologic agents have been tested as possible adjuncts to 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, 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 treatments[97]. Dr. Coimbra's group has studied the phosphodiesterase inhibitor, pentoxyfylline, already widely used for vascular disease due to its rheologic properties, as a treatment for hemorrhage because it reduces neutrophil activation and adhesion[98]. A Cochrane review recently analyzed data on the opiate antagonist Naloxone which has been studied based on the finding that central Mu, Epsilon, Kappa, and Delta receptors are activated during hemorrhagic shock and inhibit Ca^{++} channels; the data suggested 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 survival[99]. 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 already in wide 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[100, 101]. We hypothesized that histone deacetylase (HDAC) inhibitors such as valproic acid (VPA) and suberoylanilide hydroxamic acid (SAHA) may have utility 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 [102, 103, 104]. 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[105, 106, 107, 108, 109]. 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 stress.

b. Emergency Preservation and Resuscitation (EPR)

Up to 80% of trauma deaths occur in the early post-traumatic phase,[110] with exsanguination as the dominant etiology[111]. Profound shock from blood loss does not respond well to conventional methods of resuscitation[112]. Even when the underlying cause can be treated 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. 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[113, 114, 115]. 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[116, 117]. 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 period[118]. Although ground breaking, the clinical relevance of these original studies was somewhat limited by 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 dysfunction[119]. 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 survival[120]. 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 not only neurologically intact but also 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)[121, 122]. 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 [123, 124, 125]. The optimal depth of hypothermia is 10°C, and decreasing the temperature to ultra-profound levels (5°C) may actually worsen the outcome[126]. If done appropriately, the safe duration of total body preservation in poly-trauma is about 60 minutes[127], and it results in no increase in post-operative bleeding or septic complications[128]. Technically it is now feasible to induce hypothermia using small, battery operated, portable equipment (suitable for austere settings and pre-hospital environment)[129]. 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 transplant[130]. Induction of hypothermia not only modulates metabolism but also influences a vide variety of cellular and sub-cellular mechanisms[131], including alteration in transcription of numerous beneficial genes[132], the down-stream effects of which persists long after 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 sulfide[133]. It may sound futuristic, but the expertise to preserve the viability of key organs during repair of otherwise lethal injuries is now available[134], and a prospective multi-institutional clinical trial is scheduled to start later this year[135].

5. Conclusions

Treatments of shock have evolved over the last 50 years, but the changes over the last decade have been especially dramatic[136, 137, 138]. Based upon contemporary data, early goal directed fluid resuscitation should be considered the standard of care for septic shock, along with additional supportive measures as advocated by the Surviving Sepsis Guidelines[89]. The optimal approach for hemorrhagic shock is not as clear due to a relative paucity of level-1 evidence. However, according to my personal opinion the existing literature strongly supports some common sense recommendations for the treatment of hemorrhagic shock[139]. .

First, resuscitation is not a substitute for early hemorrhage control. From the moment of injury, all efforts to provide definitive control of hemorrhage as expeditiously as possible must be aggressively pursued. Second, large volume crystalloid resuscitation is deleterious and should be abandoned. Fluid resuscitation can be safely withheld in patients who have adequate cerebral perfusion (normal mental status in the absence of head injury) and a palpable radial pulse, especially if the pre-hospital transport time is expected to be brief. For situations where the time to definitive care is longer than 15–20 minutes, initiation of limited volume resuscitation is supported by the literature. Specifically, the goals should be to maintain either a SBP approximating 80–90mmHg, or clear mental status (in the absence of head injury) and a palpable radial pulse. At present, it seems that infusion of lactated Ringer's solution (containing only the L-isomer of lactate) is the best option in the pre-hospital setting, whereas early use of blood products should be strongly considered once the patient reaches the hospital[18, 23, 139]. While the ideal ratio of blood components is under investigation, there is a strong trend in favor of starting component therapy early and to administer higher ratios of FFP and platelets to PRBC. Newer methods for blood component preservation have improved their logistical profile, which may yield shelf-stable products for pre-hospital use in the near future[140, 141]. The evidence strongly suggests that applying these ratios through an institutional protocol improves delivery of care and outcomes. When blood products are not an option, blood substitutes may have a role. However, at present, the data on blood substitutes are far too mixed to recommend their use outside of trials. Finally, pharmacologic adjuncts to resuscitation may ultimately play a role is reducing the deleterious immunologic and cellular effects of hemorrhage and resuscitation. This is an exciting area of future research but their use remains to be validated in robust clinical trials. For now, early and expeditious control of hemorrhage and modest, goal directed resuscitation should be the standard of care.

