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REVIEW ARTICLE

CME

# Update in Trauma Anesthesiology: Perioperative Resuscitation Management

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The management of trauma patients has matured significantly since a systematic approach to trauma care was introduced nearly a half century ago. The resuscitation continuum emphasizes the effect that initial therapy has on the outcome of the trauma patient. The initiation of this continuum begins with prompt field medical care and efficient transportation to designated trauma centers, where lifesaving procedures are immediately undertaken. Resuscitation with packed red blood cells and plasma, in parallel with surgical or interventional radiologic source control of bleeding, are the cornerstones of trauma management. Adjunctive pharmacologic therapy can assist with resuscitation. Tranexamic acid is used in Europe with good results, but the drug is slowly being added to the pharmacy formulary of trauma centers in United States. Recombinant factor VIIa can correct abnormal coagulation values, but its outcome benefit is less clear. Vasopressin shows promise in animal studies and case reports, but has not been subjected to a large clinical trial. The concept of "early goal-directed therapy" used in sepsis may be applicable in trauma as well. An early, appropriately aggressive resuscitation with blood products, as well as adjunctive pharmacologic therapy, may attenuate the systemic inflammatory response of trauma. Future investigations will need to determine whether this approach offers a similar survival benefit. (Anesth Analg 2012;115:1326–33)

In the United States (US), trauma is the third leading cause of death in people of all ages (after heart disease and cancer) and the leading cause of death in children and adults up to 44 years of age.

The development of trauma systems throughout the US in the 1970s addressed the urgent need to treat the victims of trauma in a standardized, systematic format. R Adams Cowley was one of the first physicians to advocate treatment of trauma patients at trauma centers and innovated the concept of the "Golden Hour" when he stated, "… there is a golden hour between life and death. If you are critically injured you have less than 60 minutes to survive. You might not die right then; it may be three days or two weeks later—but something has happened in your body that is irreparable."

The concept of the Golden Hour has, however, been criticized for lacking strong scientific evidence.[1] The Golden Hour is based on data from the French military in World War I, in which patients treated by advanced medical care within 1 hour had 10% mortality, whereas those seen after 8 hours had 75% mortality.[2] This concept proposes that trauma patients benefit from rapid transport to dedicated trauma centers with specialized trauma teams. Injury initiates processes, which, if not aborted, will eventually kill the patient. Prompt resuscitation can attenuate the systemic inflammatory response of trauma. Rapid evaluation of life-threatening injuries, as well as clear decision points for intervention, are keystones of this approach. Although it is difficult to correlate a discrete minute value to the window of opportunity for trauma patients, it is fair to say that the faster a patient is resuscitated, the better.

The Advanced Trauma Life Support course developed by the Committee on Trauma of the American College of Surgeons helps physicians maximize their resuscitative efforts and avoid missing life-threatening injuries by using an organized approach in trauma care. Although few anesthesiologists participate in these courses, familiarity with Advanced Trauma Life Support guidelines facilitates more effective participation in the trauma resuscitation team and allows the formulation of perioperative management plans.

## THE RESUSCITATION CONTINUUM

The continuum of resuscitation begins at the point of injury, carries on through the operating room, and extends into the intensive care unit (ICU). Prompt transportation to designated trauma centers is an important component of a coordinated approach to trauma. Recognition of the role that early resuscitation and trauma management have in the resuscitation continuum is key to successful outcomes. Clinical decisions regarding resuscitation in the field, emergency department, and operating room can have far-reaching consequences.

## TRAUMA CENTER CARE

Specialized care for patients at designated trauma centers has demonstrated improvement in outcome. In one study

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of 18,103 patients, 56% of patients were taken to level I trauma centers.[3] Although patients that were taken to level I trauma centers had more severe injuries and more penetrating injuries than those transported to level II trauma centers, they had similar mortality. In a propensity-adjusted multivariate logistic regression analysis, patients taken to level I trauma centers had improved survival and were more likely to be discharged to a rehabilitation/skilled nursing facility or home. This included patients with serious injury (e.g., Injury Severity Score >15, Glasgow Coma Scale score <9). Not surprisingly, patients also do better if taken directly to a trauma center.[4] Patients transferred to a level I trauma center after initial treatment at another facility had higher mortality than those transported directly to a level I trauma center. Transferred patients also had longer ICU and hospital length of stay.

## MILITARY CARE

Forward critical care resuscitation is an important component of the trauma care continuum in the military. Tactical Combat Casualty Care beginning at the point of injury helps mitigate blood loss, treats pain, and provides for immediate antibiotic therapy.[5] In current military operations, a variety of medical echelons initiate damage control resuscitation en route to the combat trauma center, where surgical and radiologic intervention is undertaken in parallel with continued resuscitation. Critical Care Air Transport Teams in the US Air Force use an intensivist, nurse, and respiratory therapist, together with their equipment, to turn large cargo aircraft into an airborne critical care unit. They are able to transport 6 "stabilized," but not necessarily stable, patients (up to 3 of whom can be ventilated) to definitive surgical care outside of the war zone.[6,7] The British Medical Emergency Response Team uses a physician, nurse, and 2 paramedics to transport patients via helicopter to the combat trauma center. Their physician-based model has demonstrated improved survival in traumatic brain injury (attributable to emergency anesthesia and ventilation) and improved survival in thoracic injury (attributable to emergency anesthesia, ventilation, and chest tube drainage).[8] Current discussion in the US military addresses the potential need to develop a rotary wing critical care element to bridge the gap in the continuum of care from wounding to advanced surgical intervention.[9,10]

## DAMAGE CONTROL

In the US Navy, the term "damage control" (DC) is used for the emergency control of situations that may hazard the sinking of a ship. In the context of trauma, the term refers to providing only interventions necessary to control hemorrhage and contamination and focusing on reestablishing a survivable physiologic status.

This approach consists of a rapid abbreviated laparotomy to stop hemorrhage and peritoneal contamination, and staged sequential repair.[11] Patients would then undergo continued resuscitation and aggressive correction of the "lethal triad" of coagulopathy, hypothermia, and acidosis in the ICU before returning to the operating room for definitive repair. The DC strategy has been shown to lead to better than expected survival rates for abdominal trauma.[12,13]

Based on the DC strategy for abdominal injuries, similar principles have been applied to the management of multiply injured patients with associated long-bone and pelvic fractures (i.e., "damage control orthopedics") or with traumatic brain injury (i.e., "damage control neurosurgery"). DC orthopedics is a safer initial approach in unstable patients by significantly decreasing the initial operative exposure and blood loss.[14,15] DC neurosurgery involves stopping intracranial bleeding, evacuation of intracranial hematomas, and early surgical debridement to limit wound contamination.[16] Although DC neurosurgery may also include decompressive craniectomy, surgical reduction of intracranial pressure has not resulted in better outcomes in patients with severe traumatic brain injury.[17]

Damage control resuscitation (DCR) is a concept that has been made popular by the military and is now being investigated in the civilian trauma setting. DCR differs from current resuscitation approaches by attempting to couple the surgical control of life-threatening injury with earlier and more aggressive correction of the coagulation derangements that exacerbate hemorrhage in trauma patients. DCR centers on the application of several principles including "hypotensive resuscitation," use of blood products over isotonic fluid for intravascular volume replacement, and rapid and early correction of coagulopathy with component therapy.[18] This resuscitation strategy begins in the prehospital and emergency department settings and continues through the operating room and ICU until the resuscitation is complete.

## "HYPOTENSIVE RESUSCITATION"

Over the past few years, an alternative to high-volume fluid resuscitation termed "permissive hypotension" or "hypotensive resuscitation" has been actively investigated in the trauma setting. In contrast to standard fluid resuscitation, this strategy uses less fluids and blood products during the early treatment of hemorrhagic shock. Animal studies indicate that hypotensive resuscitation reduces blood loss and transfusion requirements in both blunt and penetrating trauma. However, in human studies, decreased blood loss and transfusion requirements have only been confirmed in penetrating injury.[19] The evidence supporting hypotensive resuscitation in patients with blunt trauma or traumatic brain injury is limited and the overall long-term outcome of this fluid resuscitation strategy has not been determined.[20,21] Concerns about the use of hypotensive resuscitation include the possibility of cardiac arrest (if small volumes of fluid are insufficient to prevent exsanguination) and late complications from organ damage sustained during hypotension. Recommendations based on expert opinion and the results of the above studies suggest titrating fluid to restore consciousness, radial pulse, and a systolic blood pressure of 80 to 90 mm Hg until definitive surgical control of bleeding can be achieved. Fluid treatment is aimed to a systolic blood pressure of at least 100 mm Hg in patients with hemorrhagic shock and head trauma.