Acknowledgments

The author would like to acknowledge research support provided by numerous grants by the Office of Naval Research, US Army Medical Research and Materiel Command, Defense Advanced Research Projects Agency, and National Institutes of Health.

References

1. Sauaia A, Moore FA, Moore EE, Moser KS, Brennan R, Read RA, et al. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38:185–193. [PubMed: 7869433]
2. Acosta JA, Yang JC, Winchell RJ, Simons RK, Fortlage DA, Hollingsworth-Fridlund P, et al. Lethal injuries and time to death in a level I trauma center. J Am Coll Surg 1998;186:528–533. [PubMed: 9583692]
3. Kaweski SM, Sise MJ, Virgilio RW. The effect of prehospital fluids on survival in trauma patients. J Trauma 1990;30:1215–1218. [PubMed: 2213930]
4. Turner J, Nicholl J, Webber L, et al. A randomized controlled trial of prehospital intravenous fluid replacement therapy in serious trauma. Health Technol Assess 2000;4:1–57. [PubMed: 11109030]
5. Greaves MW, Hussein SH. Fluid resuscitation in pre-hospital trauma care: a consensus view. J R Coll Surg Edinb 2002;47:451–7. [PubMed: 12018688]
6. Dula DJ, Wood GC, Rejmer AR, Starr M, Leicht M. Use of prehospital fluids in hypotensive blunt trauma patients. Prehosp Emerg Care 2002;6:417–20. [PubMed: 12385609]
7. Dutton RP, Mackenzie CF, Scalea TM. Hypotensive resuscitation during active hemorrhage: impact on in-hospital mortality. J Trauma 2002;52:1141–1146. [PubMed: 12045644]
8. Cannon WB, Faser J, Collew EM. The preventive treatment of wound shock. JAMA 1918;47:618.
9. Stern SA, Dronen SC, Birrer P, Wang X. Effect of blood pressure on hemorrhage volume and survival in a near-fatal hemorrhage model incorporating a vascular injury. Ann Emerg Med 1993;22:155–163. [PubMed: 8427424]

10. Selby JB, Mathis JE, Berry CF, Hagedorn FN, Illner HP, Shires GT. Effects of isotonic saline solution resuscitation on blood coagulation in uncontrolled hemorrhage. Surgery 1996;119:528–533. [PubMed: 8619208]
11. Sondeen JL, Coppes VG, Holcomb. Blood pressure at which rebleeding occurs after resuscitation in swine with aortic injury. J Trauma 2003;54(Suppl):S100–7. [PubMed: 12768110]
12. Rotondo MF, Schwab CW, McGonigal MD, Phillips GR 3rd, Fruchterman TM, Kauder DR, et al. "Damage Control": an approach for improved survival in exsanguinating penetrating abdominal trauma. J Trauma 1993;35:375–383. [PubMed: 8371295]
13. Mapstone J, Roberts I, Evans P. Fluid resuscitation strategies: a systematic review of animal trials. J Trauma 2003;55:571–589. [PubMed: 14501908]
14. Liberman M, Mulder D, Sampalis J. Advanced or basic life support for trauma: meta-analysis and critical review of the literature. J Trauma 2000;49:584–599. [PubMed: 11038074]
15. Bickel WH, Wall MJ, Pepe PE, Martin RR, Ginger VF, Allen MK, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. N Engl J Med 1994;331:1105–1109. [PubMed: 7935634]
16. Kwan I, Bunn F, Roberts I. WHO Pre-Hospital Trauma Care Steering Committee: Timing and volume of fluid administration for patients with bleeding following trauma. Cochrane Database Syst Rev 2003;(3):CD002245. [PubMed: 12917926]
17. Alam HB. An update on fluid resuscitation. Scand J Surg 2006;95:136–45. [PubMed: 17066606]
18. Committee on fluid resuscitation for combat casualties. Report of the Institute of Medicine. Washington, DC: National Academy Press; 1999. Fluid resuscitation: state of the science for treating combat casualties and civilian trauma.
19. Shires GT, Carrico CJ, Baxter CR, Giesecke AH, Jenkins MT. Principles in treatment of severely injured patients. Adv Surg 1970;4:255–324. [PubMed: 5447113]
20. Shires GT, Coln D, Carrico J, Lightfoot S. Fluid therapy in hemorrhagic shock. Arch Surg 1964;88:688–93. [PubMed: 14107023]
21. Dillon J, Lunch LJ, Myers R, Butcher HR, Moyer CA. A bioassay of treatment of hemorrhagic shock. Arch Surg 1966;93:537–55. [PubMed: 5922028]
22. Cervera AL, Moss G. Progressive hypovolumia leading to shock after continous hemorrhage and 3:1 crystalloid replacement. Am J Surg 1975;129:670–74. [PubMed: 1130612]
23. Alam HB, Rhee P. New developments in fluid resuscitation. Surg Clin North Am 2007;87:55–72. [PubMed: 17127123]
24. Cotton BA, Guy JS, Morris JA, Abumrad NN. The cellular, metabolic, and systemic consequences of aggressive fluid resuscitation strategies. Shock 2006;26:115–21. [PubMed: 16878017]
25. Daugherty EL, Hongyan L, Taichman D, et al. Abdominal compartment syndrome is common in medical intensive care unit patients receiving large volume resuscitation. J Intensive Care Med 2007;22:294–9. [PubMed: 17895487]
26. O'Mara MS, Slater H, Goldfarb IW, Caushaj PF. A prospective, randomized evaluation of intra-abdominal pressures with crystalloids and colloid resuscitation in burn patients. J Trauma 2005;58:1011–8. [PubMed: 15920417]
27. Balogh Z, Moore FA, Moore EE, Biffl WL. Secondry abdominal compartment syndrome: a potential threat for all trauma clinicians. Injury 2007;38:272–9. [PubMed: 17109861]
28. Klein MB, Hayden D, Elson C, et al. The association between fluid administeration and outcome following major burn. A multicenter study. Ann Surg 2007;245:622–628. [PubMed: 17414612]
29. Uniformed Services University of the Health Sciences. Combat Fluid Resuscitation. Sponsored by US Office of Naval Research; US Army Medical Research and Material Command; Department of Surgery; Department of Military and Emergency Medicine; Bethesda, MD. June 18–20, 2001;
30. Defense and Civil Institute of Environmental Medicine. Fluid Resuscitation in Combat. Sponsored by Defense R & D Canada, Defense and Civil Institute of Environmental Medicine, Department of Surgery, University of Toronto; and the Office of Naval Research; Toronto, Ontario. October 25–26, 2001;
31. Champion HR. Combat fluid resuscitation: Introduction and overview of conferences. J Trauma 2003;54 (supp):7–12.