## BLOOD PRODUCT ADMINISTRATION

Key concepts in trauma care are source control of hemorrhage and resuscitation with blood products. A careful evaluation of the fluids and blood products needed to resuscitate these patients is an important component of the anesthetic contribution to DCR.[22,23]

Better understanding of transfusion practices, and a more refined definition of "massive transfusion" in the trauma patient, has led to improved resuscitation with blood products.[24] In addition, appreciation for trauma-induced coagulopathy has prompted early empiric treatment, rather than a more reactive response to documented coagulation abnormalities. Many institutions have revised their massive transfusion protocols to include the use of 1:1 ratios of red blood cells (RBCs) to fresh frozen plasma (FFP) transfusion.[25] Military studies on the ratio of RBCs to FFP reported improved survival in the wounded combatant.[26] In one study, the FFP to RBC ratio was evaluated in 246 battle-wounded patients. Mortality decreased from 65% with a 1:8 ratio, to 19% with a 1:1.4 ratio. This translated well into a civilian study with equally compelling data, in which 467 massively transfused trauma patients were examined. Thirty-day survival improved in patients with FFP to RBC ratios >1:2, and platelet to RBC ratios >1:2.[27]

However, the apparent survival advantage associated with high FFP to RBC transfusion ratios could be explained by a survival bias. Because component blood products are not administered evenly and simultaneously in clinical practice, and many deaths occur early, it is possible that the survival benefit observed among patients receiving a higher FFP to RBC ratio may merely reflect the fact that they live long enough to receive the higher ratio of products. Several investigations have reported that the association between higher FFP to RBC ratios and improved survival is not statistically significant when adjusted for survival bias.[28,29] A recent prospective observational study indicates that a 1:1 FFP to RBC ratio does not provide any additional benefit over ratios of 1:2 to 3:4 and that the hemostatic benefits of plasma therapy are limited to patients with coagulopathy.[30] Some authors believe that one of the reasons for these conflicting results is that the survival benefit of using 1:1 FFP to RBCs is relatively small and only apparent within the first 3 hours of resuscitation.[31] The American Association of Blood Banks and the European task force recommend early intervention with FFP but without a preset FFP to RBC ratio.

In a recent review, Ho et al.[32] evaluated the presence of survivor bias in studies in which 1:1 FFP to RBC ratios were used during massive transfusion of trauma patients. Massive transfusion was defined as ≥10 U of packed RBCs (PRBCs) transfused over the first 24 hours of hospitalization. Twenty-six studies were identified from an initial pool of 216 abstracts selected from a MEDLINE search.

Studies in which cohorts were compared before and after a massive transfusion ratio of 1:1 was implemented (so-called "before and after" studies) were not considered to have a survivor bias, nor were studies in which the FFP:RBC ratio was considered a time-dependent covariate in the statistical analysis. Studies were considered "survivor bias-prone" if they included all patients from time of hospital admission (given that early deaths often received a lower FFP:RBC ratio). Studies in which patients were included only if they survived the first few hours of resuscitation or until ICU admission were also considered to have a survivor bias. Overall, 21 of the 26 studies evaluated demonstrated an association between 1:1 and survival. Of those, only 10 did not have a survivor bias for or against 1:1 transfusion ratios.

Ideally, a well-controlled randomized trial could answer the question of survivor bias more conclusively. The Pragmatic Randomized Optimum Platelet and Plasma Ratio (PROPPR) trial is an ongoing multicenter, prospective, randomized study that will evaluate different blood product ratios to be administered to trauma patients in need of >10 U of PRBCs in the first 24 hours. This will offer an opportunity to prospectively evaluate the ideal ratio of blood products for use in trauma.

## PHARMACOLOGIC ADJUNCTS

In addition to appropriately aggressive blood product administration, there are a number of pharmacologic modalities that can maintain arterial blood pressure, attenuate the systemic inflammatory response, and improve outcome in trauma. This is especially important in situations where a massive transfusion may not be possible, or where the patient continues to deteriorate despite massive transfusion and surgical control of bleeding.

## TRANEXAMIC ACID

Tranexamic acid is a synthetic lysine derivative that competitively inhibits lysine binding sites on plasminogen, blocking the conversion of plasminogen to plasmin. This inhibits the proteolytic action of plasmin on fibrin clot and platelet receptors, and serves as an effective antifibrinolytic.

In the CRASH-2 trial, 20,211 trauma patients were randomized to receive either tranexamic acid (1 g initial loading followed by 1 g over 8 hours) or placebo.[33] This multicenter, prospective trial demonstrated significant reductions in all-cause mortality, and in deaths due to bleeding, without increasing vascular occlusive events in the tranexamic acid group, compared with the placebo group. Further analysis by the investigators revealed that the benefit was only seen when tranexamic acid was administered within 3 hours of injury and that increase in mortality occurred when the drug was given after this period. Surprisingly, however, there was no statistical difference in blood transfusion between the tranexamic acid and placebo groups. Exactly how tranexamic acid reduced the risk of death in bleeding patients remains unanswered.

A subgroup analysis of the CRASH-2 trial included 270 adult trauma patients at risk for extracranial bleeding who also had a traumatic brain injury.[34] These patients received tranexamic acid (1 g bolus followed by infusion, as in the CRASH-2 trial) or placebo. Intracranial hemorrhage growth as measured by computed tomography was examined. Mean total hemorrhage growth between the tranexamic acid arm and placebo was no different. Likewise, new focal ischemic lesions were not significantly different in the 2 groups. The authors speculated that a decrease in the size of the intracranial hemorrhage would decrease local pressure on arteries and, therefore, decrease the risk of ischemia. This effect, however, was not demonstrated here. A follow-up study, the CRASH-3 trial, will examine head injury more closely.

The Military Application of Tranexamic Acid in Trauma and Emergency Resuscitation (MATTERs) study[35] evaluated the use of tranexamic acid in hemorrhagic shock after combat injury in 896 consecutive trauma admissions, 293 of whom received the drug. Unadjusted mortality was lower

in the tranexamic acid group, despite being more severely injured. Patients who received massive transfusion (>10 U of PRBCs within 24 hours) benefited the most from the administration of tranexamic acid, with improved survival and less coagulopathy.

Tranexamic acid can improve survival, reduce transfusion requirements, and offer a lower cost alternative in resuscitation of the trauma patient. Western European militaries (specifically the United Kingdom) use tranexamic acid as part of their resuscitation plan for the wounded combatant. The use of tranexamic acid within the first 3 hours of injury may also offer benefit to the severely injured trauma patient in the US.

## RECOMBINANT FACTOR VIIA

Recombinant activated factor VII (rFVIIa) is thought to act locally at the site of tissue injury by binding to exposed tissue factor and generating a tight fibrin hemostatic plug through increased thrombin generation. The use of rFVIIa in trauma has been the subject of great interest and investigation. An audit of a multicenter trauma registry identified 380 patients who received rFVIIa.[36] Death from hemorrhage was reported at a rate of 30%. rFVIIa nonresponders tended to have a pH <7.1, platelet counts <100,000, and systolic blood pressure ≤90 mm Hg. A wide range of rFVIIa doses, as well as a wide range of "time to first dose of rFVIIa," make interpretation of these data difficult. A case series of 81 diverse trauma patients reported that rFVIIa successfully reversed coagulopathy, as measured by a decrease in prothrombin time, in 75% of patients.[37] Although coagulation abnormalities were corrected, a demonstrated benefit against controls was not demonstrated. Lower arterial pH, higher lactate, and worse base deficit were most predictive of rFVIIa nonresponders.