32. Rhee P, Koustova E, Alam HB. Searching for the optimal resuscitation method: recommendations for the initial fluid resuscitation of combat casualties. J Trauma 2003;54(supp):52–62. [PubMed: 12544899]
33. Gwande A. Casualties of war- Military care for the wounded from Iraq and Afghanistan. New Engl J Med 2004;351:2471–2475. [PubMed: 15590948]
34. Varela JE, Cohn SM, Diaz I, Giannotti GD, Proctor KG. Splanchnic perfusion during delayed, hypotensive, or aggressive fluid resuscitation from uncontrolled hemorrhage. Shock 2003;20:476–80. [PubMed: 14560114]
35. Lu YQ, Cai XJ, Gu LH, Wang Q, Huang WD, Bao DG. Experimental study of controlled fluid resuscitation in the treatment of severe and uncontrolled hemorrhagic shock. J Trauma 2007;63:798–804. [PubMed: 18090008]
36. Xiao N, Wang XC, Diao YF, Liu R, Tian KL. Effect of initial fluid resuscitation on subsequent treatment in uncontrolled hemorrhagic shock in rats. Shock 2004;21:276–80. [PubMed: 14770042]
37. Skarda DE, Mulier KE, George ME, Beilman GJ. Eight hours of hypotensive versus normotensive resuscitation in a porcine model of controlled hemorrhagic shock. Acad Emerg Med 2008;15:845–52. [PubMed: 19244635]
38. Rafie AD, Rath PA, Michell MW, Kirschner RA, Deyo DJ, Prough DS, Grady JJ, Kramer GC. Hypotensive resuscitation of multiple hemorrhages using crystalloid and colloids. Shock 2004;22:262–9. [PubMed: 15316397]
39. Shah KJ, Chiu WC, Scalea TM, Carlson DE. Detrimental effects of rapid fluid resuscitation on hepatocellular function and survival after hemorrhagic shock. Shock 2002;18:242–7. [PubMed: 12353925]
40. Knoferl MW, Angele MK, Ayala A, Cioffi WG, Bland KI, Chaudry IH. Do different rates of fluid resuscitation adversely or beneficially influence immune responses after trauma-hemorrhage? J Trauma 1999;46:23–33. [PubMed: 9932680]
41. Santibanez-Gallerani AS, Barber AE, Williams SJ, Zhao BSY, Shires GT. Improved survival with early fluid resuscitation following hemorrhagic shock. World J Surg 2001;25:592–7. [PubMed: 11369985]
42. Haas B, Nathens AB. Pro/con debate: Is the scoop and run approach the best approach to trauma services organization? Crit Care 2008;12:224–35. [PubMed: 18828868]
43. Velasco IT, Ponieri V, Rocha M, Lopes Ou. Hyperosmotic NaCl and severe hemorrhagic shock. Am J Physiol 1980;239:H664. [PubMed: 6776826]
44. DeFelippe J Jr, Timoner IJ, Velasco IT, Lopes OU, Rocha-e-Silva M. Treatment of refractory hypovolemic shock by 7.5% sodium chloride injections. Lancet 1980;2:1002. [PubMed: 6107629]
45. Bunn F, Roberts I, Tasker R. Hypertonic versus near isotonic crystalloids for fluid resuscitation in critically ill patients. Cochrane Database of Systematic Reviews 2004;3:CD002045.
46. Wade CE, Kramer GC, Grady JJ, Fabian TC, Younes RN. Efficacy of hypertonic 7.5% saline and 6% dextran-70 in treating trauma: a meta-analysis of controlled clinical studies. Surgery 1997;122:609–616. [PubMed: 9308620]
47. Junger WG, Coimbra R, Liu FC, Herdon-Remelius C, Junger W, Junger H, et al. Hypertonic saline resuscitation: a tool to modulate immune function in trauma patients? Shock 1997;8:235–41. [PubMed: 9329123]
48. Rotstein OD. Novel strategies for immunomodulation after trauma: revisiting hypertonic saline as a resuscitation strategy for hemorrhagic shock. J Trauma 2000;49:580–3. [PubMed: 11038073]
49. Bahrami S, Zimmermann K, Szelenyi Z, Hamar J, Scheiflinger F, Redl H, et al. Small volume fluid resuscitation with hypertonic saline prevents inflammation but not mortality in a rat model of hemorrhagic shock. Shock 2006;25:283–9. [PubMed: 16552361]
50. Pascual JL, Ferri LE, Seely AJ, Campisi G, Chaudhury P, Giannias B, et al. Hypertonic saline resuscitation of hemorrhagic shock diminishes neutrophil rolling and adherence to endothelium and reduces in vivo vascular leakage. Ann Surg 2002;236:634–42. [PubMed: 12409670]
51. Murao Y, Loomis W, Wolf P, Hoyt DB, Junger WG. Effect of hypertonic saline on its potential to prevent lung tissue damage in a mouse model of hemorrhagic shock. Shock 2003;20:29–34. [PubMed: 12813365]

52. Murao Y, Hata M, Ohnishi K, Okuchi K, Nakajima Y, Hiasa Y, et al. Hypertonic saline resuscitation reduces apoptosis and tissue damage of the small intestine in a mouse model of hemorrhagic shock. Shock 2003;20:23–8. [PubMed: 12813364]
53. Sheppard FR, Moore EE, McLaughlin N, Kelher M, Johnson JL, Silliman CC. Clinically relevant osmolar stress inhibits priming-induced PMN NADPH oxidase subunit translocation. J Trauma 2005;58:752–7. [PubMed: 15824651]
54. Gonzales RJ, Moore EE, Ciesla DJ, Neto JR, Biffl WL, Silliman CC. Hyperosmolarity abrogates neutrophil cutotoxity provoked by post-shock mesenteric lymph. Shock 2002;18:29–32. [PubMed: 12095130]
55. Staudenmayer KL, Maier RV, Jelacic S, Bulger EM. Hypertonic saline modulates innate immunity in a model of systemic inflammation. Shock 2005;23:459–63. [PubMed: 15834313]
56. Cuschieri J, Gourlay D, Garcia I, Jelacic S, Maier RV. Hypertonic preconditioning inhibits macrophage responsiveness to endotoxin. J Immunol 2002;168:1389–96. [PubMed: 11801680]
57. Bulger EM, Cuschieri J, Warner K, Maier RV. Hypertonic resuscitation modulates the inflammatory response in patients with traumatic hemorrhagic shock. Ann Surg 2007;245:635–641. [PubMed: 17414614]
58. Available at: https://roc.uwctc.org/tiki/tiki-index.php
59. The nhlbi halts study of concentrated saline for patients with shock due to lack of survival benefit NIH News [serial on the Internet]. 2009 [Last accesed on 5.4.10]. [cited 2009 March 26]: Available from: http://www.nih.gov/news/health/mar2009/nhlbi-26.htm
60. The SAFE Study Investigators. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. N Engl J Med 2007;357:874–84. [PubMed: 17761591]
61. Holcomb JB, Jenkins D, Rhee P, et al. Damage control resuscitation: directly addressing the early coagulopathy of trauma. J Trauma 2007;62:307–10. [PubMed: 17297317]
62. Gonzales EA, Moore FA, Holcomb JB, et al. Fresh frozen plasma should be given earlier to patients receiving massive transfusion. J Trauma 2007;62:112–119. [PubMed: 17215741]
63. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007;63:805–813. [PubMed: 18090009]
64. Duchesne JC, Hunt JP, Wahl G, et al. Review of current blood transfusions strategies in a mature level i trauma center: Were we wrong for the last 60 years? J Trauma 2008;65:272–6. [PubMed: 18695461]
65. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. Ann Surg 2008;248:447–58. [PubMed: 18791365]
66. Snyder CW, Weinberg JA, McGwin G Jr, et al. The relationship of blood product ratio to mortality: Survival benefit or survival bias? J Trauma 2009;66:358–62. [PubMed: 19204508]
67. Malone DL, Hess JR, Fingerhut A. Massive transfusion practices around the globe and a suggestion for a common massive transfusion protocol. J Trauma 2006;60:S91–6. [PubMed: 16763487]
68. Cotton BA, Gunter OL, Isbell J, et al. Damage control hematology: The impact of a trauma exsanguination protocol on survival and blood product utilization. J Trauma 2008;64:1177–82. [PubMed: 18469638]
69. Dente CJ, Shaz BH, Nicholas JM, et al. Improvements in early mortality and coagulopathy are sustained better in patients with blunt trauma after institution of a massive transfusion protocol in a civilian level I trauma center. J Trauma 2009;66:1616–24. [PubMed: 19509623]
70. Silliman CC, Moore EE, Johnson JL, Gonzales RJ, Biffl WL. Transfusion of the injured patient: proceed with caution. Shock 2004;21:291–9. [PubMed: 15179127]
71. Chales A, Shaikh AA, Walters M, et al. Blood transfusion in an independent predictor of mortality after blunt trauma. Am Surg 2007;73:1–5. [PubMed: 17249446]
72. Offner PJ, Moore EE, Biffl WL, Johnson JL, Silliman CC. Increased rate of infection associated with transfusion of old blood after severe injury. Arch Surg 2002;137:711–17. [PubMed: 12049543]