A retrospective database review evaluated the use of rFVIIa in combat casualties with high injury severity scores who had received massive blood transfusions.[38] Forty-nine of these patients received rFVIIa, and 75 did not. Patients who did not receive rFVIIa were colder and had a lower admission systolic blood pressure. Twenty-four-hour and 30-day mortality were significantly decreased in the rFVIIa group. However, there was no statistically significant difference in death from hemorrhage between the 2 groups, nor was there an increase in the risk of pulmonary embolism, deep vein thrombosis, or stroke.

Currently, there are only 2 published studies that included randomized clinical trials evaluating the use of factor VIIa in the exsanguinating trauma patient.[39,40] These studies, which were supported by the drug manufacturer, reported a decrease in blood product use but no effect in mortality. Therefore, although rFVIIa can reverse coagulation abnormalities and decrease blood loss, a well-defined outcome benefit is less clear.

## VASOPRESSIN

Vasopressin is a potent vasoconstrictor that spares cerebral, pulmonary, and cardiac vascular beds, essentially shunting blood above the diaphragm. Pharmacologic amplification of the neuroendocrine stress response with vasopressin may provide further benefit.[41] Vasopressin levels are low in vasodilatory shock, perhaps due to depletion of neurohypophyseal stores.[42] Vasopressin is significantly more potent than norepinephrine and angiotensin II, and maintains its efficacy in hypoxia and severe acidosis, where catecholamines may not be as effective.[43]

Several studies have demonstrated improved arterial blood pressure and survival in animals with profound hypovolemic shock treated with vasopressin. One porcine model using liver injury to produce hemorrhagic shock demonstrated improved short-term survival with vasopressin.[44] In a similar study, 21 pigs subjected to a standardized liver injury were resuscitated with vasopressin (0.4 U/kg then 0.04 U/kg/min), epinephrine (45 μg/kg then 5 μg/kg/min), or saline placebo.[45] Mean arterial blood pressure was higher in the vasopressin group with no increased bleeding. Survival was also improved.

In a canine hemorrhagic shock model, 7 animals were resuscitated with vasopressin with improvement in the mean arterial blood pressure.[46] Plasma vasopressin levels, although elevated initially, were low immediately before vasopressin administration, suggesting the possibility of vasopressin depletion in late-stage hemorrhagic shock.

Although animal studies have been encouraging, human data are mainly in the form of case reports. In one remarkable case report, a 41-year-old woman suffered a fall from a roof and was resuscitated with RBCs and coagulation factors before transport to a trauma center.[47] At the trauma center, aggressive resuscitation was continued with fluids and norepinephrine; however, the patient continued to be hemodynamically unstable. An infusion of high-dose vasopressin (10 IU/min) was initiated with sufficient stabilization of the arterial blood pressure to emergently embolize bleeding pelvic blood vessels. Despite numerous orthopedic injuries, a liver injury, and a subdural hematoma, the patient was discharged from the ICU to the ward 39 days after injury with no neurologic deficit.

In other case reports of patients who had intraoperative or postoperative bleeding, low-dose vasopressin infusions (0.04 U/min) improved short-term survival.[48] One patient had systolic blood pressures in the 50s with a base deficit of −21 after a portal vein injury during surgery. After surgical correction of the injury, fluid resuscitation, and a norepinephrine infusion, the patient continued to be resuscitated in the ICU with a regimen that included a low-dose vasopressin infusion. The authors speculate that in cases of advanced hemorrhagic shock, acidotic, vasodilated patients who are poorly responsive to intravascular fluid administration and catecholamines may benefit from vasopressin. Other reports document cases of aortic and liver surgery in which patients had profound and prolonged hypotension secondary to hemorrhage.[49] Low-dose vasopressin infusions were part of an aggressive resuscitation in which patients survived.

Despite evidence of the utility of vasopressin in animal models, there is a paucity of data in human trials. Because the limitations of case report data are well described, more detailed investigations of vasopressin in hemorrhagic shock have been suggested.[50,51]

There is an ongoing multicenter European trial that will evaluate prehospital administration of vasopressin versus normal saline.[52,53] Further clinical trials will help define the role of vasopressin in the trauma patient with hemorrhagic shock.