73. Dunne JR, Malone DL, Tracy JK, Napolitano LM. Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. Surg Infect (Larchmt) 2004;5:395–404. [PubMed: 15744131]
74. Moore FA, Moore EE, Sauaia A. Blood transfusion. An independent risk factor for postinjury multiple organ failure. Arch Surg 1997;132:620–4. [PubMed: 9197854]
75. Moore EE. Blood substitutes: the future is now. J Am Coll Surg 2003;196:1–17. [PubMed: 12517544]
76. Sloan EP, Koenigsberg M, Gens D, Cipolle M, Runge J, Mallory MN, Rodman G Jr. Diaspirin cross-linked hemoglobin (dclhb) in the treatment of severe traumatic hemorrhagic shock: A randomized controlled efficacy trial. JAMA 1999;282:1857–64. [PubMed: 10573278]
77. Kerner T, Ahlers O, Veit S, Riou B, Saunders M, Pison U. Dcl-hb for trauma patients with severe hemorrhagic shock: The european “On-scene” Multicenter study. Intensive Care Med 2003;29:378–85. [PubMed: 12541156]
78. Moore EE, Moore FA, Fabian TC, et al. Human polymerized hemoglobin for the treatment of hemorrhagic shock when blood is unavailable: The USA multicenter trial. J Am Coll Surg 2009;208:1–13. [PubMed: 19228496]
79. Natanson C, Kern SJ, Lurie P, Banks SM, Wolfe SM. Cell-free hemoglobin-based blood substitutes and risk of myocardial infarction and death: A meta-analysis. JAMA 2008;299:2304–12. [PubMed: 18443023]
80. [Last accessed on 5/3/10]. http://clinicaltrials.gov/ct2/show/NCT00301483?term=HBOC201&rank=1
81. Jahr JS, Mackenzie C, Pearce LB, Pitman A, Greenburg AG. HBOC-201 as an alternative to blood transfusion: efficacy and safety evaluation in a multicenter phase III trial in elective orthopedic surgery. J Trauma 2008;64:1484–97. [PubMed: 18545113]
82. Rivers E, Nguyen B, Havstad S, et al. Early Goal-Directed Therapy Collaborative Group. Early goal directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368–1377. [PubMed: 11794169]
83. Sebat F, Johnson D, Musthafa AA, et al. A multidisciplinary community hospital program for early and rapid resuscitation of shock in nontrauma patients. Chest 2005;127:1729–1743. [PubMed: 15888853]
84. Kortgen A, Niederprum P, Bauer M. Implementation of an evidence based “standard operating procedure” and outcome in septic shock. Crit Care Med 2006;34:943–949. [PubMed: 16484902]
85. Shapiro NI, Howell MD, Talmor D, et al. Implementation and outcomes of the Multiple Urgent Sepsis Therapies (MUST) protocol. Crit Care Med 2006;34:1025–1032. [PubMed: 16484890]
86. Nguyen HB, Corbett SW, Steele R, et al. Implementation of a bundle of quality indicators for the early management of severe sepsis and septic shock is associated with decreased mortality. Crit Care Med 2007;35:1105–1112. [PubMed: 17334251]
87. Shorr AF, Micek ST, Jackson WL Jr, Kollef MH. Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs? Crit Care Med 2007;2007;35:1257–1262. [PubMed: 17414080]
88. SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247–2256. [PubMed: 15163774]
89. Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: International guidelines for management of severe sepsis and septic shock: 2008. Crit Care Med 2008;36(1):296–327. [PubMed: 18158437]
90. Hollenberg SM, Ahrens TS, Annane D, et al. Practice parameters for hemodynamic support of sepsis in adult patients: 2004 update. Crit Care Med 2004;32:1928–1948. [PubMed: 15343024]
91. LeDoux D, Astiz ME, Carpati CM, Rackow EC. Effects of perfusion pressure on tissue perfusion in septic shock. Crit Care Med 2000;28:2729–32. [PubMed: 10966242]
92. Mullner M, Urbanek B, Havel C, et al. Vasopressors for shock. Cochrane database of Systematic Reviews 2004;(3):CD003709.
93. Russell JA. Vasopressin in vasodilatory and septic shock. Curr Opin Crit Care 2007;13:383–91. [PubMed: 17599007]