## OTHER PHARMACOLOGIC ADJUNCTS

Administration of hydrocortisone can help compensate for the exhaustion of the hypothalamic-pituitary-adrenal axis seen during critical illness.[54,55] The intense mineralocorticoid activity of hydrocortisone improves sensitivity to catecholamines, decreases inflammatory markers, and decreases vasopressor requirements, while avoiding some of the unwanted side effects of glucocorticoid administration. Although it would be ideal to verify a cortisol level before administration of hydrocortisone, one can assume some degree of adrenal insufficiency and catecholamine depletion in a trauma patient with hemorrhagic shock. Thirty-four trauma patients were stimulated with cosyntropin and defined as "nonresponders" if serum cortisol increased <9 μg/dL.[56] Forty-seven percent of patients were nonresponders immediately after the early resuscitative phase, with 25% of those patients remaining as nonresponders after 1 week. Although mortality between responders and nonresponders was similar, nonresponders had a longer duration of norepinephrine infusion and more total infused drug.

Administration of hydrocortisone can decrease vasopressor requirements in trauma patients.[57] Twenty-three trauma patients at the end of the resuscitative period (27 ± 15 hours after trauma) received a stepwise dose of phenylephrine before and after a dose of hydrocortisone 50 mg. Hydrocortisone decreased the $ED_{50}$ (dose leading to half-maximum theoretical effect on mean arterial blood pressure) of the phenylephrine infusion by 37%.

The benefit of hydrocortisone in other critically ill patient populations is less clear. Patients who were given etomidate to facilitate endotracheal intubation were randomized to receive either hydrocortisone or placebo for etomidate-related adrenal insufficiency. There was no significant difference in the proportion of patients with Sequential Organ Failure Assessment (SOFA) scores of 3 or 4. The hydrocortisone group did, however, show a decrease in required norepinephrine dose.[58]

The citrate preservative in blood products can chelate calcium during administration of blood and contribute to hypotension. Administration of calcium chloride improves smooth muscle tone and is a simple, often overlooked therapy for hypotension in the context of resuscitation. The risks of hypocalcemia, such as unremitting hypotension, are greater than the risks of mild hypercalcemia (e.g., nausea, vomiting, constipation, ileus, shortened QT interval, nephrocalcinosis).

In one cohort study, ionized calcium concentration was related to mortality in 352 patients experiencing "critical bleeding requiring massive transfusion." A concentration-dependent increase in mortality was seen in patients with hypocalcemia. Acidosis and the amount of FFP transfused were identified as the main risk factors for hypocalcemia.[59]

The use of sodium bicarbonate for the treatment of severe lactic acidosis from shock remains controversial, because it has not been shown to improve outcomes. Although sodium bicarbonate has been reported to improve cardiac contractility in animal models,[60] its use can exacerbate intracellular hypercarbia and acidosis and have a negative impact in patients.[61] Some authors have suggested that if bicarbonate therapy is used, it should only be considered if the pH is less than 7.0 to 7.2.[61,62] In addition, simple correction of the acidosis by bicarbonate therapy does not seem to correct the negative effects of acidemia on coagulation.[63]

## POSTRESUSCITATIVE CARE

The postresuscitative phase carries the continuum of care into the ICU where appropriate critical care can improve outcomes in trauma. The acute respiratory distress syndrome (ARDS) is a well-known entity in critical illness. The resulting decrease in lung compliance causes an increase of plateau pressures and makes ventilation difficult. Lower tidal volumes offer some relief from poor compliance,[64] even though hypercarbia sometimes results from decreasing minute ventilation ("permissive hypercarbia"). Oxygenation is maintained with the use of positive end-expiratory pressure and escalating concentrations of oxygen. This lung-protective strategy is the only strategy that has been demonstrated to reduce mortality for patients with ARDS. Although outcome improvements from other interventions have been difficult to quantify, a recent study evaluating the use of neuromuscular blockade with cisatracurium demonstrated a survival benefit.[65] However, confounding variables such as off-label use of cisatracurium, and the use of prone positioning and inhaled nitric oxide, make the results of this study difficult to interpret.