94. Russell JA, Walley KR, Singer JS, Gordon AC, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. N Engl J Med 2008;358 :877–87. [PubMed: 18305265]
95. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion in critical care. N Engl J Med 1999;340:409–417. [PubMed: 9971864]
96. Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. Crit Care Med 2009;37:3124–57. [PubMed: 19773646]
97. Yu HP, Chaudry IH. The role of estrogen and receptor agonists in maintaining organ function after trauma-hemorrhage. Shock 2009;31:227–37. [PubMed: 18665049]
98. Deree J, Martins J, de Campos T, Putnam JG, Loomis WH, Wolf P, Coimbra R. Pentoxifylline attenuates lung injury and modulates transcription factor activity in hemorrhagic shock. J Surg Res 2007;143:99–108. [PubMed: 17950078]
99. Boeuf B, Poirier V, Gauvin F, Guerguerian AM, Roy C, Farrell CA, Lacroix J. Naloxone for shock. Cochrane Database Syst Rev 2003:CD004443. [PubMed: 14584016]
100. Lin T, Alam HB, Chen H, Britten-Webb J, Rhee P, Kirkpatrick J, Koustova E. Cardiac histones are substrates of histone deacetylase activity in hemorrhagic shock and resuscitation. Surgery 2006;139:365–76. [PubMed: 16546502]
101. Alam HB, Shults C, Ahuja N, Ayuste EC, et al. Impact of resuscitation strategies on the acetylation status of cardiac histones in a swine model of hemorrhage. Resuscitation 2008;76:299–310. [PubMed: 17822827]
102. Gonzales ER, Chen H, Munuve RM, Mehrani T, Nadel A, Koustova E. Hepatoprotection and lethality rescue by histone deacetylase inhibitor valproic acid in fatal hemorrhagic shock. J Trauma 2008;65:554–65. [PubMed: 18784568]
103. Shults C, Sailhamer EA, Li Y, Liu B, Tabbara M, Butt MU, Shuja F, Demoya M, Velmahos G, Alam HB. Surviving blood loss without fluid resuscitation. J Trauma 2008;64:629–38. [PubMed: 18332802]
104. Alam H, Shuja F, Butt M, Duggan M, Li Y, Zacharias N, Fukudome E, Liu B, deMoya M, Velmahos G. Surviving blood loss without blood transfusion in a swine poly-trauma model. Surgery 2009;146:325–33. [PubMed: 19628092]
105. Sailhamer EA, Li Y, Smith EJ, Shuja F, Shults C, Liu B, Soupir C, deMoya M, Velmahos G, Alam HB. Acetylation: A novel method for modulation of the immune response following trauma/hemorrhage and inflammatory second hit in animals and humans. Surgery 2008;144:204–16. [PubMed: 18656627]
106. Li Y, Yuan Z, Liu B, Sailhamer EA, Shults C, Velmahos GC, Demoya M, Alam HB. Prevention of hypoxia-induced neuronal apoptosis through histone deacetylase inhibition. J Trauma 2008;64:863–70. [PubMed: 18404049]
107. Li Y, Liu B, Sailhamer EA, Yuan Z, Shults C, Velmahos GC, deMoya M, Shuja F, Butt MU, Alam HB. Cell protective mechanism of valproic acid in lethal hemorrhagic shock. Surgery 2008;144:217–24. [PubMed: 18656628]
108. Butt M, Sailhamer E, Li Y, Liu B, Shuja F, Velmahos G, deMoya M, King D, Alam H. Pharmacologic resuscitation: Cell protective mechanisms of histone deacetylase inhibition in lethal hemorrhagic shock. J Surg Res 2009;156:290–6. [PubMed: 19665733]
109. Li Y, Liu B, Zhao H, Sailhamer E, Zhang X, Kheirbek T, Finkelstein R, GCV, deMoya M, Hales C, et al. Protective effect of suberoylanilide hydroxamic acid against LPS-induced septic shock in rodents. Shock 2009;146:325–33.
110. Demetriades D, Murray J, Charalambides K, et al. Trauma fatalities: time and location of hospital deaths. J Am Coll Surg 2004;198:20–6. [PubMed: 14698307]
111. Acosta JA, Yang JC, Winchell RJ, et al. Lethal injuries and time to death in a level I trauma center. J Am Coll Surg 1998;186:528–533. [PubMed: 9583692]
112. Liberman M, Mulder D, Sampalis J. Advanced or Basic Life Support for Trauma: Meta-analysis and Critical Review of the Literature. J Trauma 2000;49:584–599. [PubMed: 11038074]
113. Tisherman SA, Safar P, Radovsky A, et al. Therapeutic deep hypothermic circulatory arrest in dogs: A resuscitation modality for hemorrhagic shock with “irreparable injury”. J Trauma 1990;30:836–847. [PubMed: 2381001]