Acute tubular necrosis in the trauma patient can result from a low intravascular volume state. Hypovolemia leads to a prerenal syndrome resulting in tubular necrosis. Urine output often remains low even after normal renal hemodynamics have been restored. This is thought to be attributable to tubular obstruction by necrotic cells at the pars recta, where the proximal tubule meets the loop of Henle. Fluid resuscitation is the therapy of choice, with the objective being urine output of 1 to 2 mL/kg/h. Prompt fluid resuscitation can decrease the incidence of posttraumatic acute kidney injury (AKI).[66] Although dopamine in low doses of approximately 2 μg/kg/min (so-called "renal dose") can increase renal and mesenteric blood flow, it does not affect the prevention, development, or course of AKI. It also does not decrease mortality or the need for renal replacement therapy, including hemodialysis. In short, there is no role for low-dose dopamine in the treatment of posttraumatic AKI.[67]

The inflammatory response that accompanies hemorrhagic shock is not unlike that of sepsis. A similar approach to these patients may offer clues to treatment, particularly in the postresuscitative phase. The concept of early goal-directed therapy used in sepsis may be applicable in trauma as well.[68] Early resuscitation with blood products and adjunctive pharmacologic therapy may attenuate the systemic inflammatory response of trauma. Future investigations will need to determine whether this approach also offers a survival benefit.

## AREAS FOR POTENTIAL INVESTIGATION

Therapeutic hypothermia has been identified as a modality that can improve survival in out-of-hospital cardiac arrest due to ventricular fibrillation.[69] Although hypothermia (along with acidemia and coagulopathy) is a component of the trauma "triad of death," therapeutic hypothermia has

been encouraging in animal models of hemorrhagic shock.[70] In one study, 27 dogs were exsanguinated over 5 minutes.[71] The animals then received an aortic flush with 2°C isotonic saline until temperatures of 20°C, 15°C, or 10°C were reached. The animals underwent closed chest cardiopulmonary bypass and 12 hours of postarrest hypothermia to 34°C. Outcome was evaluated via Overall Performance Category (OPC), Neurologic Deficit Score (NDS), and Histologic Damage Score (HDS). Normal OPC and NDS and mild HDS were seen in animals at 15°C for 60 minutes, and at 10°C for 60 and 90 minutes. Results were less promising for dogs at 20°C for 60 minutes, as well as for dogs at 10°C for 120 minutes, suggesting a threshold for temperature and length of cooling, beyond which hypothermia is less effective.

A thorough review of induced hypothermia finds encouraging preclinical data and describes an upcoming human trial in penetrating trauma that will induce temperatures of 10° centigrade using cardiopulmonary bypass. The benefit of induced hypothermia is less clear, however, for blunt trauma and head injury.[72]

In spinal cord injury, therapeutic hypothermia to 33° centigrade via intravascular cooling devices offers some improvement in function. The number of patients in many of these studies, however, is small. Larger randomized, multicenter trials would offer more powerful evidence of the benefit of therapeutic hypothermia.[73]

Although the potential for induced hypothermia is exciting, it should be noted that nontherapeutic hypothermia can potentially worsen the aforementioned trauma triad of death. As such, the role of therapeutic hypothermia in the resuscitation of trauma patients has yet to be determined.

## CONCLUSION

Prompt transportation to designated trauma centers and immediate management of threats to life are the first steps in the resuscitation continuum. Resuscitation with RBCs and plasma, in parallel with surgical or interventional radiologic source control of bleeding, are the cornerstones of trauma management. Adjunctive therapy can assist with resuscitation. Tranexamic acid is used in Europe with promising results, and its use is now steadily increasing in the US. rFVIIa can correct abnormal coagulation values, but its outcome benefit is less clear. Vasopressin shows promise in animal studies and case reports, but has not been subjected to a large clinical trial. Appropriate critical care management of ARDS and acute tubular necrosis extends the resuscitation continuum into the ICU, where future therapies may involve therapeutic hypothermia. ■

## DISCLOSURES

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**Contribution**: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
**Attestation**: Joshua M. Tobin approved the final manuscript.
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**Contribution**: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
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