114. Tisherman SA, Safar P, Radovsky A, et al. Profound hypothermia (<10oC) compared with deep hypothermia (15oC) improves neurologic outcome in dogs after two hours circulatory arrest induced to enable resuscitative surgery. J Trauma 1991;31:1051–1062. [PubMed: 1875431]
115. Capone A, Safar P, Radovsky A, Wang Y, Peitzman A, Tisherman SA. Complete recovery after normothermic hemorrhagic shock and profound hypothermic circulatory arrest of 60 minutes in dogs. J Trauma 1996;40:388–395. [PubMed: 8601855]
116. Behringer W, Prueckner S, Kentner R, et al. Rapid hypothermic aortic flush can achieve survival without brain damage after 30 minute cardiac arrest in dogs. Anesthesiology 2000;93:1491–1499. [PubMed: 11149445]
117. Behringer W, Safar P, Wu X, et al. Survival without brain damage after clinical death of 60–120 minutes in dogs using suspended animation by profound hypothermia. Crit Care Med 2003;31:1523–1531. [PubMed: 12771628]
118. Taylor MJ, Bailes JE, Elrifai AM, Shih S-R, Teeple E, Leavitt ML, et al. A new solution for life without blood: Asanguineous low-flow perfusion of a whole body perfusate during 3 hours of cardiac arrest and profound hypothermia. Circulation 1995;91:431–444. [PubMed: 7805248]
119. Rhee P, Talon E, Eifert S, et al. Induced hypothermia during emergency department thoracotomy: an animal model. J Trauma 1999;48:439–449. [PubMed: 10744281]
120. Alam HB, Bowyer MW, Koustova E, et al. Learning and memory is preserved following induced asanguineous hyperkalemic hypothermic arrest in a swine model of traumatic exsanguination. Surgery 2002;132:278–288. [PubMed: 12219024]
121. Alam HB, Chen Z, Honma K, Koustova E, et al. The rate of induction of hypothermic arrest determines the outcome in a swine model of lethal hemorrhage. J Trauma 2004;57:961–969. [PubMed: 15580018]
122. Alam HB, Rhee P, Honma K, Honma K, et al. Does the rate of rewarming from profound hypothermic arrest influences the outcome in a swine model of lethal hemorrhage. J Trauma 2006;60:134–146. [PubMed: 16456447]
123. Chen Z, Chen H, Rhee P, Koustova E, Ayuste E, Honma K, Nadel A, Alam HB. Induction of profound hypothermia modulates the immune/inflammatory response in a swine model of lethal hemorrhage. Resuscitation 2005;66(2):209–216. [PubMed: 16053944]
124. Alam HB, Chen Z, Ahuja N, Chen H, et al. Profound hypothermia preserves neurons and astrocytes, and protects cognitive functions in a swine model of lethal hemorrhage. J Surg Res 2005;126:172–181. [PubMed: 15919416]
125. Shuja F, Tabbara M, Li Y, Liu B, Butt MU, Velmahos GC, DeMoya M, Alam HB. Profound hypothermia decreases cardiac apoptosis through Akt survival pathway. J Am Coll Surg 2009;209(1):89–99. [PubMed: 19651068]
126. Alam HB, Chen Z, Li Y, et al. Profound hypothermia is superior to ultra-profound hypothermia in improving survival in a swine model of lethal injuries. Surgery 2006;140:307–314. [PubMed: 16904984]
127. Alam HB, Duggan M, Li Y, et al. Putting life on hold-for how long? Profound hypothermic cardiopulmonary bypass in a Swine model of complex vascular injuries. J Trauma 2008;64:912–922. [PubMed: 18404056]
128. Sailhamer EA, Chen Z, Ahuja N, et al. Profound hypothermic cardiopulmonary bypass facilitates survival without a high complication rate in a swine model of complex vascular, splenic and colon injuries. J Am Coll Surg 2007;204:642–53. [PubMed: 17382224]
129. Casas F, Alam H, Reeves A, Chen Z, William WA. A suspended animation forward lines casualty management system. Artificial Organs 2005;29:557–563. [PubMed: 15982284]
130. Taylor MJ, Rhee P, Chen Z, Alam HB. Design of preservation solutions for universal tissue preservation in vivo: Demonstration of efficacy in pre-clinical models of profound hypothermic cardiac arrest. Transplant Proc 2005;37:303–307. [PubMed: 15808626]
131. Kheirbek T, Kochanek AR, Alam HB. Hypothermia in bleeding trauma: a friend or a foe? Scand J Trauma Resusc Emerg Med 2009 Dec 23;17(1):65. [Epub ahead of print]. [PubMed: 20030810]
132. Alam HB, Hashmi S, Finkelstein RA, Shuja F, Fukudome EY, Li Y, Liu B, deMoya M, Velmahos GC. Alterations in gene expression after induction of profound hypothermia for the treatment of lethal hemorrhage. J Trauma. 2010 (accepted).

133. Blackstone E, Morrison M, Roth MB. H2S induces suspended animation-like state in mice. Science 2005;308:518. [PubMed: 15845845]

134. Fukudome EY, Alam HB. Hypothermia in multisystem trauma. Crit Care Med 2009;37(Suppl):S265–72. [PubMed: 19535957]

135. [last accessed on 5.4.10.]. http://clinicaltrials.gov/ct2/show/NCT01042015?term=EPR&rank=2

136. Velmahos GC, Alam HB. Advances in surgical critical care. Curr Probl Surg 2008;45:453–516. [PubMed: 18503823]

137. Pepe PE, Dutton RP, Fowler RL. Preoperative resuscitation of the trauma patient. Curr Opin Anaesthesiol 2008;21:216–21. [PubMed: 18443492]

138. Boldt J. Fluid choice for resuscitation of the trauma patient: a review of the physiological, pharmacological, and clinical evidence. Can J Anaesth 2004;51:500–13. [PubMed: 15128639]

139. Santry H, Alam HB. Fluid resuscitation: Past, present and the future. Shock 2010;33:229–41. [PubMed: 20160609]

140. Spoerke N, Zink K, Cho SD, et al. Lyophalized plasma for resuscitation in a swine model of severe injuries. Arch Surg 2009;144:829–34. [PubMed: 19797107]

141. Shuja F, Shults C, Duggan M, Tabbara M, Butt MU, Fisher TH, Schreiber M, Tieu B, Holcomb JB, Sondeen JL, Demoya M, Velmahos GC, Alam HB. Development and testing of freeze dried plasma for the treatment of trauma associated coagulopathy. J Trauma 2008;65:975–85. [PubMed: 19001961]